DOI: 10.7860/JCDR/2016/19887.8336

Original Article

Internal Medicine Section

Comparative Effect of Insulin Sensitizers and Statin on Metabolic Profile and Ultrasonographical Score in Non Alcoholic Fatty Liver Disease

HIMANSHU RANA[1], SURAJ SINGH YADAV[2], HIMANSHU D. REDDY[3], SHUBHAM SINGHAL[4], DINESH KUMAR SINGH[5], KAUSER USMAN[6]

ABSTRACT

Introduction: Non Alcoholic Fatty Liver Disease (NAFLD) is a metabolic disorder involving fat accumulation in the liver. The initial management for patients with NAFLD includes lifestyle modification and weight loss in overweight or obese patients.

Aim: The present study was conducted to compare the efficacy of insulin sensitizers and statin in the patients of NAFLD.

Materials and Methods: The study included 98 patients diagnosed with NAFLD on USG (Ultrasonography) abdomen, divided into three Groups randomly and administered Metformin (Group I), Rosuvastatin (Group II) or Pioglitazone (Group III) along with dietary intervention and lifestyle modification. Their Body Mass Index (BMI), liver function tests, fasting lipid profile, USG scores for fatty liver were done and followed up at 4 weeks, 12 weeks and 24 week for change in above parameters.

Results: Out of the three Groups, Group II showed a maximum improvements in usg scores for NAFLD ($p<0.001$) and fasting lipid profile. Group II also showed maximum derangement of liver enzymes at 24 weeks though none of the subjects had more than three times elevation of liver enzymes.

Conclusion: Rosuvastatin may be an effective therapy as add on treatment to dietary and lifestyle intervention in patients of NAFLD. As an add-on treatment Rosuvastatin was superior to Pioglitazone or Metformin and acute decompensation is unlikely with this drug. Metformin was not effective as add on therapy for NAFLD, rather rapid weight loss in short period of time resulted in worsening of hepatic steatosis.

Keywords: NAFLD, Metformin, Pioglitazone, Rosuvastatin, pharmacotherapy

INTRODUCTION

Non Alcoholic Fatty Liver Disease (NAFLD) is pathological entity involving fat accumulation in the liver and consists of two clinicopathological entities that include Non Alcoholic Fatty Liver (NAFL) and Non Alcoholic Steato Hepatitis (NASH). Fatty liver is defined as the accumulation of fat especially triglycerides in the liver with no evidence of injury in the form of ballooning degeneration of the hepatocytes [1]. Non-alcoholic fatty liver disease has been defined by American Association of the Study of Liver Disease (AASLD) as fat accumulation in the liver exceeding 5% to 10% by weight of liver [2]. It is estimated that worldwide prevalence of NAFLD in the general population, defined the world wide prevalence varying from 6.3% to 33% with a median of 20% based on a variety of assessment methods [3].

The standard of care for patients with NAFLD is lifestyle modification with weight loss as the mainstay of therapy [2]. Several small uncontrolled trials utilising different caloric restriction regimens and combinations of carbohydrate, protein and lipid diets have been performed as well as studies on the effect of increased exercise. So far, there is no established pharmacological treatment for NAFLD. Treatment strategies for NAFLD aim to improve insulin sensitivity, modify underlying metabolic risk factors, or to protect the liver from further insult by reducing oxidative stress. Multiple pharmacological interventions have been attempted with variable success. These include pentoxifylline [4], orlistat [5], vitamin E [6,7], ursodeoxycholic acid [8,9] and lipid-lowering agents [10]. Studies of insulin sensitizing agents such as metformin [11,12] and thiazolidinediones [13,14] have yielded promising results. Our study was conducted to assess the effectiveness of insulin sensitizers against NAFLD in the population of northern India. According to our knowledge no head–on comparison between Pioglitazone and Rosuvastatin for treating NAFLD, making this finding interesting. The results of the study may significantly add to our knowledge and go a long way in devising a standard therapy for NAFLD.

