ORIGINAL ARTICLE

Evaluating Pioglitazone for Managing Type 2 Diabetes Mellitus in Patients with Nonalcoholic Fatty Liver Disease

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Received: 11 February 2025; *Accepted:* 15 July 2025

Abstract

Background: Among liver disorders, nonalcoholic fatty liver disease (NAFLD) is the most common and is associated with metabolic syndromes, particularly type 2 diabetes mellitus (T2DM). This study aimed to assess the effectiveness of pioglitazone in the management of T2DM with NAFLD.

Methods: This retrospective, single-center, observational study was carried out at Dr Panikar's Speciality Care Centre from 1st September 2022 to 1st February 2024. The data were collected from the medical records of diabetic patients with NAFLD who received pioglitazone. Patients aged between 18 and 80 years who had diabetes along with NAFLD were included in the study.

Results: A total of 3,350 patients were enrolled in this study, of whom 2,074 were male, with a mean age of 48.6 years. The mean estimated A1C (eA1C) showed a significant reduction at 6 months compared to baseline (6.87 vs 7.6%; mean difference (95% CI): 0.50% (0.39, 0.61); $p < 0.001$). At baseline, the mean controlled attenuation parameter (CAP) was significantly higher than at 6 months ($p = 0.032$). Similarly, the mean cholesterol level was significantly higher at baseline compared to 6 months ($p = 0.020$). A 25.7% decrease in grade 3 fatty liver was noted over the 6-month period from baseline. In terms of the decrease in fibrosis severity, a 37.5% reduction in F2, a 25.8% reduction in F1, and a 17.6% reduction in F4 were observed from baseline to 6 months.

Conclusion: In T2DM patients with NAFLD, pioglitazone improves glycemic control and reduces both fatty liver grades and fibrosis stages.

Journal of The Association of Physicians of India (2025): 10.59556/japi.73.1250

Introduction

Nonalcoholic fatty liver disease (NAFLD) is a liver condition marked by liver damage that is not associated with alcohol consumption. This condition can develop into nonalcoholic steatohepatitis (NASH), which may further advance to severe fibrosis as well as hepatocellular carcinoma (HCC).[1] The rapid rise in NAFLD and NASH is due to several factors. The primary contributors are the epidemic levels of type 2 diabetes mellitus (T2DM), obesity, and various elements of metabolic syndrome.[2] A recent study has shown a high occurrence of hepatic steatosis (75.1%) among patients with T2DM.[3]

As an agonist of peroxisome proliferator-activated receptor (PPAR), pioglitazone may enhance plasma adiponectin concentrations. This elevation is associated with improved insulin sensitivity and helps in mitigating inflammation and fibrosis in the treatment of NAFLD.[4] Among anti-diabetic medications, pioglitazone has the most substantial evidence supporting its effectiveness in NAFLD treatment, demonstrating improvements in liver histology for patients with biopsy-proven NASH.[5] To shed light on this, the current study aimed to assess the effectiveness of pioglitazone in the management of T2DM with NAFLD.

Methods

Study Design

A retrospective, single-center, observational study was carried out at Dr Panikar's Speciality Care Centre from 1st September 2022 to 1st February 2024. The study utilized medical record data from diabetic patients with NAFLD who received pioglitazone therapy.

Inclusion and Exclusion Criteria

This study included patients aged between 18 and 80 years who had diabetes and NAFLD, while those with any other chronic diseases were excluded.

Data Collection

Data on demographic characteristics, disease duration, glycemic and lipid parameters, and liver function tests were obtained from medical records verified by physicians during routine management.

Statistical Analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) software, version 23. Descriptive statistics were used to present categorical variables as frequency (percentage), and continuous variables were described as mean with standard deviation (SD). Comparison of qualitative data between two groups was performed by applying two independent sample *t*-tests, based on the normality distribution. Paired *t*-tests were conducted to compare the data from baseline to 6 months. *p*-value < 0.05 was considered statistically significant.

