IJCRR
Vol 05 issue 09
Section: Healthcare
Category: Research
Received on: 16/03/13
Revised on: 12/04/13
Accepted on: 26/04/13

THE EFFECT OF ROSIGLITAZONE ON LIVER IN TYPE 2 DIABETES PATIENTS

Manish Jain[1], Jitendra Ahuja[2]

[1]Department of pharmacology, Geetanjali medical college and Hospital, Udaipur Manwa Khera, Udaipur (Rajasthan), India
[2]Dept. of Biochemistry, Geetanjali Medical College and Hospital, Udaipur (Raj), India

E-mail of Corresponding Author: drmanish76jain @gmail.com

ABSTRACT

Objectives: The most important fundamental pathology in type 2 diabetes is insulin resistance. Thiazolidinedione is one of the drugs of choice to combat the insulin resistance. Different studies show conflict about thiazolidinedione and its effect on liver functions. In this study, we weighed up the outcome of rosiglitazone on liver functions in type 2 diabetes. **Materials and Methods:** One hundred patients with type 2 diabetes taking rosiglitazone 4 mg daily were enrolled in this 2-month study. Biochemical parameters of liver and diabetes mellitus were estimated monthly during the treatment period of case and controls. **Results:** At starting point, difference between the Normal Liver Function (NLF) and Abnormal Liver Function (ABLF) groups in body mass index, fasting plasma glucose, hemoglobin A1c (HbA1c), and lipid profiles were not significant. After 3 month of the treatment, HbA1c was significantly lowered in both groups (P = 0.0001). More importantly, serum concentrations of both serum glutamate oxaloacetate transferasease (SGOT), serum glutamate pyruvate transferasease (SGPT) and Gamma glutamryl transpeptidase (GGT) in the ABLF group decreased significantly (SGOT: 59.7±21.9 to 49.7±22.4U/L, P=<0.0001; SGPT: 82.78±50.44 to 63.9±39.4U/L, P=< 0.0001, GGT: 50.29±28.03 to 35.77±27.4 p= <0.0001 respectively) while in the NLF group, a significant changes were not found. **Conclusion:** Rosiglitazone have a positive effect on liver function in type 2 DM patients with elevated liver enzymes, after 3-month rosiglitazone treatment significantly improve SGPT,SGOT and GGT levels in type 2 diabetes with abnormal liver enzymes. Though our results support the fact that abnormal liver function are not a contraindication for rosiglitazone as earlier studies suggests.

Key words: rosiglitazone, type 2 diabetes, Normal Liver Function (NLF) group and Abnormal Liver Function (ABLF) group.

INTRODUCTION

It is estimated that 40.9 million people, i.e., 4.0% of the Indian population, have diabetes (1).Type 2 diabetes was responsible for 109 thousand deaths in 2004 and 1.157 million years of life lost in 2004 India (2) 2.263 million disability adjusted life years (DALYs) in India during 2004 because of Type 2 diabetes. (3)

Liver disease is a significant reason of death in type 2 diabetes. Cirrhosis was the fourth foremost cause of death of diabetes associated deaths according to Verona Diabetes Study.(4) In a further prospective cohort study ,cirrhosis explained for 12.5% of deaths in patients with diabetes. (5)

The treatment of patient of type 2 diabetes with liver diseases is, most of the time same as that without liver disease. But theoretically patients whose are affected with liver failure, may alter drug metabolism and hepatotoxicity. Besides, there is no supporting data available that liver disease patients are liable to hepato- toxicity

(6). On the other hand deep-rooted liver disease may cause misdiagnosis and raise the drug-induced liver disease.