MATERIALS AND METHODS

Study Design and Enrolment of Patients

Study has been conducted in tertiary level medical institute of northern India, King George's Medical University, Lucknow, India. The study was a randomized trial with nested control of 24 weeks. The study was approved by Institutional Ethics committee (Ref. Code No. 66 ECM II-B/P4). Written informed consent was obtained from all the participants prior to enrollment. Patient attending medicine OPD or those admitted in indoor medical wards and having fatty liver on Abdominal Ultrasonography were enrolled over a period of one year (August 2013 to July 2014) after screening for the predesigned inclusion and exclusion criteria. Total of 98 subjects who consented for the study were subsequently enrolled. The subjects were re-evaluated with USG abdomen to calculate USG score for fatty liver by a competent radiologist who was blinded for the study. Subjects with history of significant alcohol consumption i.e., more than 20gm/day of alcohol consumption (as per AUDIT-C1 Questionnaire devised by WHO) were excluded. Subjects with acute liver failure (i.e., liver enzymes > 3 times the upper limit of normal) and chronic liver disease, cardiac failure, renal failure, clinical suspicion of autoimmune hepatitis, positive for hepatitis B and hepatitis C viral markers, macular oedema on fundoscopy, previously on insulin sensitizers and hypolipidemic drugs, pregnant females, prior history of drug reactions with any of the drugs under study, less than 18 years of age and subjects who did not consented for the study were excluded.

Group Allocation

Study subjects were randomly allocated to all the three Groups and administered Metformin (Group I), Rosuvastatin (Group II) and Pioglitazone (Group III) with lifestyle modification and dietary intervention being common to all. All the three Groups were advised dietary intervention and lifestyle modification by a trained dietician as per American Association of the Study of Liver Disease guidelines. All the cases were advised low calorie, low fat along with high fibre diet.

Diagnosis of Fatty Liver

Sonography was used for the diagnosis of fatty liver. A score has been devised by Gore R. M., for grading hepatic steatosis on the basis of sonographic findings [15]. This included four sonographic findings of diffuse fatty change in the liver, two for high score viz. Loss of definition of the diaphragm, liver echogenicity exceeding that of renal cortex, poor delineation of the intrahepatic architecture, attenuation of the ultrasound wave with each finding assigned a score of one. A score of two or more was used as working definition of fatty liver. All USG studies were done at the Department of Radiology using mid-range colour Doppler and ultrasonography, manufactured by TOSHIBA (model XAIRO-660A) with 3.5 MHz and 10 MHz transducer.

Data Collection, Follow-up and Statistical Analysis

All study participants were interviewed and examined in detail during the study period to collect baseline socio-demographic details. The patients were followed at 4 weeks, 12 weeks and 24 weeks and checked for adherence to dietary intervention and lifestyle modification along with assessment of weight, BMI, compliance to drugs and development of any side effects. Also all the Groups were evaluated at 12 weeks and 24 weeks for liver function tests, fasting lipid profile, USG scores for NAFLD. The statistical analysis was done using SPSS (Statistical Package for Social Sciences) Version 15.0 Statistical Analysis Software. A p-value of <0.05 was considered significant for the study. At the end of the study weight, BMI, liver enzymes, and lipid profile at different Follow-up periods was compared using ANOVA test. InterGroup comparison of USG scores at different Follow-up periods was done using Kruskal Wallis test. Also, Wilcoxon Ranked test was then applied to assess the change in USG scores at different Follow-ups during the study.

RESULTS

InterGroup difference in weight and BMI was not found to be statistically significant at any of the Follow-up except of BMI at 12 weeks and 24 weeks which was found to be significantly higher in Group III than Group I and Group II ($p<0.05$). Group II showed an increasing trend of liver enzymes while Group I and Group III showed a decreasing trend of liver enzymes. InterGroup difference in SGOT levels were found to be statistically significant at 1st visit ($p<0.001$) and at 24 weeks ($p=0.012$). Difference in SGPT levels were found to be significant only at the time of first visit ($p<0.001$) and was not found to be statistically significant at 12 weeks and at 24 weeks [Table/Fig-1].

