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Assessing the Impact of Pioglitazone on Fibrosis Progression amongst People with Type 2 Diabetes Mellitus (T2D): A Retrospective, Multi-centric Real-World Study in Indian Population

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Abstract

Background: NAFLD (Non-Alcoholic Fatty Liver Disease) or metabolic dysfunction-associated steatotic liver disease (MASLD) encompasses a spectrum of liver disorders and is the primary cause of chronic liver disease worldwide. The present study seeks to evaluate the effect of Pioglitazone on fibrosis progression, assessed by Fibrosis 4 (FIB-4) in individuals with type 2 diabetes mellitus (T2D).

Materials and Methods: In the present two-center retrospective study, adults with T2D who had at least 2 visits and 2 FIB-4 values measured at least 90 days apart (from April 2021 to May 2024) were enrolled. Data was analyzed for descriptive statistics and compared for significance between groups. Statistical differences between the groups were determined by applying the Wilcoxon Signed-Rank Test and paired t-test.

Results: 54 individuals with a mean age of 57.5 years (±12.7) were included for analysis. HbA1c [from 8.93% to 7.58% ($p<0.01$)] significantly improved while the BMI remained unchanged. Mean FIB-4 scores also significantly dropped from 1.99 at baseline to 1.54 at follow-up ($p<0.01$). FIB-4 scores declined from baseline in both the indeterminate and high-risk groups.

Conclusion: HbA1c and FIB-4 scores were reduced with pioglitazone. It has a protective role against fibrosis progression in people with T2D.

Keywords: Type 2 Diabetes Mellitus (T2D); Pioglitazone; Fibrosis-4 (FIB-4); HbA1c

Abbreviations

T2D: Type 2 Diabetes Mellitus; NAFLD: Non-Alcoholic Fatty Liver Disease; MASLD: Metabolic Dysfunction-Associated Steatotic Liver Disease; NASH: Non-Alcoholic Steatohepatitis; ICMR: Indian Council of Medical Research; IRB: Institutional Review Board.

Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD) or non-alcoholic fatty liver disease (NAFLD) is the most common cause of long-standing liver disease worldwide. It is strongly associated with obesity, metabolic syndrome, and type 2 diabetes mellitus (T2D) [1]. The

disease encompasses a wide spectrum of liver conditions [simple steatosis, non-alcoholic steatohepatitis (NASH), liver cirrhosis and hepatocellular carcinoma (HCC)] [2]. Management of NAFLD and T2D should focus on early screening and diagnosis, lifestyle modifications, and medication to reduce the risk of complications. Younossi, et al. (80 studies, n=49419) in a systematic review and meta-analysis, reported the prevalence of NAFLD [55.5% (68% in Europe)], NASH (37.3%) and advanced fibrosis (17%) in individuals with T2D across the globe [3]. Among individuals with T2D in India, the prevalence of NAFLD ranges from 45-72%, affecting close to 50 million individuals [4]. Of these, an estimated 12.4 million people have advanced liver fibrosis related to NAFLD [5]. NAFLD is frequently associated with other comorbidities, obesity (51%), T2D (23%), hyperlipidemia (69%), hypertension (39%) and metabolic syndrome (43%) [6].

Current clinical guidelines recommend screening individuals with diabetes, metabolic syndrome, or obesity for steatotic liver disease using the fibrosis-4 (FIB-4) score, followed by imaging tests such as vibration-controlled transient elastography and controlled attenuation parameters to assess fibrosis severity [7]. Patients with an indeterminate FIB-4 score (1.30-2.67) can be managed initially in primary care with interventions such as weight loss, lifestyle modifications, pharmacotherapy, and bariatric surgery, with referrals to hepatologists considered for those at high risk (FIB-4 > 2.67) [8].

Various pharmacological agents have been explored for their potential effectiveness in treating NAFLD and NASH [9]. Thiazolidinediones (PPAR-γ agonists), function as insulin sensitizers in muscle, adipose tissue, and the liver [10]. Several randomized controlled trials have provided robust evidence of the benefits of pioglitazone in improving histological outcomes in NASH [11-13]. Notably, pioglitazone has demonstrated superior efficacy in reducing the NAFLD activity score, particularly in decreasing steatosis and fibrosis. A systematic review and meta-analysis by Wang Z, et al. [14] (7 articles, n=614), found that pioglitazone significantly improved lipid profiles, liver enzymes, and liver histopathology, regardless of the patient's diabetes status [14]. Lian J, et al. [15] (4 studies) found that pioglitazone administration in individuals with prediabetes or T2D who also had NAFLD led to improvements in steatosis and the resolution of steatohepatitis with no improvement in fibrosis [15].

