ORIGINAL ARTICLE

Effect of Losartan in Comparison with Pioglitazone on Atherogenic Indices in a Rat Model of Type 2 Diabetes Mellitus

FAROOQ KHAN[1], HAFIZ MOHAMMED DAWOOD[2], SHAHNAZ FATIMA[3], *MUHAMMAD NAUMAN SHAD[4] AJAZ FATIMA[5], SYED MUHAMMAD ALI[6]*

[1]Assistant Professor of Radiology, Sahara Medical College, Narowal.
[2]Assistant Professor of Community Medicine, Sahara Medical College, Narowal.
[3]Assistant Professor of Pharmacology, Sahara Medical College, Narowal.
[4]Associate Professor of Pharmacology, Sahara Medical College.
[5]Associate Professor of Pharmacology, Lahore Medical & Dental College, Lahore.
[6]Demonstrator, Pharmacology, Sahara Medical College, Narowal
Correspondence to Dr. Muhammad Nauman Shad, Email: mnauman2002saj@yahoo.com Cell: 0334-5062652

ABSTRACT

Background: Atherogenic indices (AI) are strong markers for predicting the risk of atherosclerosis and coronary heart disease. Objective of this study was to compare the effect of losartan with pioglitazone on atherogenic indices in a on an animal model of diabetes.

Methods: Forty five Sprague-Dawley rats were randomly divided into three groups. All these rats, which were 5 weeks of age, were fed a diet high in fat and sucrose. Rats in groups HFD-PIO and HFD-LOS were given Pioglitazone or losartan respectively, along with this diet, while group HFD was kept as control. Every week body weight and fasting blood glucose levels were determined. Serum samples were obtained from all the animals at the end of 12 weeks and the lipid profile was determined using kit method and the Friedewald's formula. Atherogenic indices were calculated from their formulae.

Results: Losartan showed an insignificant decrease in major atherogenic indices. However there was no statistical significance in results of atherogenic indices between losartan and pioglitazone

Conclusion: Losartan may decrease the atherogenic potential, comparable to pioglitazone

Keywords: Losartan, Pioglitazone, Atherogenic indices

INTRODUCTION

The leading cause of death worldwide is cardiovascular disease (CVD), with more than half due to coronary heart disease (CHD)[1]. Patients with adverse lipid profile are at high risk of developing atherosclerosis and coronary heart disease[2].

A diet rich in fat and carbohydrates plays a major role in the pathogenesis of type 2 diabetes mellitus and dyslipidemia[3]. Insulin resistance, β-cell dysfunction, type 2 DM and dyslipidemia can be caused from such an adverse diet that causes oxidative stress[4].

Among drugs used to treat type 2 diabetes mellitus, the glitazones have consistently shown to protect beta cells from lipotoxicity by improving beta cell function[5].

An improvement in lipid profile including a decrease in total cholesterol, triglycerides and low-density lipoproteins (LDL) and an increase in high-density lipoprotein (HDL) has been shown by Pioglitazone[6].

The association between obesity, metabolic syndrome, dyslipidemia, insulin resistance, chronic kidney disease, and hypertension has been linked to the renin-angiotensin-aldosterone system[7].

Positive effects on lipid profiles in children with the metabolic syndrome have been shown by ACE Inhibitors. Significant decrease in LDL & triglyceride levels and significant increase in HDL levels were seen in one study[8].

New screening tools for better evaluation of cardiovascular diseases are now necessary due to their high prevalence and severity. For more accurately predicting the risk of atherosclerosis and coronary heart disease, Atherogenic index (AI) (LDL-C/HDL-C), coronary risk index (CRI) (TC/HDL-C) and Atherogenic Index of Plasma (AIP) Log (Triglycerides/HDL) can be performed which are all strong markers for such chronic heart diseases[9].

Observation of the effects of the dual ARB/PPAR-γ agonist losartan on atherogenic indices and comparison with pioglitazone was one of the primary objectives of this study.

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MATERIAL AND METHODS

This was a randomized control trial. Animals were randomly divided into 3 groups each containing fifteen rats. Throughout the study period of 12 weeks, all the three groups of rats were fed a diet high in fat and sucrose. First group, labeled as HFD (high fat diet) group, was daily given distilled water in the morning through a NG tube. Second group, labeled as HFD-PIO group, was daily given pioglitazone in a single dose of 10 mg/kg body weight in the morning via NG tube for 12 weeks. Third group, labeled as HFD-LOS group was daily given losartan in a single dose of 10 mg/kg body weight in the morning via a NG tube for 12 weeks.