In our study the significant change in baseline characteristics during Follow-up [Table/Fig-2] was observed. InterGroup difference in cholesterol levels was statistically insignificant at first week and 12 weeks ($p=0.065$) while at 24 weeks ($p=0.162$) differences was found to be statistically significant ($p<0.001$). InterGroup difference in triglyceride levels were found to be statistically significant at 1st visit ($p<0.001$) and at 24 weeks ($p<0.001$) while difference was not found to be statistically significant at 12 weeks ($p=0.560$). InterGroup difference in VLDL levels was not statistically significant at 1st visit ($p=0.561$) and at 12 weeks ($p=0.432$) while difference was found to be statistically significant at 24 weeks ($p=0.008$). InterGroup difference in LDL levels were not statistically significant at 1st visit ($p=0.736$) while difference was found to be statistically significant at 12 weeks ($p=0.005$) and 24 weeks ($p<0.001$). InterGroup difference in HDL levels was statistically insignificant at subsequent Follow-up visits.

In Group I, II and III decline in cholesterol values from that at 1st Visit was observed at all-time intervals and these changes were found to be statistically significant. In both the study Groups, decline in VLDL values from that at 1st Visit was observed at all-time intervals and these changes were found to be statistically significant except change in Group II between Visit I and 12 weeks. Maximum decline was found between 1st Visit and 24 weeks and minimum decline between Week 12 and Week 24. In both the above study Groups, an increase in HDL values from that at 1st Visit was observed at all-time intervals and these changes were found to be statistically significant. Maximum increase was found between 1st Visit and 24 weeks in both the Groups, while minimum increase between 1st Visit and 12 Weeks.

[Table/Fig-3,4] shows baseline USG score in all Groups and changes occurred during Follow-up in all three Groups. In Group I, USG scores showed an increase in later half of the study though the increase was not found to be statistically significant. In Group II, USG score declined with time and this change was found to be statistically significant between all the time intervals except for change in USG grade between 1st Visit and 12 weeks. In Group III, USG score declined with time and this change in USG grade was found to be statistically significant as compared to the USG scores at the start of the study.

DISCUSSION

In our study out of 98 subjects, 30% were females and 70% were males. Many recent studies have reported that male gender was a risk factor for fatty liver disease [16]. Maruti et al., conducted a study on 26,527 subjects undergoing medical checkups, and found that the prevalence of NAFLD was 31% in men and 16% in women [17]. Group I (Metformin) and Group II (Rosuvastatin) showed a decline in weight during the course of the study as was attributable to the dietary intervention and life style modification done in all the three Groups. But Group III (Pioglitazone) showed an initial decline in weight followed by a later increase in weight. The increase in weight was significant at 12 weeks and 24 weeks as compared to previous visits. This increase in weight was most probably due to Pioglitazone as it is known to cause weight gain via Peroxisome Proliferator Accelerated Receptor (PPAR) mediated sodium and water retention. BMI also followed trend similar to that of weight in all the three Groups. Studies also showed an increase in abdominal fat content in patients on Pioglitazone. Belfort et al., studied the effect of Pioglitazone (45 mg/day) in a Randomized Controlled Trial (RCT) in subjects with NASH having impaired glucose tolerance or T2DM [18]. Subjects in the study showed a significant weight gain (2.5 ± 0.5 kg) with Pioglitazone, but it also showed significant improvement in aminotransferase levels, steatosis, hepatocellular ballooning, and inflammation. Shadid and Jansen, in 2003 also reported gain in weight with the use of Pioglitazone [19].