Metformin is a treatment of choice in most Diabetic patients but lactic acidosis is a limiting factor for the advanced hepatic disease. The most important fundamental pathology in type 2 diabetes is insulin resistance and insulin resistance is also the causal defect in fatty liver disease, the combination of both disorders can be made for thiazolidinediones (TZDs) as preferred therapy in these patients.(7,) Thiazolidinedione (TZD), can direct genes expression to improve insulin sensitivity by binding with the peroxisome proliferation activation receptor - g (PPAR-g). (8) importantly,There are some episodes of severe liver injury with the use of the first generation, troglitazone,so this drug was withdrawn 3 years later from market.(8) Another drug from this group like rosiglitazone and pioglitazone were then marketed in 1999. Some post-marketing studies are evidence for these Drugs are not associated with increased risk of hepato-toxicity.(9) Some infrequent cases of acute hepatitis, including one death are reported, rosiglitazone may be credited for that, while other causes cannot be completely expelled in these cases.(10,11,12) Recent trials are reveled healing effect of pioglitazone and rosiglitazone in liver histology (13,14).These effects, therefore, imply the possible function of TZD in the management of type 2 diabetes patients with liver disorders.

Even though there are a so many studies on the function of rosiglitazone on liver disorders, but some disagreements are also exist. This study is planned to assess the outcome of rosiglitazone in treatment of type 2 diabetes with normal and abnormal liver function at the baseline.

MATERIALS AND METHODS

Subjects and study design

This study was not financially supported by manufacturers of rosiglitazone. The study was single observer; cross – sectional, uni- centric, non interventional, questionnaire and clinical examination based pilot study.

Brief detail about past and present medical/ surgical history, family medical history, personal history, socioeconomic status, occupation, drug intake, hygiene etc was taken. Permission was taken from the Institutional Ethics Committee and all subjects provided written informed consent before participation.

Inclusion criteria

- Fifty Seven diagnosed patients of type 2 diabetes mellitus were enrolled.
- Men and women from the ages of 30 to 80 years.
- Women were preferably to be postmenopausal or presently applying a contraception method which is not affecting Blood sugar and liver function.

Exclusion criteria

- Patients with other disorders which might affect liver functions, such as significant peripheral edema, congestive heart failure, de-compensated liver cirrhosis and chronic renal failure.
- Patients with BMI values more than 38 or less than 22 kg/m^2 were not included.
- Patients were taking medication that might affect the liver function were not included.

Procedure

Participants were subjected to complete physical examination and proper history was taken. At Baseline and the follow-up visits (0,4,8 and 12 weeks), blood pressure and weight were recorded, and blood samples were taken for measurement of glucose,HbA1c,liver enzymes, lipids, creatinine, and electrolytes.All subjects were divided into two groups basis of their first liver function tests: those with both normal serum Glutamate oxaloacetate aminotransferase

(SGOT, reference ranges < 40 U/L) and Serum Glutamate pyruvate aminotransferase (SGPT, reference range < 40 U/L) levels were considered as normal liver function group (NLF, n=43), while, High level of SGOT (above 45 I.U. / L), SGPT (above 45 I.U. /L), Alkaline Phosphatase (above 129I.U./L) Gamma glutamaryl transferase (above 25 I.U. /L), respectively was defined as abnormal liver function group (ABLF, n=57).

These patients were advised for taking their regular treatment with glibenclamide and/or metformin .All the patients took rosiglitazone 4mg daily for 3 months. They were instructed to continue their other medication like antihypertensive drugs and lipid lowering agent, previous lifestyle, including diet and exercise throughout the study period. The identical metabolic investigations were evaluated at monthly intervals and to assess them for adverse events, including liver dysfunction.

Laboratory Investigations

The blood sample (fasting) was taken, Serum was separated from blood within one hour and blood glucose level was estimated by glucose oxidase- peroxidase method through auto analyzer.Serum value of cholesterol and LDL were measured by cholesterol oxidase peroxidase method through auto analyzer and calculated by Friedwadl's Formula respectively. Serum SGOT estimated by IFCC with pyridoxal phosphate activation colorimetric method through auto analyzer and Serum SGPT estimated by alanin aminotransferase according to IFCC colorimetric method through auto analyzer and serum Alkaline Phosphatase estimated by liquid according to IFCC colorimetric method through auto analyzer. Serum bilirubin estimated by colorimetric method trough autoanalyzer. (HbA1c) was evaluated by the latex agglutination turbidity method trough autoanalyzer.

