ORIGINAL RESEARCH

Comparative study of efficacy and safety of Metformin v/s Saroglitazar in non alcoholic fatty liver disease patients with newly diagnosed type 2 Diabetics and prediabetics

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ABSTRACT:
Introduction: The association between Non-alcoholic fatty liver disease (NAFLD) and type 2 diabetes mellitus (T2DM) has been well established, Newer class of drugs like saroglitazar could be a potential therapeutic option for treating NAFLD and NASH associated with metabolic syndrome. **Aim**: To compare metformin vs saroglitazar on glycemic control and lipid parameters alongwith evaluation of its efficacy and safety levels in the newly diagnosedT2DM and prediabetic patients with NAFLD. **Material and Methods:** The study comprised of 100 patients of either sex in the age group of 30 to 70 years with NAFLD with newly diagnosed T2DM and prediabetes. They were divided randomly into two groups A and B comprising of 50 patients each. Group A comprised of the patients who received metformin (0.5-3gm) OD/divided dose a day orally for 24 weeks. Group B comprised of patients who received saroglitazar (4 mg) once a day orally for 24 weeks. Basic parameters consisting of lipid profile including total serum cholesterol, serum triglyceride, HDL, LDL and VLDL; HbA_{1c} FBS; B.Urea, S.Creatinine; SGOT,SGPT,USG for fatty liver grading levels were repeated at 12 weeks and 24 weeks from baseline. The assays were carried out using A25 biosystem analyser. **Results**: There was a significant decrease in HbA1c level and FBS in both the groups. But it was marginally more in the group B as compared to group A. Both drugs saroglitazar and metformin show significant reduction in serum triglycerides, serum cholesterol, LDL and VLDL at 12 and 24 weeks treatment. The reduction in serum triglycerides, serum cholesterol and VLDL was more with saroglitazar as compared to metformin except LDL reduction, which was marginally more with metformin but it was found to be statistically non-significant. No significant side-effects were observed in the study population. **Conclusion**: From the study, it was concluded that saroglitazar was more efficacious drug than metformin in patients of NAFLD with newly diagnosed T2DM and pre-diabetes in terms of improvement in fatty liver grading on the basis of USG. Both the drugs were efficacious in term of improving glycemic and lipid parameters.
Key words: Non-alcoholic fatty liver disease, type 2 diabetes mellitus, lipid profile, saroglitazar, metformin

INTRODUCTION:

Non-alcoholic fatty liver disease (NAFLD) is a common health problem that affects 1/3rd of the adult population and an increasing number of children in developed countries.[1] It includes a wide spectrum of histologic abnormalities ranging from hepatic steatosis to non-alcoholic steatohepatitis (NASH), that may progress to cirrhosis, subsequent end-stage liver disease and hepatocellular carcinoma (HCC) in the absence of excessive alcohol intake.[2,3,4]
It is characterized by fat accumulation in the liver in patients with no statistically significant alcohol consumption, and is particularly associated with metabolic syndrome comprising of hypertension,

insulin resistance, obesity and dyslipidemia. NAFLD has been shown to be strongly and independently associated with an increased risk of type 2 diabetes mellitus (T2DM) and cardiovascular disease.[5,6]

NAFLD and T2DM are common conditions that regularly co-exist and can act synergistically to drive adverse outcomes.[7] The presence of both increases the likelihood of the development of complications of diabetes (including both macro and micro vascular complications) as well as augmenting the risk of more severe NAFLD, including cirrhosis, HCC and death.

The association between NAFLD and T2DM has been well established, which could be explained by the insulin-resistance (IR) and compensatory hyperinsulinemia progressing to defective lipid metabolism and hepatic triglyceride (TG) accumulation in NAFLD or to β-cell dysfunction in T2DM.[8] Compared with non-diabetic subjects, patients with T2DM appear to have an increased risk of developing NAFLD and certainly have a heightened risk of developing advanced liver diseases, such as hepatic fibrosis, cirrhosis and HCC.[9,10]

Studies suggest diet, exercise, and hypoglycemic drugs may alter the course of the disease. Insulin sensitizers like metformin and thiazolidinediones are commonly used for IR in those with NAFLD.[11] Newer class of drugs i.e. peroxisome proliferator-activated receptor (PPAR) agonists like saroglitazar could be a potential therapeutic option for the treating NAFLD and NASH associated with metabolic syndrome.[12]

Thus this present study was undertaken to compare metformin vs saroglitazar on glycemic control and lipid parameters alongwith evaluation of its efficacy and safety levels in the newly diagnosedT2DM and prediabetic patients with NAFLD.