We have also studied the effect of the individual drugs on the natural history of hepatic steatosis and for this we used the USG scoring as described before. Initially there was no statistically significant difference among the three Groups for baseline USG score. When followed up at 12 weeks and 24 weeks, Group II and Group III showed a declining trend in the mean USG scores for NAFLD at 12 weeks as well as 24 weeks. The favourable results in Group II and Group III suggest that apart from dietary modification and lifestyle intervention advised to both these Groups of the study, Rosuvastatin and Pioglitazone appears to have beneficial effects in reversing the steatosis in patients of NAFLD. USG

Variables	Group I (Metformin) (n=31)			Group II (Rosuvastatin) (n=34)		
	1st Visit	12 Weeks	24 Weeks	1st Visit	12 Weeks	24 Weeks
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Weight	75.85±6.72	73.18±6.06	71.10±5.60	75.50±7.79	73.03±7.14	71.25±6.96
Body Mass Index (BMI)	27.96±2.13	26.97±1.94	26.21±1.80	27.68±1.96	26.79±1.89	26.14±1.89
SGOT	55.19 ± 17.86	46.45±15.47	41.13±8.18	44.59±17.78	50.41±24.44	52.94±27.34
SGPT	66.10 ± 24.42	57.29±18.08	50.55±7.82	51.88±17.45	55.06±23.33	59.94±30.64
Cholesterol	193.98±34.66	180.35±26.43	173.06±19.59	205.08±29.29	168.84±17.69	146.80±18.98
Triglyceride (TG)	235.70±43.16	200.58±30.08	178.74±18.78	260.69±21.43	195.66±15.50	138.06±14.22
Very Low Density Lipoprotien (VLDL)	41.85 ± 4.39	40.16±3.82	38.91±3.84	43.42±9.54	38.99±6.71	35.41±4.88
Low Density Lipoprotein (LDL)	118.14±47.57	100.55±36.42	90.74± 29.26	113.19±38.25	82.14±20.60	59.44±12.49
High Density Lipoprotein (HDL)	37.45 ± 4.94	39.19±3.90	41.35± 3.19	37.86±5.05	39.06±4.57	40.35±4.55

Variables	Group III (Pioglitazone) (n=33)			Statistical Significance (ANOVA)		
	1st Visit	12 Weeks	24 Weeks	1st Visit	12 Weeks	24 Weeks
	Mean ± SD	Mean ± SD	Mean ± SD	'p'	'p'	'p'
Weight	74.30±6.99	73.92±7.21	74.33±7.15	0.662	0.850	0.089
Body Mass Index (BMI)	28.21±2.64	28.06±2.70	28.22±2.67	0.628	0.044	**<0.001**
SGOT	65.97±22.41	53.60±18.57	42.24±8.90	**<0.001**	0.363	0.012
SGPT	75.43±26.68	61.12±19.24	50.76±9.99	**<0.001**	0.474	0.085
Cholesterol	191.90±26.08	179.42±21.41	169.09±17.43	0.162	0.065	**<0.001**
Triglyceride (TG)	228.45±28.12	201.27±22.31	182.27±27.25	**<0.001**	0.560	**<0.001**
Very Low Density Lipoprotien (VLDL)	41.61±7.22	40.71±5.57	38.12±5.15	0.561	0.432	0.008
Low Density Lipoprotein (LDL)	120.80±34.61	105.29±30.87	90.35±24.48	0.736	0.005	**<0.001**
High Density Lipoprotein (HDL)	37.68±5.40	39.70±3.80	41.90±3.18	0.950	0.800	0.228

[Table/Fig-1]: Intergroup comparison of various parameters in study population at different Follow-up periods.
SGPT= Serum glutamic-pyruvic transaminase, SGOT = Serum glutamic-oxaloacetic transaminase.