Statistical analysis

Independent t-test was used to evaluate liver function between the two groups. Paired t-test was used to assess the alterations of liver function of subjects in the two groups before and after rosiglitazone treatment. All statistical data were two-sided and a P value <0.05 was considered to be statistically significant.

RESULTS

Mean age for control group is 37.38 years and in case group 61.21 years. Subjects in the Control (NLF) group were younger than those in the case (ABLF) group. Mean BMI of Case group was 24.4Kg/M^2 and control was 22.86 Kg/M^2.At baseline FPG, HbA1c, and lipid profiles were not significantly different between the control and case groups, with the exception of for higher levels of liver function in the case group which was criteria for grouping of subjects.

Table 1: Glycemic control, lipids and liver enzymes of the patients with normal and abnormal liver function at baseline and after 3 months of rosiglitazone treatment

N	Controls (NLF) n=47			Case (ABLF) n=53		
	Baseline	After 3 Month	P value	Baseline	After 3 Month	P value
FPG	205.9±13.1	187.8±25.5	< 0.0001	213.0±34.2	176.2±30	< 0.0001
HbA1c	9.2±1.9	8.7±1.8	< 0.0001	9.84±1.67	7.95±1.78	< 0.0001
TG	223.8±46.51	227.3±53.2	0.4751	236.3±54.9	231.4±50.0	0.6150
TC	203.4±28.63	199.9±29.2	0.5801	233.56±27.4	235.33±26.0	0.7235
HDL	45.06±5.90	41.9±7.6	0.0340	43.02±4.23	39.5±6.7	< 0.0001
SGOT	23.04±7.6	22.1±7.8	0.5774	59.7±21.9	49.7±22.4	< 0.0001
SGPT	20.7±8.4	20.6±8.8	0.9802	82.78±50.44	63.9±39.4	< 0.0001
GGT	15.7±8.2	14.3±8.0	0.4352	50.29±28.03	35.77±27.4	< 0.0001

NLF=Normal liver Function, ABLF=Abnormal Liver Function ,BMI=Body mass index, FPG=Fasting plasma glucose, TG =Triglyceride ,TC=Total cholesterol, HDL-c= High density Lipoprotein Cholesterol,HbA1C=Hemoglobin A1c,SGOT= serum Glutamate oxaloacetate aminotransferase.SGPT= Serum Glutamate pyruvate aminotransferase ,GGT=Gammaglutamaryl transferase.

Table 1 Showing different metabolic parameters at baseline and after 3 months of rosiglitazone treatment in both groups. Both FPG and HbA1c were declined from baseline to 3 month after the treatment with rosiglitazone in both groups. FPG and HbA1c achieve statistical significance in the NLF group (*P*=0.0001) and in the ABLF group (*P*=0.0001). The Value of SGOT, SGPT and GGT significantly improved in the ABLF group, whereas, only compliant non significant changes were distinguished in the NLF group. There were no significant variations before and after treatment in case of the lipids levels.

Healing of liver tissue was showed by the comparison of serum concentrations of SGOT/, SGPT and GGT at the baseline and after 3 month .The value of these enzymes reduced significantly at the end of the third month of treatment in the ABLF group. (SGOT: 59.7±21.9 to 49.7±22.4U/L, *P*=<0.0001; SGPT: 82.78±50.44 to 63.9±39.4U/L, *P*=< 0.0001, GGT: 50.29±28.03 to 35.77±27.4 p= <0.0001 respectively).Serum concentrations of SGOT, SGPT and GGT demonstrate no significant distinct results in the NLF group. Levels

DISCUSSION

At present scenario, pioglitazone and rosiglitazone are a common element of prescription in management of diabetic patients. Troglitazone are safer and good enough hepatotoxic patients in comparison to their predecessor. Tolman KG *et al*. found that in so many studies suggested that rosiglitazone did not associated with any hepatotoxic effects. (15) In another study done by Neuschwander-Tetri *et al*. observed that after 48 week treatment with rosiglitazone the 25 patients had significantly improved insulin sensitivity and mean Serum Glutamate pyruvate aminotransferase (SGPT) levels. Improving insulin sensitivity with rosiglitazone, an observation suggesting that insulin resistance contributes to its development of liver disease. However, the cohort was small and there was no control group. (16) We designed the present study to observe the effect of rosiglitazone on liver markers after 3 months of treatment in diabetic Indian population. Compared to the baseline, SGPT, SGOT and GGT concentrations decreased significantly at the end of treatment in the ABLF group, while there was no similar change in the NLF group. The results of this study are parallel to some earlier studies but our study have a control group (NLF Group) which make It different from others and additionally it establish that rosiglitazone could reduce liver enzymes, but does not increase them.