MATERIAL AND METHODS:

This randomized, prospective study of 24 weeks duration was conducted in the department of Medicine, Government Medical College, Amritsar. The approval of institutional thesis and ethical committee was taken before the start of the study. The study comprised of 100 patients of either sex in the age group of 30 to 70 years with NAFLD with newly diagnosed T2DM and prediabetes attending the OPD/ward of department of Medicine, Guru Nanak Dev Hospital, Amritsar. They were divided randomly into two groups A and B comprising of 50 patients each. Group comprised of the patients who received metformin (0.5-3gm) OD/divided dose a day orally for 24 weeks. Group B comprised of patients who received saroglitazar (4 mg) once a day orally for 24 weeks.

Patients with NAFLD along with newly diagnosed T2DM or prediabetic patients between age 30 and 70 years were included in this study. Those patients who were on any hypolipidemic medication, were alcoholic and smokers, critically ill ,with Chronic kidney diseases, on oral contraceptives and other lipid modifying drugs and with Cardiovascular, respiratory, and renal disease were excluded from the study.

The patients who met the inclusion criteria were recruited in study after taking written informed consent. Detailed history was taken regarding presenting complaints, dietary habits, alcohol consumption, smoking or any drug abuse or any other addiction and were noted in the proforma. Generally physical examination was done in detail and all the systems were thoroughly examined. Patients underwent biochemical tests like CBC, Fasting Blood Sugar, HbA_{1c}, Blood urea, Serum creatinine, SGOT, SGPT, Urine complete examination, Ultrasonography whole abdomen and Serum triglyceride, serum HDL, serum cholesterol, LDL and VLDL at 0, 12 and 24 weeks.

At 24 weeks of study, results were compared among both groups. Basic parameters consisting of lipid profile including total serum cholesterol, serum triglyceride, HDL, LDL and VLDL; HbA_{1c} levels , FBS; USG for fatty liver grading were repeated at 12 weeks and 24 weeks from baseline. The assays were carried out using A25 biosystem analyser.

STATISTICAL ANALYSIS:

The data thus derived was analyzed statistically using appropriate methods. Mean change in the parameters was seen in both the groups. For intra-group comparison ANOVA and for inter-group comparison Student t-test and x^2 were applied to the results. The difference between the groups was considered to be statistically significant if the p value was found to be < 0.05.

RESULTS:

The present study included a total sample of 100 patients which were divided equally into two groups. Group comprised of the patients who received metformin (0.5-3gm) OD/divided dose a day orally for 24 weeks. Group B comprised of patients who received saroglitazar (4 mg) once a day orally for 24 weeks.

The mean age of patients was 47.70yrs in Group A and 46.50 yrs in Group B which was found to be statistically non -significant between the groups (p > 0.05). Gender distribution showed males with 48% population while female formed 52% of study population.

Mean and standard deviation of FBS and HbA_{1C} in group A and group B at 0, 12 and 24 weeks were recorded and mean change was also observed for both the groups as tabulated in table 1. We observed that although mean change at 24 weeks was more in group B than group A, the change was found to be statistically non significant between the groups (p-value >0.05).

TABLE 1: SHOWING MEAN CHANGE OF FBS AND HbA$_{1C}$ IN BOTH GROUPS

Week interval	Mean change of FBS (mg/dl)		Mean change of HbA$_{1C(\%)}$		p-value of HbA$_{1C}$			p-value of FBS		
	Group A	Group B	Group A	Group B	Group A	Group B	Group A/B	Group A	Group B	Group A/B
0-12	59.10	69.60	0.95	0.98			0.892			0.211
12-24	14.86	18.32	0.26	0.3	0.001	0.001	0.776	0.001	0.001	0.797
0-24	73.96	87.92	1.21	1.28			0.626			0.115

Table 2: AGE DISTRIBUTION OF USG GRADING OF FATTY LIVER IN BOTH GROUPS

Age group in years	Group A			Group B		
	Grade I	Grade II	Grade III	Grade I	Grade II	Grade III
30-40	4	5	4	7	5	8
41-50	4	10	7	6	4	7
51-60	4	5	1	3	2	3
61-70	3	3	0	1	4	0
Total	15	23	12	17	15	18

Table 2 shows the age distribution of USG grading of fatty liver in both groups. Number of patients showing fatty liver Grade I, II and III changes in 30-40 years age group were 4, 5 and 4 in Group A & 7,5 and 8 in Group B respectively. Number of patients showing fatty liver Grade I, II and III changes in 41-50 years age group were 4,10 and 7 in Group A & 6,4 and 7 in Group B respectively. Number of patients showing fatty liver Grade I, II and III changes in 51-60 years age group were 4,5 and 1 in Group A &3,2 and 3 in Group B respectively. Number of patients showing fatty liver Grade I, II and IIIchanges in 61-70 years age group were 3, 3 and 0 in Group A &1, 4 and 0 in Group B respectively.

