Original Article

Effect of Pioglitazone on Nonalcoholic Fatty Liver Disease in Morbid Obese Patients; a Randomized Controlled Trial

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Abstract

Background: Nonalcoholic fatty liver disease (NAFLD) is a common obesity-related disease. In this study, we aimed to investigate the effects of pioglitazone on NAFLD in morbid obese patients.

Materials and Methods: This is a randomized controlled trial study that was performed in 2020–2021 on 44 patients who had grade 3 NAFLD. At the beginning of the study, we collected the following data: age, gender, body mass index (BMI), fasting blood glucose (FBS), lipid profile, aspartate aminotransferase, alanine aminotransferase (ALT), and the total size and volume of the liver and the left lobe of the liver. Patients in the control group were given a special diet. For patients in the treatment group, pioglitazone 15 mg tablets were administered twice daily for 4 months.

Results: At the beginning of the study, all patients in both groups had grade 3 of NAFLD. After the treatments, 50% of the pioglitazone group had grade 1 NAFLD, and 50% of other patients had grade 2 that showed significant improvements in patients ($P < 0.001$). We also found significant improvements in the following items in the intervention group: liver size ($P < 0.001$), size of the left liver lobe ($P < 0.001$), FBS ($P = 0.036$), ALT ($P = 0.011$), and BMI ($P < 0.001$). No significant improvements were found in the control group ($P > 0.05$).

Conclusion: The use of pioglitazone for 4 months resulted in improvements in fatty liver stage, liver size, BMI, FBS, and lipid profile. These data show the effectiveness of pioglitazone in NAFLD.

Keywords: Bariatric surgery, fatty liver disease, NAFLD, obesity, pioglitazone, RCT

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Introduction

Nonalcoholic fatty liver disease (NAFLD) is a common obesity-related complication that is related with metabolic syndrome.[1] The disease is characterized by the accumulation of fat in hepatocytes of the liver unrelated to consumption. NAFLD is a hepatic component of the metabolic syndrome diagnosed with obesity, type 2 diabetes, dyslipidemia, and hypertension.[2] With the increasing prevalence of obesity in communities, it is predicted that NAFLD will become the main cause of liver transplantation in patients in the coming years.[3,4]

The overall prevalence of nonalcoholic fatty liver is estimated to be more than 25%, which is up to 75.8% among obese people and even up to 96% among people with obesity who undergo bariatric surgery.[5,6] The exact prevalence of fatty liver disease in patients undergoing obesity surgery is unknown. In a study with liver biopsy, 41 patients were candidates for obesity

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surgery, 20% of whom had NAFLD.[7] However, in another study in 2015, the prevalence of fatty liver among patients undergoing obesity surgery was reported to be 84%, which was severe in 32% of patients with fatty liver.[8,9] Differences in the statistics of different studies can be due to differences in diagnostic methods, which in any case indicates the high prevalence of this disease in people with obesity.

On the other hand, the relationship between fatty liver and obesity is bilateral because it has been seen that the average body mass index of patients diagnosed with fatty liver was 31–34 kg/m^2.[10] Fatty liver disease in particular can progress to more dangerous forms, which is more likely in obese people.[11,12] We should also note that the grades of fatty liver could have massive influence on the type of bariatric surgery chosen by the surgeon. Sleeve gastrectomy is preferred in cases with higher grades of fatty liver disease, while other types of bariatric surgeries could be conducted on cases that respond to the treatments before surgeries.

Treatment of NAFLD is more focused on addressing the underlying cause such as obesity and insulin resistance.[13] Pioglitazone is a hypoglycemic drug used in patients with type 2 diabetes. Pioglitazone reduces insulin resistance in body tissues, and in addition to increasing glucose uptake by peripheral tissues, it also reduces liver glucose output.[14,15]

The results of previous studies have shown that bariatric surgery, pioglitazone, and surgical treatment + drug therapy are all effective in improving NAFLD.[16,17] However, according to our best search results, no study has been performed to evaluate the effect of pioglitazone on morbid obese patients who are scheduled for bariatric surgery. In the present study, we aimed to investigate the effects of preoperative pioglitazone therapies in improving NAFLD among patients that are candidates of bariatric surgeries.

Materials and Methods

This is a randomized clinical trial that was performed in 2020–2021 in hospitals affiliated to the author's Medical University. The current study was conducted on 44 patients that were candidates for bariatric surgery who had grade 3 NAFLD in ultrasound examinations. The study protocol was approved by the Research Committee of author's Medical University, and the Ethics committee has confirmed it (Ethics code: IR.MUI.MED.REC.1398.053, Clinical Trials code: IRCT20210614051574N3).