Evidence to assess and understand the impact of oral antihyperglycemic agents on liver parameters amongst Indians is sparse. This paper presents the exploratory assessment, using retrospective data collected from electronic medical records (EMR), of the effectiveness of Pioglitazone on Fibrosis Progression, with FIB-4 as the primary outcome, amongst people with T2D.

Materials and Methods

Study Design & Population

This was a retrospective, two-center study where participant data was extracted from the electronic health record (EHR). The study population was from two healthcare centers in Uttar Pradesh and Ahmedabad, India. Participants were adults diagnosed with T2D and undergoing routine treatment at these centers. Inclusion criteria included adult participants diagnosed with type 2diabetes, having at least two visits separated by 90 to 150 days between April 2021 and May 2024. Additional criteria considered for inclusion in the study were that these participants be treated with Pioglitazone (15 mg) at baseline, as monotherapy, or in combination with other oral antihyperglycemic agents. Have values to calculate the FIB-4 score at baseline and have the follow-up FIB-4 score recorded separately by at least 90 days.

Data Collection and Variables

Data was extracted programmatically from the MEDEVA EHR using the abovementioned inclusion criteria. Patient identifiers were not included in the extraction process, and patient confidentiality measures were taken throughout the data extraction, processing, and analysis stages. Variables included age (numeric), gender (categorical), dates of visits (dd/mm/yyyy), BMI (numeric), HbA1c laboratory evaluation order (LOINC), diagnosis of type 2 diabetes (SNOMED CT), laboratory evaluation order (LOINC) - ALT, AST and Platelet count and medications.

FIB-4 is calculation [16]:

FIB-4 index = (Age [years] × AST [U/L]) / (platelet [10^9/L] × ALT [U/L]).

FIB-4 is non-invasive and aids in determining the presence of advanced fibrosis. The scores are categorized into low (<1.30), indeterminate (1.30–2.67), or high (>2.67) risk of fibrosis [17].

Ethical Clearance and Informed Consent

All participants signed the informed consent form for routine care, which mentioned that their anonymized data without any protected health information may be used for future research and publication to improve patient care. The study adhered to the ethical guidelines of the Indian Council of Medical Research (ICMR) for biomedical research in human subjects. The study was conducted in compliance with ethical standards and the principles outlined in the Declaration of Helsinki. The Udyaan Healthcare Institutional

Review Board (IRB) reviewed and approved the study protocol, PFIA/01.

Statistical Analysis

Data was cleaned, and the study variables and groups were calculated from the data described in the previous section. Descriptive tables and visual graphs were generated to understand data patterns and trends. Based on normality tests, parametric or non-parametric tests were employed to test different hypotheses. Python 3.6 was used to explore data and for basic understanding and overview. To improve comprehension of the data structure and quality, multiple visualizations were created. SPSS (version 18) and Jamovi were used for statistical analysis. Descriptive statistics like mean, median, and mode, along with standard deviation, were used to analyze the data and to compare the significance between patient groups on a number of characteristics.

A planned statistical analysis was performed using SPSS version 18 and Jamovi. The data were also analyzed for descriptive statistics like mean, median, mode, and standard deviation and compared for significance between patient groups on various parameters. The statistical difference among the groups was observed using the pairwise comparisons t-test or Wilcoxon Signed-Rank Test.

Data Extraction and Final Numbers

A total of 591 subjects with a diagnosis of T2D and prescribed Pioglitazone as part of routine consultation were selected as baseline samples. 462 subjects also had a follow-up visit between 90 and 150 days from baseline. 185 subjects had values to calculate the FIB-4 score at baseline, and 54 subjects also had follow-up FIB-4 scores and were taken to the final analysis (Figure 1).