Parameters	Group I (Metformin) (n=31)				Group II (Rosuvastatin) (n=34)	
	1st Visit – 12 weeks		1st Visit – 24 weeks		1st Visit – 12 weeks	
	Mean± SD	'p'	Mean± SD	'p'	Mean± SD	'p'
Weight	-2.677± 0.890	**<0.001**	-4.758± 1.466	**<0.001**	-2.471± 0.984	**<0.001**
Body Mass Index (BMI)	-0.983± 0.307	**<0.001**	-1.747± 0.504	**<0.001**	-0.892± 0.325	**<0.001**
SGOT	-8.742± 9.423	**<0.001**	-14.065± 16.525	**<0.001**	5.824± 16.749	**0.051**
SGPT	-8.806± 11.566	**<0.001**	-15.548± 23.948	**0.001**	3.176± 15.000	**0.226**
Cholesterol	-13.632± 9.658	**<0.001**	-20.916± 17.709	**<0.001**	-36.247± 25.519	**<0.001**
Triglyceride (TG)	-35.116±16.315	**<0.001**	-56.955± 27.488	**<0.001**	-65.029±12.997	**<0.001**
Very Low Density Lipoprotien (VLDL)	-1.690± 1.525	**<0.001**	-2.945± 2.840	**<0.001**	-4.432± 3.387	**<0.001**
Low Density Lipoprotein (LDL)	-17.587±13.607	**<0.001**	-27.394± 22.287	**<0.001**	-31.053± 20.125	**<0.001**
High Density Lipoprotein (HDL)	1.742± 2.768	**0.001**	3.903± 4.407	**<0.001**	1.197± 1.762	**<0.001**

Parameters	Group II (Rosuvastatin) (n=34)		Group III (Pioglitazone) (n=33)			
	1st Visit – 24 weeks		1st Visit – 12 weeks		1st Visit – 24 weeks	
	Mean± SD	'p'	Mean± SD	'p'	Mean± SD	'p'
Weight	-4.250± 1.195	**<0.001**	-0.682± 0.975	**<0.001**	0.030± 1.096	**0.875**
Body Mass Index (BMI)	-1.539± 0.366	**<0.001**	-0.260± 0.368	**<0.001**	0.008± 0.414	**0.907**
SGOT	8.353± 25.681	**0.067**	-12.370±12.243	**<0.001**	-23.725±19.620	**<0.001**
SGPT	8.059± 24.565	**0.064**	-14.307±15.272	**<0.001**	-24.671±23.045	**<0.001**
Cholesterol	-58.285±35.393	**<0.001**	-12.480± 8.411	**<0.001**	-22.803±15.726	**<0.001**
Triglyceride (TG)	-122.629±23.417	**<0.001**	-27.182± 9.129	**<0.001**	-46.182±20.878	**<0.001**
Very Low Density Lipoprotien (VLDL)	-8.009± 6.149	**<0.001**	-0.903± 5.642	**0.365**	-3.497±6.309	**0.003**
Low Density Lipoprotein (LDL)	-53.756±37.486	**<0.001**	-15.506±10.891	**<0.001**	-30.455±18.115	**<0.001**
High Density Lipoprotein (HDL)	2.488± 3.038	**<0.001**	2.012± 2.214	**<0.001**	4.212± 3.965	**<0.001**

[Table/Fig-2]: InterGroup comparison of change in various parameters in study population at different Follow-up
SGPT= Serum glutamic-pyruvic transaminase, SGOT = Serum glutamic-oxaloacetic transaminase

Variables	Group I (Metformin) (n=31)	Group II (Rosuvastatin) (n=34)	Group III (Pioglitazone) (n=33)	Statistical Significance	
	Mean ± SD	Mean± SD	Mean± SD	χ^2	'p'
USG Score					
1st visit	2.35 ± 0.49	2.59 ±0.50	2.45±0.51	3.554	0.169
At 12 weeks	2.35 ± 0.49	2.00 ± 0.08	2.27±0.45	13.870	0.001
At 24 weeks	2.42 ± 0.81	1.32 ± 0.47	1.76±0.71	28.352	<0.001

[Table/Fig-3]: Intergroup comparison of USG score in study population at different Follow-up periods (Non-Parametric test :Kruskal Wallis Test).
USG = Ultrasonography