The inclusion criteria were having grade 3 NAFLD, body mass index (BMI) more than 40 or more than 35 and associated with diabetes or other comorbidities, candidates of bariatric surgery, and signing the written informed consent to participate in this study. The exclusion criteria were daily consumption of more than 40 g and 20 g of alcohol for men and women, respectively, having other liver diseases, liver cancer, taking hepatotoxic drugs such as estrogen, corticosteroids, amiodarone and sodium valproate, having HIV, inflammatory bowel disease, and congestive heart failure. Other exclusion criteria were lack of proper compliance to the study protocols and patient's will to exit the study.

The criterion for grade 3 NAFLD in patients was based on ultrasound. If liver parenchyma echo and renal cortex echo and intrahepatic vessels were observed, grade 0 of fatty liver was considered. Diffuse and mild increase in liver parenchyma echo and clear observation of diaphragm and hepatic arteries was considered as grade 1 of NAFLD. Diffuse and slightly more increase in the liver parenchyma and failure to detect the boundaries and contours of the vessels inside the liver was considered as grade 2 of NAFLD for the patient. Diffuse and severe increase in liver echo and indeterminate boundaries of intrahepatic vessels and uncertainty of the posterior or deep part of the right lobe of the liver was considered grade 3 for the patient.[18]

After obtaining the ethics license from the ethics committee of the medical school, the current research plan was explained to the patients and after obtaining the written consent of all patients, sampling was done. Sampling of the present study was accessible and easy method. Thus, among the patients referred to the laparoscopic surgery clinic of hospitals affiliated to the author's Medical University, patients that had the mentioned criteria were recruited to complete the ceiling of the sample size required for the study.

We should also note that we used the drug tolerance checklist for follow-up of patients. The patients were asked to check daily if they have used the drugs (placebo or pioglitazone), and the checklist was observed during the visits.

Patients in this study were randomly divided into treatment and control groups using Random allocation software the Statistical Package for Social Sciences (SPSS) (version 24, SPSS Inc., Chicago, IL) each containing 25 patients. At the beginning of the study, the demographic data of patients including age, gender, and BMI were collected. We also gathered laboratory data regarding fasting blood glucose (FBS), cholesterol (Chol), triglyceride (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), aspartate aminotransferase (AST), and alanine aminotransferase (ALT) at the beginning of the study. The total size and volume of the liver and the left lobe of the liver were also measured at the beginning by a single radiologist that was unaware of the groups of patients. All patients were advised not to eat at least 8 h before the ultrasound. To perform ultrasound, patients were first placed in a supine position or lateral decubitus. An ultrasound probe was impregnated with a lubricant gel to prevent artifacts, and an ultrasound was performed. All images were taken from a longitudinal view of the liver and kidneys.

After collecting the above information, patients in the control group were given a special diet. To increase the ratio of omega 6–3 fats and reduce oxidative stress and inflammation in the liver, patients were advised to consume vegetable oils such as olive oil. Carbohydrate intake should have been half

the previous intake. The diet should have included plenty of vegetables and fruits. They were advised to take foods every 3 h and not to consume industrial juices. They should have replaced red meat with chicken and fish and limit fast foods as much as possible. The placebo tablets were also given to the control group with similar appearance to pioglitazone tablets but containing starch. For patients in the treatment group, in addition to dietary recommendations similar to the control group, pioglitazone 15 mg tablets (Sami Saz Co.) were administered twice daily for 4 months.

During 4 months, all patients in the treatment group were evaluated for symptoms of heart failure such as heart pain, shortness of breath, chronic fatigue, and edema. If the above symptoms occurred, they were excluded from the study and referred to a cardiologist for further evaluations.

At the end of the 2month of drug administration, the measured variables before the start of treatment plus fatty liver grade were remeasured and recorded.

The obtained data were entered into the SPSS version 24. We used independent *t*-test and repeated measure tests to compare data between different timelines and different groups. $P < 0.05$ was considered as significance threshold.

Results

In the present study, 44 patients were recruited based on the criteria and were divided into two groups each having 22 individuals [Figure 1].

Primary analysis showed that the mean age of patients was 41.55 ± 8.18 years ranging from 31 to 61 years. Seventeen patients (38.6%) were male and 27 patients (61.4%) were female. No significant differences were observed between two groups regarding age and gender ($P > 0.05$). We also indicated that no significant differences could be observed between two groups regarding previous medical diseases ($P = 0.19$) [Table 1].

At the beginning of the study, all patients in both groups had grade 3 of NAFLD. After the treatments, 50% of the intervention group had grade 1 NAFLD, and 50% of other patients had grade 2 that showed significant improvements in patients ($P < 0.001$). On the other hand, patients in the control group showed no significant improvements after the study duration ($P = 0.482$). These data are summarized in Table 2.