There are so many mechanism of TZD by which it can reduce liver marker enzyme in diabetic patients. The two main mechanisms might be implicated; first, improving insulin sensitivity and, second, the anti-inflammatory effect of TZD. In current scenario, ever more studies make obvious that obesity, insulin resistance and inflammatory mediators are involved in liver pathology in diabetic patients.(17,18) These inflammatory mediators like plasma tumor necrosis factor-alpha (TNF-a) and interleukin-6 (IL-6) take part in the development of NASH. (19). generally obese people and type 2 diabetes have elevated levels of these inflammatory markers; they suppress the insulin signal transduction which further hinder with insulin action. (20)

Rosiglitazone increases insulin sensitivity by activation of PPAR-γ, nuclear transcription factor further insulin slow down lipolysis and reduce free fatty acid release and promotes free

fatty acid uptake and triglyceride increase in the muscle, consequently reduces the inflammatory reaction of hepatocyte to dietary lipid load.(21)In addition, rosiglitazone also encourage the uptake and storage of free fatty acid in adipocytes and associated with an increase in adiposity in subcutaneous but not visceral body regions, which lessens hepatic cell damage. (22)

In addition according some studies rosiglitazone could diminish inflammatory mediators, such as IL-6, interleukin-1β, resistin, and TNF-α. Hong *et al*. explained that rosiglitazone could directly regulate primary human monocytes to inhibit the secretion of TNF-a (20).

Rosiglitazone attenuate the inflammation of hepatocytes by anti-inflammatory effects through different mechanisms and promote the strengthening of liver function.

When we compare results of ABLF group with NLF, there were no significant changes of liver function in the NLF group during the 3 months follow-up period in our study. We compared the outcome of rosiglitazone on the NLF and ABLF groups at the same time, which make our study different from others.

However, some limitations might affect on our study. Like we have not include other liver functions, we consider that these findings may be valuable Further assessment of liver function with other biochemical markers such as alkaline phosphate, albumin, bilirubin, prothrombin time abdominal sonogram and liver biopsy and will verify our results. The short period of the study and a small number of study population were other restrictions. More studies with a larger population and longer follow-up period are logical.

CONCLUSION

In conclusion, rosiglitazone have a positive effect on liver function in type 2 DM patients with elevated liver enzymes, after 3-month rosiglitazone treatment significantly improve SGPT,SGOT and GGT levels in type 2 diabetes with abnormal liver enzymes. Though our results give some support that abnormal liver function are not a contraindication for rosiglitazone as earlier thought, further studies are desirable to assess whether rosiglitazone is favorable for diabetic patients with elevated liver enzymes.

ACKNOWLEDGEMENT

Authors acknowledge the great help received from the scholars whose articles cited and included in references of this manuscript. The authors are also grateful to authors / editors / publishers of all those articles, journals and books from where the literature for this article has been reviewed and discussed. Authors are grateful to IJCRR editorial board members and IJCRR team of reviewers who have helped to bring quality to this manuscript.