Variables	Group I (Metformin) (n=31)		Group II (Rosuvastatin) (n=34)		Group III (Pioglitazone) (n=33)	
	Mean ± SD	'p'	Mean±SD	'p'	Mean±SD	'p'
USG Score						
1st Visit–12 weeks	0 ± 0	–	-0.588 ± 0.500	**<0.001**	-0.182 ± 0.392	**0.014**
12 weeks–24 weeks	0.065± 0.680	0.593	-0.676 ± 0.475	**<0.001**	-0.515 ± 0.619	**<0.001**
1st Visit–24 weeks	0.065 ± 0.680	0.593	-1.265 ± 0.864	**<0.001**	-0.697 ± 0.847	**<0.001**

[Table/Fig-4]: Intergroup comparison of change in USG score in study population at different Follow-up periods (Wilkoxon Ranked Test).
USG = Ultrasonography

scores for NAFLD showed an early stationary trend followed by an insignificant increase in USG scores during the later course of the study. This increase could be due to eight subjects in Group I developing a rapid loss of weight during the initial 12 weeks of the study period which in turn could have precipitated hepatic steatosis in these subjects. This was also corroborated by the increase in the USG scores in the same subjects during the latter part of the study.

Baseline liver enzymes were comparable when the study started. Group I and Group III showed decline in SGOT levels and SGPT levels whereas, in Group II the liver enzymes showed progressive increase from 1st visit towards the end of the study. Though, there was an increase in liver enzymes in Group I, none of the subjects had shown a rise of more than three times of the upper limit of normal which would have been suggestive of inflammatory liver injury. Previous studies have shown that statins cause hepatocellular inflammation and were associated with derangement of liver enzymes [20]. Therefore, it is advisable to monitor for liver enzymes while treating patients of NAFLD with statins and to avoid them in patients with liver enzymes of more than three times of the baseline. The improvement in lipid profile was significant in all the three Groups at both the Follow-up visits (at 12 weeks and 24 weeks). This was much better in Group II as compared to Group I and Group III. As compared to Group I and Group III the decline in serum cholesterol was greater in Group II. Triglycerides also showed a declining trend towards the end of the study period in all the three Groups. Serum VLDL showed a significant decline in all the three Groups during the course of the study. All the three Groups also showed an increase in serum HDL levels. This robust improvement across the fractions lipid profile parameters in all three Groups could be attributed to the well validated effects of change in dietary habits and lifestyle modifications. Our findings were supported by a previous study which reported that there was improved metabolic response in the form of decrease in serum triglyceride levels after 16 weeks of calorie-restricted low-glycaemic index diet and Metformin in subjects with impaired glucose tolerance [21]. A similar response was reported with Pioglitazone with respect to serum triglyceride levels [16]. It is previously reported that Rosuvastatin administration was associated with improvements in lipid profiles especially decrease in serum cholesterol levels [17]. The decline in serum VLDL as observed in our study is further supported by a previous study using Metformin and Pioglitazone [22,23].

The role of Rosuvastatin on serum HDL levels is still inconclusive as various studies have shown conflicting results. One of the study reported that Rosuvastatin administration was associated with improvement in serum HDL levels [24], while in other study Deguchi et al., 2014 observed a significant decline in serum HDL levels in dyslipidemic subjects with cerebral infarction when treated with rosuvastatin [25].

CONCLUSION

Thus it appears that Rosuvastatin and Pioglitazone could have better effects in reversing the changes of NAFLD as compared to Metformin when used as add on therapy over dietary intervention and lifestyle modification. As Pioglitazone being already incorporated in the treatment guidelines by AASLD, Rosuvastatin as well may be useful as a pharmacotherapy for treating patients with NAFLD. Rosuvastatin use for prolonged periods may lead to increase in liver enzymes but acute decompensation is unlikely. Pioglitazone when used for prolonged periods may lead to weight gain and increase in BMI. Rapid weight loss in short period of time may lead to worsening of hepatic steatosis. Dietary and life style intervention has favourable effect on hepatic steatosis as observed by USG scores. A further aspect of clinical research from the above study is that the improvement in USG scores for NAFLD by Rosuvastatin used in the study is a molecule effect of Rosuvastatin per se or is the effect of class of drug.