Comparison of laboratory data before and after treatments showed significant improvements in the following items in the case group: liver size ($P < 0.001$), size of the left liver lobe ($P < 0.001$), FBS ($P = 0.036$), Chol ($P = 0.001$), TG ($P = 0.001$), HDL ($P = 0.003$), LDL ($P = 0.021$), ALT ($P = 0.011$), and BMI ($P < 0.001$). No significant progression was observed in the control group regarding the mentioned tests after treatments ($P > 0.05$ for all) [Table 3 and Figure 2].

Table 1: Demographic data of the patients

	Case, *n* (%)	Control, *n* (%)	*P*
Age category			
<40	10 (45.5)	9 (40.9)	0.18
40-50	9 (40.9)	10 (45.4)	
>50	3 (13.6)	3 (13.7)	
Sex			
Male	8 (36.4)	9 (40.9)	0.42
Female	14 (63.6)	13 (59.1)	

Table 2: Comparison of fatty liver grade before and after treatments

	Fatty liver grade	Case, *n* (%)	Control, *n* (%)
Before treatment	1	0	0
	2	0	0
	3	22 (100)	22 (100)
After treatment	1	11 (50)	0
	2	11 (50)	4 (18.2)
	3	0	18 (81.8)
P		<0.001	0.482

Discussion

NAFLD is one of the common findings among obese patients that are candidates for bariatric surgeries. One other complication among these patients is increased size of the liver, especially the left lobe. This could lead to further problems during surgical operations. As a result, developing a special technique to reduce these issues has great importance.

In the present study, we treated patients with the special diet and daily tablets of pioglitazone and observed significant improvements in the grade of NAFLD along with reduction in total liver size and also improvements in lipid profile of patients and BMI. These data show the effectiveness of pioglitazone in treatments of NAFLD and also reducing the lipid profile of patients. There have been researches on the effects of pioglitazone among patients with fatty liver disease, but the important novelty of our study was that we evaluated patients with obesity and conducted a 4 months study while most previous studies have used pioglitazone for at least 6 months and on nonobese cases.

Recently, in 2021, Lian *et al.* conducted a meta-analysis on the effects of pioglitazone for NAFLD patients. They reviewed data of 4 trials and showed that pioglitazone can significantly improve the histological properties of the liver resulting in improvements of NAFLD. Furthermore, they reported that the FBS, ALT, AST, and glycosylated hemoglobin of patients decreased significantly after treatments with pioglitazone. On the other hand, they showed that further research is required.[19] An important point of our study was that we used pioglitazone for NAFLD patients in 4 months, while most previous studies have prescribed pioglitazone for 6 months.

In 2017, a study was conducted by Ito *et al.* on 66 patients with type to diabetes mellitus. They treated patients with

Table 3: Comparison of laboratory data between two groups before and after interventions

	Case (mean±SD)		*P*	Control (mean±SD)		*P*
	Before	After		Before	After	
SVL	1623.09±285.5	1511.77±268.9	<0.001	1647.09±232.5	1652.17±212.4	0.24
SV	814.50±151.2	744.36±150.5	<0.001	825.30±132.4	810.35±132.4	0.078
FBS	121.86±56.1	105.77±14.9	0.036	127.26±51.0	124.17±47.1	0.12
Cholesterol	241.73±46	226.55±41.6	0.001	238.70±39	242.72±45	0.46
TG	225.50±67.7	195.73±48.4	0.001	217.30±63.4	210.21±52.4	0.66
HDL	41.00±6.3	43.27±5.9	0.003	40.80±5.1	41.56±4.1	0.14
LDL	147.09±24.6	143.18±66.5	0.021	144.09±27.6	145.17±21.4	0.74
AST	39.23±21	34.95±12.5	0.194	38.73±23	39.61±20	0.23
ALT	51.41±27.6	42.05±17.8	0.011	54.43±26.2	56.42±22.1	0.41
BMI	42.71±6.4	41.25±6.5	<0.001	42.61±7.2	42.64±6.1	0.27

SD: Standard deviation, FBS: Fasting blood glucose, TG: Triglyceride, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, BMI: Body mass index, SVL: Snout-vent length, SV: Splenic vein