Results

A total of 3,350 patients were included in the study. The mean (SD) age was 48.6 (9.2) years. Of the total patients, 2,074 were male. No significant difference was observed in mean weight between baseline and the 6-month follow-up. At baseline, the mean body mass index (BMI) was significantly lower compared to 6 months (25.92 vs 26.55 kg/m^2; mean difference (95% CI): −0.61 kg/m^2 (−0.78, −0.43); $p < 0.001$). At baseline, the mean estimated A1C (eA1C) was significantly higher

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How to cite this article: Panikar V, Gupta A, Nasikkar N, *et al.* Evaluating Pioglitazone for Managing Type 2 Diabetes Mellitus in Patients with Nonalcoholic Fatty Liver Disease. J Assoc Physicians India 2025;73(11):17–19.

compared to 6 months (7.36 vs 6.87%; mean difference (95% CI): 0.50% (0.39, 0.61); $p < 0.001$). Mean triglyceride (TG) was significantly higher at baseline than at 6 months (160.64 vs 144.04 mg/dL; mean difference (95% CI): 15.97 mg/dL (1.40, 30.54); $p = 0.032$). The mean liver stiffness measurement (LSM) did not show significant changes between baseline and 6 months. No significant change was observed in the average fibrosis index based on four factors (FIB 4) between baseline and 6 months (Table 1).

The average serum glutamic oxaloacetic transaminase (SGOT) was comparable between baseline and 6 months. The mean serum glutamic pyruvic transaminase (SGPT) values showed no significant difference between baseline and the 6-month follow-up. At baseline, the mean controlled attenuation parameter (CAP) was significantly higher compared to 6 months (285.7 vs 273.7 dB/m; $p = 0.032$). The mean glycated hemoglobin (HbA1C) was significantly higher at baseline than at 6 months (7.40 vs 6.20%; $p < 0.001$). The mean cholesterol was significantly higher at baseline than at 6 months (157.04 vs 151.04 mg/dL; $p = 0.020$). No significant differences were observed in the average levels of high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) between baseline and the 6-month follow-up (Table 2).

The severity of fatty liver and fibrosis at subsequent follow-ups is depicted in Table S1. At baseline, 14.9, 23.0, and 47.1% of patients had grade 1, 2, and 3 fatty liver, respectively. The proportion of patients with grade 3 fatty liver decreased from 47.1% at baseline to 35% at the 6-month follow-up, indicating a 25.7% reduction in grade 3 fatty liver over 6 months (Fig. 1). In F2 fibrosis, there was a 37.5% reduction observed from baseline to 6 months (Fig. 2).

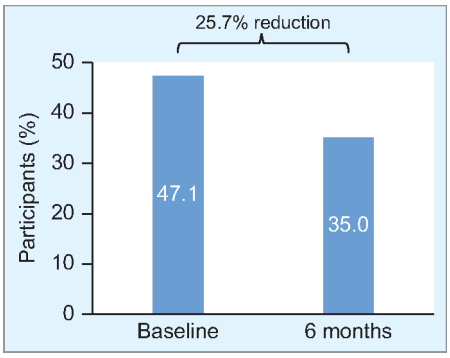

Fig. 1: Change in grade 3 fatty liver from baseline to 6 months

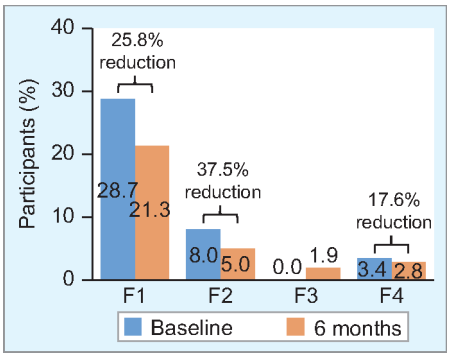

Fig. 2: Severity of fibrosis at baseline and 6 months

Table 1: Comparison of parameters in patients receiving pioglitazone from baseline to 2- and 6-month follow-up ($N = 3350$)

Parameter	*Baseline*	*2 months*	*6 months*	*Mean difference (95% CI); p-value*	
				Baseline to 2 months	*Baseline to 6 months*
Weight (kg)	($n = 3134$) 74.71 (14.22)	($n = 3134$) 74.66 (14.30)	($n = 3130$) 74.76 (14.34)	0.04 (–0.05, 0.14); $p = 0.388$	–0.07 (–0.18, 0.04); $p = 0.212$
BMI (kg/m^2)	($n = 2289$) 25.92 (48.10)	($n = 2289$) 26.12 (48.67)	($n = 2274$) 26.55 (48.67)	–0.20 (–0.30, –0.10); $p < 0.001$	–0.61 (–0.78, –0.43); $p < 0.001$
eA1C (%)	($n = 1887$) 7.36 (2.27)	($n = 1887$) 6.87 (1.62)	($n = 1883$) 6.87 (1.69)	0.50 (0.39, 0.61); $p < 0.001$	0.50 (0.39, 0.61); $p < 0.001$
TG (mg/dL)	($n = 234$) 160.64 (133.34)	($n = 234$) 144.04 (73.57)	($n = 252$) 131.62 (58.80)	16.60 (–1.19, 34.40); $p = 0.067$	15.97 (1.40, 30.54); $p = 0.032$
LSM (kPa)	($n = 4$) 7.58 (2.61)	($n = 4$) 8.65 (2.78)	–	–1.08 (–4.40, 2.25); $p = 0.379$	–
FIB-4	0.98 (0.37)	0.88 (0.30)	0.80 (0.25)	–	0.09 (–0.18, 0.37); $p = 0.365$