ACKNOWLEDGEMENT

Authors are thankful to the study participants for giving consent to perform this study. Authors acknowledge the technical and supporting staff of Medicine Department.

REFERENCES

[1] Weiss R. Fat distribution and storage: how much, where, and how? *Eur J Endocrinol* 2007;157 Suppl 1:S39-45.
[2] Chalasani N, Younossi Z, Lavine JE, Diehl AM, Brunt ME, Cusi K, et al. The diagnosis and management of non-alcoholic fatty liver disease: practice guideline by the american association for the study of liver diseases, american college of gastroenterology, and the american gastroenterological association. *Hepatology*. 2012;55(6):2008.
[3] Sanyal AJ, Banas C, Sargeant C, Luketic VA, Sterling RK, Stravitz RT, et al. Similarities and differences in outcomes of cirrhosis due to non-alcoholic steatohepatitis and hepatitis C. *Hepatology*. 2006;42:132-38.
[4] Zeng T, Zhang CL, Zhao XL, Xie KQ. Pentoxifylline for the treatment of non-alcoholic fatty liver disease:a meta-analysis ofrandomized double-blind, placebo-controlled studies. *Eur J Gastroenterol Hepatol*. 2014;26(6):646-53.
[5] Harrison SA, Fecht W, Brunt EM, Neuschwander-Tetri BA. Orlistat for overweight subjects with nonalcoholic steatohepatitis: A randomized, prospective trial. *Hepatology* 2009;49:80–86.
[6] Lavine JE. Vitamin E treatment of nonalcoholic steatohepatitis in children: a pilot study. *J Pediatr*. 2000;136:734–38.
[7] Nobili V, Manco M, Devito R, Di Ciommo V, Comparcola D, Sartorelli MR, et al. Lifestyle intervention and antioxidant therapy in children with nonalcoholic fatty liver disease: a randomized, controlled trial. *Hepatology*. 2008;48:119–28.
[8] Vajro P, Franzese A, Valerio G, Iannucci MP, Aragione N. Lack of efficacy of ursodeoxycholic acid for the treatment of liver abnormalities in obese children. *J Pediatr*. 2000;136:739–43.
[9] Dufour JF, Oneta CM, Gonvers JJ, Bihl F, Cerny A, Cereda JM, et al. Randomized placebo-controlled trial of ursodeoxycholic acid with vitamin E in nonalcoholic steatohepatitis. *Clin Gastroenterol Hepatol*. 2006;4:1537–43.
[10] Van Rooyen DM, Gan LT, Yeh MM, Haigh WG, Larter CZ, Ioannou G, et al. Pharmacological cholesterol lowering reverses fibrotic NASH in obese, diabetic mice with metabolic syndrome. *J Hepatol*. 2013;59:144–52.
[11] Mazza A, Fruci B, Garinis GA, Giuliano S, Malaguarnera R, Belfiore A. The role of metformin in the management of NAFLD. *Exp. Diabetes Res*. 2012;2012:716404.
[12] Loomba R, Lutchman G, Kleiner DE, Ricks M, Feld JJ, Borg BB, et al. Clinical trial: Pilot study of metformin for the treatment of non-alcoholic steatohepatitis. *Aliment Pharmacol Ther*. 2009;29:172–82.
[13] Kintscher U, Law RE. PPAR gamma-mediated insulin sensitization: The importance of fat versus muscle. *Am J Physiol Endocrinol Metab*. 2005;288:287–91.
[14] Bourron O, Daval M, Hainault I, Hajduch E, Servant JM, Gautier, JF, et al. Biguanides and thiazolidinediones inhibit stimulated lipolysis in human adipocytes through activation of AMP-activated protein kinase. *Diabetologia*. 2010;53:768–78.
[15] Gore RM. Diffuse liver disease. In:Gore RM, Levine MS, Laufer I, eds. Textbook of gastrointestinal radiology. Philadelphia: Saunders, 1994:1968–2017