Table 3: IMPROVEMENT IN USG GRADING LEVEL OF FATTY LIVER IN BOTH GROUPS

Ultrasound grading of fatty liver	Group A		Group B		p-value (0-24 weeks)		
	Improved	Not improved	Improved	Not improved	Group A	Group B	Group A/B
III	0	13	3	15			
II	1	20	6	9	0.494	0.013	0.008
I	0	16	0	17			
Total	1	49	9	41			

FIGURE 1: IMPROVEMENT IN USG GRADING LEVEL OF FATTY LIVER AT 0- 24 WEEKS IN GROUP A
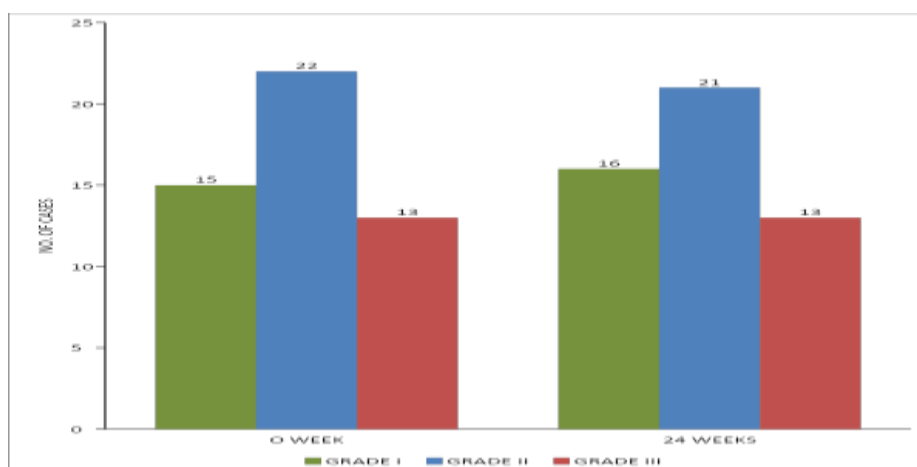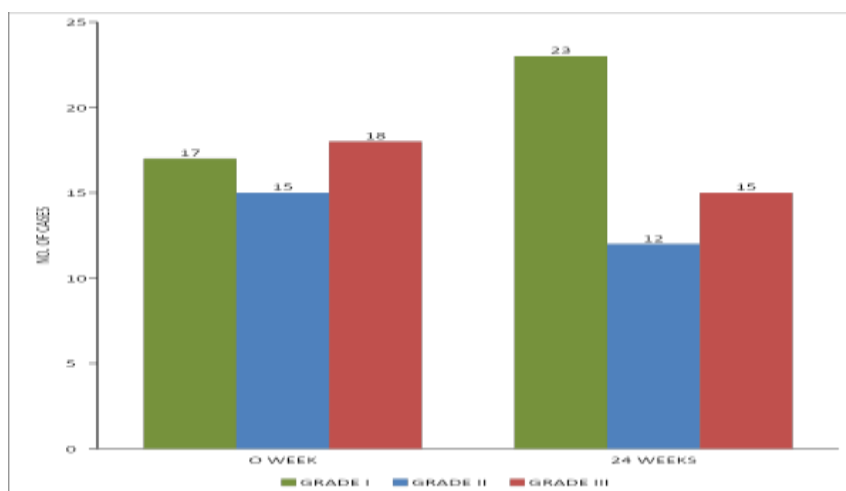
FIGURE 2: IMPROVEMENT IN USG GRADING LEVEL OF FATTY LIVER AT 0-24 WEEKS IN GROUP B

LIPID PROFILE:

The mean triglyceride level at the start of study was 221.62 mg/dl and 222.08 mg/dl in the study groups A and B respectively. There was significant decrease in serum triglycerides – baseline 221.62 ± 59.59 mg/dl, at 12weeks 178.74 ± 44.81mg/dl and at 24weeks 160.34 ± 37.43 mg/dl in group A and baseline 222.08 ± 48.90 mg/dl, at 12 weeks 175.96 ± 29.78 mg/dl and at 24 weeks 154.30 ± 3.91mg/dl in group B respectively.