Data presented as mean (SD); BMI, body mass index; eA1C, estimated A1C; FIB-4, fibrosis index based on four factors; LSM, liver stiffness measure; TG, triglycerides

Table 2: Comparison of parameters in patients receiving pioglitazone from baseline to 6-month follow-up

Parameters	*Baseline*	*6 months*	*p-value*
SGOT (U/L)	($n = 295$) 26.16 (12.05)	($n = 709$) 33.32 (152.53)	0.290
SGPT (U/L)	($n = 306$) 29.21 (23.34)	($n = 727$) 31.27 (21.88)	0.114
CAP (dB/m)	($n = 86$) 285.7 (51.2)	($n = 365$) 273.7 (48.0)	0.032
HbA1c (%)	($n = 522$) 7.40 (2.85)	($n = 571$) 6.20 (3.11)	<0.001
Cholesterol (mg/dL)	($n = 697$) 157.04 (43.35)	($n = 919$) 151.04 (36.81)	0.020
HDL-cholesterol (mg/dL)	($n = 650$) 43.96 (13.98)	($n = 877$) 43.82 (15.90)	0.508
LDL-cholesterol (mg/dL)	($n = 644$) 85.77 (33.43)	($n = 868$) 81.96 (29.19)	0.073

Data presented as mean (SD); CAP, controlled attenuation parameter; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein

Discussion

Among the most prevalent liver conditions, NAFLD is rapidly emerging as a global public health concern,[6] driven by the rising prevalence of obesity and T2DM. This increasing prevalence of NAFLD and NASH cases has led to substantial morbidity and mortality.[7] Management strategies for NAFLD primarily emphasize lifestyle modifications and early treatment of associated metabolic conditions.[8] Pioglitazone is a promising agent for treating NAFLD/NASH.[7]

In the current study, at 6 months, the eA1C was significantly improved compared to baseline ($p < 0.001$). This significant decrease in eA1C indicates improved glycemic control over the study period, which is linked to a reduced likelihood of diabetes-related complications, including neuropathy, retinopathy, and cardiovascular diseases.[9] The present study indicated that the average TG level was significantly higher at baseline compared to the level observed at 6 months. In an earlier study by Belfort et al.,[5] treatment with pioglitazone led to a significant improvement in mean HbA1C levels compared to baseline ($p < 0.001$).[10] Similarly, in the current study, at 6 months, the average HbA1C was significantly improved compared to baseline ($p < 0.001$).

The present study observed that the average CAP score was significantly higher at baseline compared to 6 months ($p = 0.032$). This aligns with the results of a previous study by Chehrehgosha et al., which reported a significantly lower mean CAP score at week 24 compared to baseline ($p < 0.001$).[11] The current study showed that the average HDL-C level was comparable at baseline and at 6 months. Conversely, a previous study by Chehrehgosha et al. reported a statistically significant improvement in HDL-C levels at week 24 compared to baseline in patients treated with pioglitazone.[11]

Conclusion

In patients with T2DM and coexisting NAFLD, pioglitazone was shown to significantly improve glycemic control, reduce liver fat, and regress fibrosis. These results underscore the therapeutic potential of pioglitazone in this population, providing a much-needed tool for managing both diabetes and liver disease in parallel.

Author Contributions

All authors met ICMJE criteria, and all those who fulfilled these criteria are listed as authors. All authors provided direction and comments on the summary, made the final decision about where to publish the summary, and approved submission to the journal.

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Table S1: Severity of fatty liver and fibrosis at subsequent follow-ups

Parameter	*Baseline*	*2 months*	*6 months*
Fatty liver			
Grade 1	14.9	18.0	17.4
Grade 2	23.0	22.8	24.5
Grade 3	47.1	34.1	35.0
Fibrosis			
F1	28.7	23.0	21.3
F2	8.0	6.4	5.0
F3	–	1.51	1.9
F4	3.4	1.51	2.8

Data presented as percentage