[16] Betteridge DJ. Effects of pioglitazone on lipid and lipoprotein metabolism. *Diabetes Obes Metab*. 2007;9(5):640-47.
[17] Maruti S, Baig MS, Gade PR, Khandelwal PN. A comparative evaluation of safety and efficacy of rosuvastatin, simvastatin, and atorvastatin in patients of type 2 diabetes mellitus with dyslipidemia. *Int J Diabetes Dev Ctries*. 2009;29(2):74–79.
[18] Belfort R, Harrison SA, Brown K, Darland C, Finch J, Hardies J, et al. A placebo-controlled trial of pioglitazone in subjects with non-alcoholic steatohepatitis. *N Engl J Med*. 2006;355:2297-307.
[19] Shadid S, Jensen MD. Effect of pioglitazone on biochemical indices of non-alcoholic fatty liver disease in upper body obesity. *Clinical Gastroenterology and Hepatology*. 2003;1(5):384–87.
[20] Gillett RC, Norrell A. Considerations for safe use of statins: liver enzyme abnormalities and muscle toxicitiy. *Am Fam Physician*. 2011;83:711–16.
[21] Costa THM, Silva FB, Reis CEG, Casulari LA. Improved metabolic response after 16 weeks of calorie-restricted low-glycaemic index diet and metformin in impaired glucose tolerance subjects. *Nutr Hosp*. 2014;29(5):1081-87.
[22] Schneider J, Erren T, Zöfel P, Kaffarnik H. Metformin-induced changes in serum lipids, lipoproteins, and apoproteins in non-insulin-dependent diabetes mellitus. *Atherosclerosis*. 1990;82(1-2):97-103.
[23] Nagashima K, Nagashima K, Lopez C, Donovan D, Ngai C, Fontanez N, et al. Effects off PPAR agonist pioglitazone on lipoprotein metabolism in patients of type 2 diabetes mellitus. *J Clin Invest*. 2005;115:1323-32.
[24] Robert S. Rosenson, James D. Otvos, and Judith Hsia. Effects of rosuvastatin and atorvastatin on LDL and HDL particle concentrations in patients with metabolic syndrome. *Diabetes Care*. 2009;32(6):1087–91.
[25] Deguchi I, Horiuchi Y, Hayashi T, Sehara Y, Kato Y, Ohe Y, et al. Effects of rosuvastatin on serum lipids and arteriosclerosis in dyslipidemic patients with cerebral infarction. *J Stroke Cerebrovasc Dis*. 2014;23(8):2007-11.

PARTICULARS OF CONTRIBUTORS:
1. Junior Resident, Department of Medicine, King George's Medical University, Lucknow, Uttar Pradesh, India.
2. Senior Resident, Department of Pharmacology, King George's Medical University, Lucknow, Uttar Pradesh, India.
3. Associate Professor, Department of Medicine, King George's Medical University, Lucknow, Uttar Pradesh, India.
4. Junior Resident, Department of Medicine, King George's Medical University, Lucknow, Uttar Pradesh, India.
5. Junior Resident, Department of Medicine, King George's Medical University, Lucknow, Uttar Pradesh, India.
6. Professor, Department of Medicine, King George's Medical University, Lucknow, Uttar Pradesh, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Prof. Kauser Usman,
Department of Medicine, King George's Medical University, Lucknow-226003, Uttar Pradesh, India.
E-mail: profkauserusman@gmail.com

FINANCIAL OR OTHER COMPETING INTERESTS: None.

Date of Submission: **Mar 01, 2016**
Date of Peer Review: **Apr 16, 2016**
Date of Acceptance: **Apr 27, 2016**
Date of Publishing: **Aug 01, 2016**