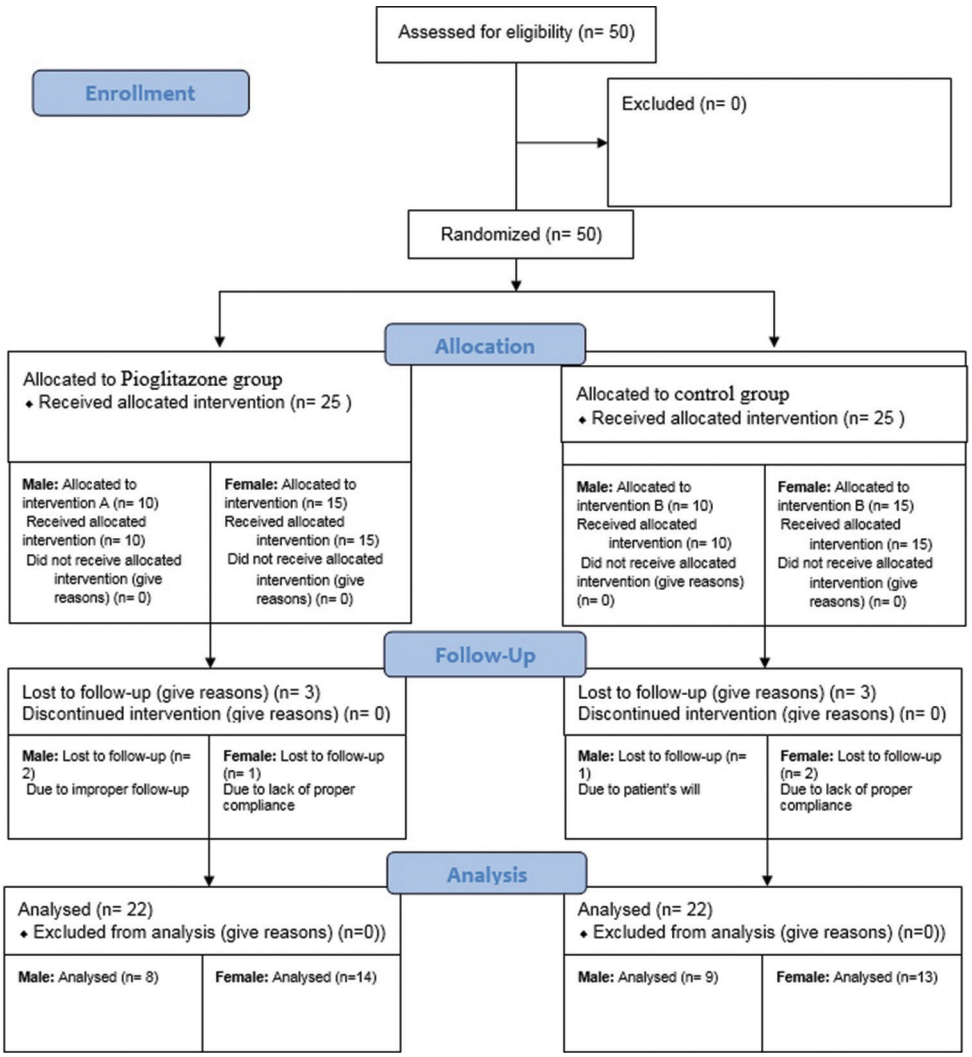

Figure 1: The CONSORT flow diagram of the study

pioglitazone and ipragliflozin for 6 months and reported that treatments with pioglitazone resulted in significant improvements in NAFLD and better glycemic control. In this study, they showed that the grade of NAFLD reduced significantly inpatients but using pioglitazone had no significant effects on BMI or lipid profile.[20] The results of our study were somehow consistent with this study, but we also found significant improvements in the lipid profile and

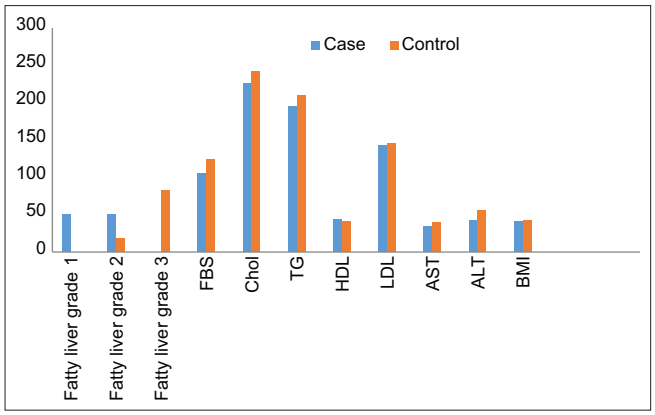

Figure 2: Comparison of different variables at the end of the study

BMI of patients. We believe that these differences could be due to the variations in study populations.

Based on the results of our study and former studies, pioglitazone could have significant effects in patients with NAFLD and also patients that are candidates of bariatric surgery. Restriction in the study population and not evaluating the liver size with more advanced methods due to high costs account as important limitations of our study, but we believe that these results are highly reliable. We suggest that surgeons should improve the use and beneficial effects of this medicine in clinical practice.

Conclusion

The use of pioglitazone for 4 months resulted in improvements in fatty liver stage, liver size, BMI, FBS, and lipid profile. These data were consistent with previous studies showing the effectiveness of pioglitazone in NAFLD. We also recommend that further research on larger populations should be conducted.

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Conflicts of interest

There are no conflicts of interest.

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