The mean cholesterol at the start of study was 245.10 mg/dl in group A and 240.38 mg/dl in group B respectively. There was significant decrease in serum cholesterol – baseline 245.10 ± 88.42mg/dl, at 12 weeks 198.52 ± 66.25mg/dl and at 24 weeks 173.26 ± 53.25mg/dl in group A and baseline 240.38 ± 71.45 mg/dl, at 12 weeks 188.08 ± 53.16mg/dl and at 24 weeks 160.84 ± 33.68 mg/dl in group B respectively.

Similarly, There was significant decrease in serum LDL – baseline 124.36 ± 44.23 mg/dl, at 12 weeks 102.54 ± 30.51mg/dl and at 24 weeks 93.34 ± 24.17 mg/dl in group A and baseline 113.56 ± 37.9 mg/dl, at 12 weeks 97.20 ± 28.56 mg/dl and at 24 weeks 88.64 ± 22.45 mg/dl in group B respectively. Although mean change at 24 weeks was more in group A than group B, the change was found to be statistically non-significant between the groups (p-value >0.05).

There was significant decrease in VLDL – baseline 43.44 ± 12.28mg/dl, at 12 weeks 35.46 ± 9.11mg/dl and at 24 weeks 31.50 ± 7.58 mg/dl in group A and baseline 45.48 ± 13.23 mg/dl, at 12 weeks 35.72 ± 9.62mg/dl and at 24 weeks 30.58 ± 5.11mg/dl in group B respectively.

The mean HDL at start of study was 43.58mg/dl in group A and 44.98 mg/dl in group B respectively. There was non-significant increase in HDL – baseline 43.58 ± 7.90 mg/dl, at 12 weeks 44.12 ± 7.34mg/dl and at 24 weeks 44.42 ± 7.38 mg/dl in group A and baseline 44.40 ± 8.27 mg/dl, at 12 weeks 44.98

± 7.68mg/dl and at 24 weeks 45.80 ± 7.87 mg/dl in group B respectively.

Hence, overall when we compared the mean change of S. triglyceride, total serum cholesterol, HDL and VLDL between both the groups, it was observed that although at 24 weeks decrease in values were more in group B than group A and this change was found to be statistically non- significant between the groups (p-value >0.05). Whereas, mean change of only LDL was observed to be more in group A than group B, and this change was also statistically non- significant (p-value >0.05).

Further, we also observed that the mean, standard deviation and mean change of Blood urea, SGOT,SGPT at 24 weeks was more in group A than group B but this change was also statistically non-significant between the groups (p-value >0.05).

Lastly the mean, standard deviation and mean change of S. creatinine at 24 weeks was equal in both group A and group B, which was also found to be statistically non- significant between the groups (p-value >0.05).

DISCUSSION:

This study was aimed to assess the efficacy and safety of metformin v/s saroglitazar in patients of NAFLD with newly diagnosed T2DM and prediabetes. The present study was carried out in 100 newly diagnosed cases of T2DM and prediabetics with NAFLD, presenting to Guru Nanak Dev Hospital attached to Government Medical College, Amritsar for the study.

The study was done on 100 patients of either sex in the age group of 30 to 70 years who were attended the OPD/ward of department of Medicine, Guru Nanak Dev Hospital, Amritsar. They were divided randomly into two groups A and B comprising of 50 patients each. In group A, the patients received metformin (0.5-3gm) OD/divided dose a day orally for 24 weeks. In group B, patients received saroglitazar (4 mg) once

a day orally for 24 weeks. At 12 weeks and 24 weeks of study, results were compared among both groups

The mean age of patients was 47.70yrs in Group A and 46.50yrs in Group B with female female predominance. The average age of onset of T2DM is 51.35±6.37yrs in India according to study by Ramachandran [13] whereas age group is higher (>65yrs) in the developed countries according to study by Wild et al.[14]

We observed a significant decrease in HbA$_{1c}$ baseline and FBS – baseline at 12 weeks and at 24 weeks in both groups. In accordance to ours, Hirst et al[15] reported that Metformin monotherapy lowered HbA$_{1C}$ by 1.12% (95% CI 0.92-1.32; I(2) = 80%) versus placebo. Haukeland et al[16] also observed beneficial effects of metformin in glucose (p=0.032) and HbA$_{1c}$ (p=0.020) in forty-eight patients with biopsy-proven NAFLD for 6 months.

Similarly, Shetty et al[17] and Chatterjee et al[18] also reported that saroglitazar significantly reduced HbA$_{1c}$ at 24 weeks in their studies. As there was a significant decrease in HbA$_{1c}$ and FBS in both groups suggesting a good anti-diabetic role of saroglitazar and metformin. Although reduction in HbA$_{1c}$ and FBS was more in saroglitazar as compared to metformin,the change was found to be statistically non-significant between the groups.