Blood Sampling: Blood samples were collected by cardiac puncture after twelve weeks and keeping the rats on a twelve hour fast. This was followed by a five-minute centrifugation of the samples at room temperature.

Lipid Profile: Calorimetric kit method was used to obtain total cholesterol, HDL-cholesterol and triglyceride levels. Friedewald's formula was used to determine LDL-cholesterol levels

Atherogenic Indices
Atherogenic index (AI)
AI = LDL/HDL[10]
Atherogenic Coefficient (AC)
AC = Total Cholesterol – HDL /HDL[11]
Coronary risk index (CRI)
CRI = Total Cholesterol/HDL[11]
Atherogenic Index of Plasma
AIP = Log (Triglycerides/HDL) [12]
Drugs: Mass Pharmaceuticals provided the drugs pioglitazone and losartan for the present research study.
Statistical analysis: Latest version of SPSS was used to analyze the data after it was entered. Mean ± S.D. was given for quantitative variables like AI, CRI, AC and AIP. To compare the above variables among the groups, one-way ANOVA was applied. To see whether variances were statistically significant, Bonferri's test was applied.

RESULTS

At 12 weeks, mean and SD values of all atherogenic indices were higher in the control group than in the HFD-PIO and HFD-LOS groups. Values of CRI and AC were very significantly different ($p < 0.001$) between the control and HFD-PIO groups. It was also slightly different ($p < 0.05$) between the control and HFD-PIO groups. There was no statistical difference in AIP between the control and HFD-PIO groups. The study found no significant statistical difference in any of the parameters between the control HFD and the HFD-LOS groups and between HFD-PIO and HFD-LOS groups (Table 1).

Table 1: Mean and SD of AI, AC, CRI and AIP of different groups of rats at end of 12 week study period with statistical differences

Groups	CRI	p-value	AC	p-value	AIP	p-value*	AI	p-value
HFD	6.873 ± 1.041	-	5.873 ± 1.041	-	0.918 ± 0.072	-	4.193± 0.783	-
HFD-PIO	5.307 ± 1.378	***< 0.001	4.307 ±1.378	***<0.0001	0.812 ±0.099	NS> 0.05	2.981 ±1.068	*< 0.05
HFD-LOS	6.068 ±1.696	NS> 0.05	5.068 ±1.696	NS> 0.05	0.860 ±0.117	NS > 0.05	3.569 ±1.281	NS> 0.05

P-values were computed in comparison with control HFD group
Comparison between HFD-PIO vs HFD-LOS showed non-significant p-value > 0.05 in all variables

DISCUSSION

Dyslipidemia is described as an abnormal plasma concentration of lipids (triglyceride (TG) and total cholesterol (TC) and their blood transporting lipoproteins: HDL Cholesterol (HDL-C), LDL-Cholesterol (LDL-C) and VLDL-Cholesterol (VLDL-C). A strong association between incidence of CVD and high levels of LDL-C and low levels of HDL-C was shown in several scientific studies. Therefore the LDL-C/HDL-C ratio (atherogenic index) is often calculated to estimate cardiovascular risk; the higher this ratio, the higher the risk[9].

A strong marker for predicting the risk of atherosclerosis and coronary heart disease is the Atherogenic Index of Plasma (AIP). AIP reflects a true relationship between protective and atherogenic lipoproteins and is associated with the size of pre- and anti-atherogenic lipoprotein particle[13].

It has been seen in a clinical study that pioglitazone significantly decreased AIP. AIP was inversely associated with insulin sensitivity measures, i.e., the homeostasis model measurement (HOMA-S) and the quantitative insulin sensitivity check index (QUICKI) in this study like other studies[14].

It has also been seen in several studies that pioglitazone decreases insulin resistance[15] and also has shown beneficial effects on lipid profile[16]. Losartan also showed the same but results were not statistically significant.

The present study showed a similar pattern. Pioglitazone (HFD-PIO) showed very much significant decrease in Coronary risk index (CRI) and Atherogenic Coefficient (AC) and a slightly significant decrease in atherogenic index (AI) as compared to control HFD rats. Losartan showed a non-significant decrease in all the atherogenic indices as compared to the control group. However the difference in all the atherogenic indices between pioglitazone and losartan was not significant.