REFERENCES

1. V. Mohan, S. Sandeep, R. Deepa, B. Shah, C. Varghese Epidemiology of type 2 diabetes: Indian scenario. Indian J Med Res 125, March 2007, pp 217-230
2. Venkataraman K, Kannan AT, Mohan V. Challenges in diabetes management with particular reference to India. International Journal of Diabetes in Developing Countries, 2009, 29:103–109.
3. ICMR. Assessment of Burden of NCDs. Indian Council of Medical Research, 2006.
4. de Marco R, Locatelli F, Zoppini G, Verlato G, Bonora E, Muggeo M: Cause-specific mortality in type 2 diabetes: The Verona Diabetes Study. Diabetes Care 22:756 –761, 1999
5. Balkau B, Eschwege E, Ducimetiere P,Richard JL, Warnet JM: The high risk of death by alcohol related diseases in subjects diagnosed as diabetic and impaired glucose tolerant: the Paris Prospective Study after

15 years of follow-up. J Clin Epidemiol 44:465– 474, 1991

6. Zimmerman HJ: Drug-induced liver disease.In Hepatotoxicity: The Adverse Effects of Drugs and Other Chemicals on the Liver. 2nd ed. Philadelphia, Lippincott Williams and Williams, 1991, p. 430
7. Chisholm DJ, Campbell LV, Kraegen EW:Pathogenesis of the insulin resistance syndrome (syndrome X). Clin Exp Pharmacol Physiol 24:782–784, 1997
8. Parulkar AA, Pendergrass ML, Granda-Ayala R, Lee TR, Fonseca VA. Nonhypoglycemic effects of thiazolidinediones. Ann Intern Med 2001;134:61-71
9. Henrion HR. The Treatment of Non-Alcoholic Steatohepatitis With Thiazolidinediones; Review Article. Aliment Pharmacol Ther 2005;22:897-5.
10. Dhawan M, Agrawal R, Ravi J, Gulati S, Silverman J, Nathan G, et al. Rosiglitazone-induced granulomatous hepatitis. J Clin Gastroenterol 2002;34:582-4.
11. Gouda HE, Khan A, Schwartz J, Cohen RI. Liver failure in a patient treated with long-term rosiglitazone therapy. Am J Med 2001;111:584-5.
12. Bonkovsky HL, Azar R, Bird S, Szabo G, Banner B. Severe cholestatic hepatitis caused by thiazolidinediones: Risks associated with substituting rosiglitazone for troglitazone. Dig Dis Sci 2002;47:1632-7.
13. Neuschwander-Tetri BA, Brunt EM,Wehmeier KR, Sponseller CA, Hampton K, Bacon BR: Interim results of a pilot study demonstrating the early effects of the PPAR-gamma ligand rosiglitazone on insulin sensitivity, aminotransferases, hepatic steatosis and body weight in patients with non-alcoholic steatohepatitis. J Hepatol 38:434–440, 2003
14. Promrat K, Lutchman G, Uwaifo GI,Freedman RJ, Soza A, Heller T, Doo E, Ghany M, Premkumar A, Park Y, Liang TJ, Yanovski JA, Kleiner DE, Hoofnagle JH: A pilot study of pioglitazone treatment for nonalcoholic steatohepatitis. Hepatology 39:188 –196, 2004
15. Tolman KG, Fonseca V, Dalpiaz A, Tan MH. Spectrum of liver disease in type 2 diabetes and management of patients with diabetes and liver disease. Diabetes Care. 2007 Mar;30(3):734-43.
16. Neuschwander-Tetri BA, Brunt EM,Wehmeier KR, Oliver D, Bacon BR: Improved nonalcoholic steatohepatitis after 48 weeks of treatment with the PPAR-gamma ligand rosiglitazone. Hepatology 38:1008–1017, 2003
17. Fuentes L, Rőszer T, and Ricote M . Inflammatory Mediators and Insulin Resistance in Obesity: Role of Nuclear Receptor Signaling in Macrophages. Mediators of Inflammation Volume 2010 (2010), Article ID 219583, 10 pages doi:10.1155/2010/219583
18. Meshkania R,Adelib K. Hepatic insulin resistance, metabolic syndrome and cardiovascular disease. Clinical Biochemistry2009; 42,(13–14) 1331–1346
19. Day CP. Non-alcoholic steatohepatitis (NASH): Where are we now and where are we going? Gut 2002;50:585-8.
20. Hong G, Davis B, Khatoon N, Baker SF, Brown J. PPAR gamma-dependent anti-inflammatory action of rosiglitazone in human monocytes: Suppression of TNF alpha secretion is not mediated by PTEN regulation. Biochem Biophys Res Commun 2003;303:782-7.