At 24 weeks change in the ultrasound grading of fatty liver was seen in 1 patient out of 50 in group A and 9 patients out of 50 in group B. Improvement in ultrasound grading is more in saroglitazar group as compared to metformin, which was found to be statistically significant. In accordance to our results Joshi et al[19] also found that Saroglitazar significantly improved fatty liver. Saroglitazar can thus be a potential therapeutic option for the treatment of NAFLD and NASH associated with metabolic syndrome.

Oliveira et al[20] reported no improvement was noted in lobular inflammation or hepatocellular ballooning. The NASH activity score was significantly improved after treatment. In similarity Haukeland et al[16] also reported similar results.

The mean triglyceride level at the start of study was 221.62 mg/dl and 222.08 mg/dl in the study groups A and B respectively, suggesting high prevalence of hypertriglyceridemia in newly diagnosed diabetic population in the study. There was significant decrease in serum triglycerides at 12weeks and at 24 weeks in both groups.

Further in our study overall we observed that the mean, standard deviation and mean change of S. triglycerides, HDL, VLDL and total serum cholesterol in group A and group B at 24 weeks was more in group B than group A, the change was found to be statistically non- significant between the groups. Whereas, for LDL it was more in group A than group B, the change was found to be statistically non-significant between the groups.

Blood urea, SGOT, SGPT at 24 weeks was more in group A than group B, the change was found to be statistically non-significant between the groups. Lastly the mean, standard deviation and mean change of S. creatinine at 24 weeks equal in group A and group B, which was also found to be statistically non-significant between the groups.

In Haukeland et al[16] study, the use of metformin for 6 months beneficial in a reduction in serum levels of cholesterol, LDL-cholesterol, glucose and HbA$_{1c}$, serum cholesterol, LDL-cholesterol, glucose and on HbA$_{1c}$.

In our study, mean change (increase) in HDL was 0.54 mg/dl and 0.84 mg/dl at 12 and 24 weeks which was found to be statistically non-significant in group 1. While the mean change in HDL was found to be 0.82mg/dl and 1.40 mg/dl at 12 and 24 weeks respectively in group 2, which was also found to be statistically non- significant.

In Wulffele et al[21] study, metformin has no intrinsic effect on blood pressure, HDL cholesterol and triglycerides in patients with T2DM (p>0.05). Chatterjee et al[18] conducted a 58 weeks observation study of Saroglitazar in 158 patients with diabetic dyslipidemia and found significant reduction in TG, non-HDL-C and HbA$_1$. Saboo et al[22] observed that Saroglitazar significantly decreased TG and ALT in 31 NAFLD patients with diabetic dyslipidemia. Kaul et al[23] study showed significant decrease in non-HDL-C, sd-LDL-C and HbA$_{1c}$ in the 104 patients with diabetic dyslipidemia at 24 weeks treatment with saroglitazar.

Both drugs saroglitazar and metformin show significant reduction in serum triglycerides, HDL, serum cholesterol, LDL and VLDL at 12 and 24 weeks treatment. The reduction in serum triglycerides, serum cholesterol HDL and VLDL was more with saroglitazar as compared to metformin except LDL reduction, which was marginally more with metformin but it was found to be statistically non-significant.

Loomba et al[24] reported that Metformin leads to improvements in liver histology and ALT levels in 30% of patients with NAFLD and NASH, probably by its effects in causing weight loss. Improvement in the NAFLD activity score happened largely in patients that lost ≥5% of body weight.

No significant side-effects were observed in the study population receiving metformin and saroglitazar as seen by effect on renal parameters and hepatic parameters. In the U.K. Prospective Diabetes Study[25], metformin was the only effective and safe medication that reduced diabetes and related deaths, heart attacks, and stroke.

One study confirmed safety profile of saroglitazar and concluded generally safe and well tolerated drug with no serious adverse events and no persistent change in laboratory parameters.

The limitation of this study was that it was done on a small number of patients for relatively short duration

of time, so further larger studies are needed with a longer duration in order to exactly determine the effectiveness with long term safety of saroglitazar and metformin.

CONCLUSION:

saroglitazar was more efficacious drug than metformin in patients of NAFLD with newly diagnosed T2DM and pre-diabetes in terms of improvement in fatty liver grading on the basis of USG. Both the drugs were efficacious in term of improving glycemic and lipid parameters. Although improvement in glycemic and lipid parameters were marginally more with saroglitazar as compare to metformin except for LDL improvement, which was marginally more with metformin but the changes were found to be statistically non-significant between the groups. There was no significant adverse effect seen with both drugs during 24 weeks of treatment.

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