CONCLUSION

Losartan showed an insignificant decrease in major atherogenic indices which were however comparable to pioglitazone. This opens up research for the potential of other Angiotensin receptor blockers in improving lipid profile and decreasing atherogenic potential.

REFERENCES

1. Vilahur G, Badimon J, Bugiardini R and Badimon L. Perspectives: The burden of cardiovascular risk factors and coronary heart disease in Europe and worldwide. *European Heart Journal Supplements*; 2014. Volume 16, Issue suppl_A
2. Nelson R. Hyperlipidemia as a Risk Factor for Cardiovascular Disease. *Prim Care*. 2013. 40(1): 195–211.
3. Gastaldelli A. Abdominal fat: does it predict the development of type 2 diabetes? *Am J Clin Nutr,* 2008. 87(5):1118-9.
4. Tanvarasittichai S. Oxidative stress, insulin resistance, dyslipidemia and type 2 diabetes mellitus. *World J Diabetes*. 2015. 15; 6(3): 456–480
5. Kathleen A and Reisman T. Interventions to Preserve Beta-Cell Function in the Management and Prevention of Type 2 Diabetes. *Curr Diab Rep*. 2013. 13(2): 252–260.
6. Hussian M, Arain AQ and Chiragh S. Pioglitazone improves serum lipid profile in diet induced hyperlipidaemic non diabetic rats. *Journal of Pakistan Medical Association*. 2016; 66 (10): 1286-1290
7. Thethi T, Kamiyama M and Kobori H. The Link between the Renin-Angiotensin-Aldosterone System and Renal Injury in Obesity and the Metabolic Syndrome. *Curr Hypertens Rep*. 2012; 14(2): 160–169.
8. Bitkin EC, Boyraz M, Taşkın N, Akçay A, Ulucan K, Akyol MB and Akçay T. Effects of ACE Inhibitors on Insulin Resistance and Lipid Profile in Children with Metabolic Syndrome. *J Clin Res Pediatr Endocrinol*. 2013; 5(3): 164–169.
9. Kazemi T. Hajihosseini M, Moossavi M, Hemmati M and Ziaee M. Cardiovascular Risk Factors and Atherogenic Indices in an Iranian Population: Birjand East of Iran. *Clin Med Insights Cardiol*. 2018; 12: 1179546818759286.

10. Popa CD, Arts E, Fransen J and van Riel PLCM. Atherogenic Index and High-Density Lipoprotein Cholesterol as Cardiovascular Risk Determinants in Rheumatoid Arthritis: The Impact of Therapy with Biologicals. *Mediators of Inflammation*. 2012; Article ID 785946, 9 pages, http://doi.org/10.1155/2012/785946
11. Singh M, Pathak MS and Paul A. A study on Atherogenic Indices of Pregnancy Induced Hypertension Patients as Compared to Normal Pregnant Women. *Journal of Clinical and Diagnostic Research*. 2015; 9(7): BCO5-BCO-8
12. Niroumand S, Khajedaluee M and Dadgarmoghaddam M. Atherogenic Index of Plasma (AIP): A marker of cardiovascular disease. *Med J Islam Repub Iran*. 2015; 29 : 240
13. Myat Su Bo, Whye Lian Cheah, Soe Lwin, Tin Moe Nwe, Than Than Win, and Myint Aung, Understanding the Relationship between Atherogenic Index of Plasma and Cardiovascular Disease Risk Factors among Staff of an University in Malaysia. *Journal of Nutrition and Metabolism*. 2018, Article ID 7027624, 6 pages, https://doi.org/10.1155/2018/7027624.
14. Dobiasova M. Atherogenic Index of Plasma [Log(Triglycerides/HDL-Cholesterol)]: Theoretical and Practical Implications. *Clinical Chemistry*. 2004, 50 (7) 1113-1115
15. Shad MN, Zaheer Z, Kausar S and Chiragh S. Comparative effects of Losartan and Pioglitazone on Insulin Resistance in Rats. *Biomedica*. 2014. 30(3): 1-5.
16. Shad MN, Sair M, Jalal A, Chiragh S and Ahmad Z. Effect of Losartan in Comparison with Pioglitazone on Lipid Profile in a Rat Model of Type 2 Diabetes Mellitus. *JIMDC*.2018; 7(1):36-40.