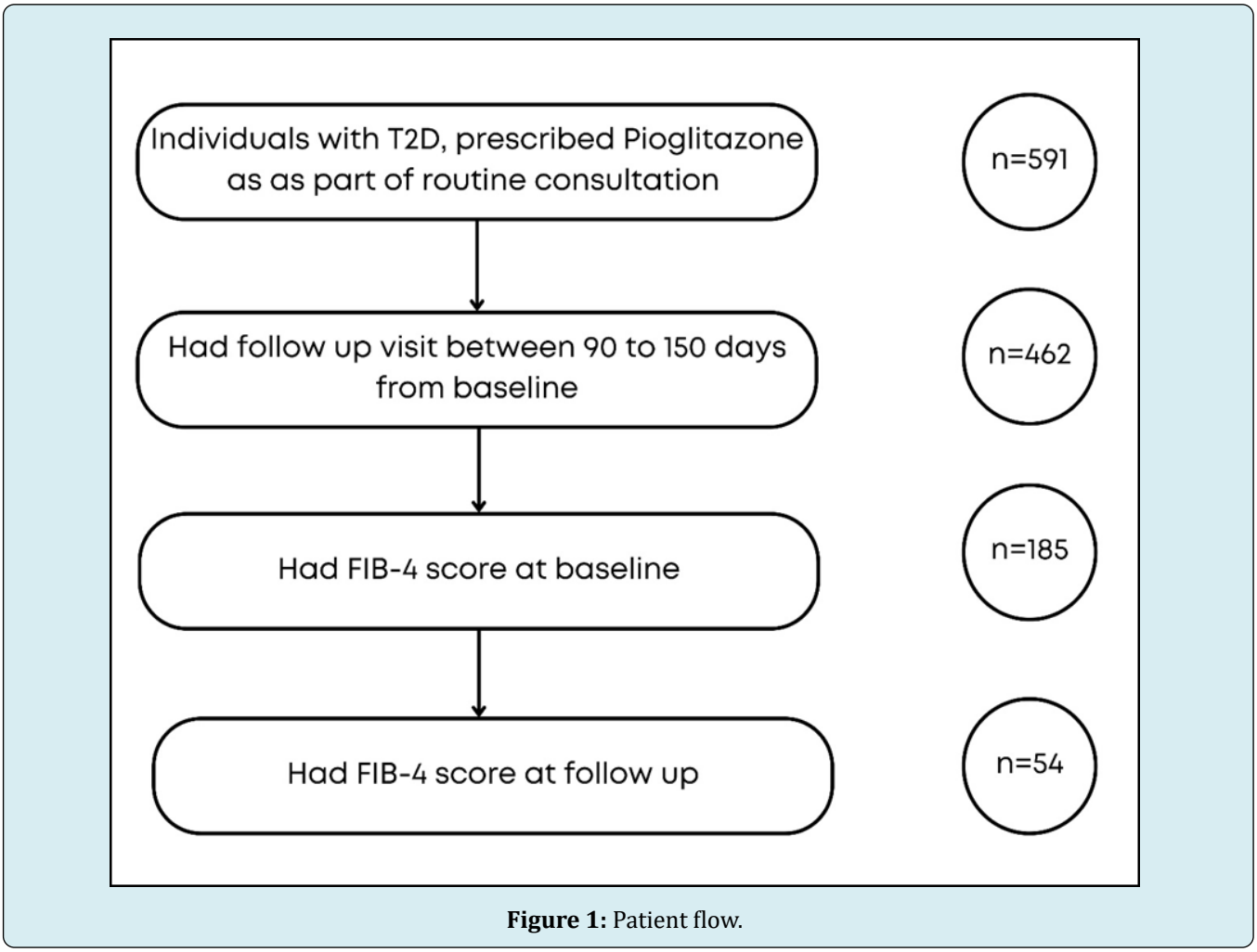

Figure 1: Patient flow.

Results

A total of 54 subjects' records were analyzed, with a mean age of 57.5 years (±12.7), a gender distribution of 57% Male and 43% female participants. Average BMI was 25.75 (±5.0) Kg/m^2. Demographic details of the sample analyzed can be found in Table 1.

Characteristics	Value
Age in years, Mean (SD)	57.5 (12.7)
Gender	
Male (%)	57%
Female (%)	43%
HbA1C, Mean % (SD)	8.93 (2.15)
BMI, Mean (SD)	25.75 (5.01)
FIB-4, Mean (SD)	1.99 (1.17)
Grouping by FIB-4 (%)	
<1.30	40.70%
1.30 -2.67	33.30%
>2.67	25.90%
Anti-diabetes medications (apart from Pioglitazone)	
Metformin	85%
Dipeptidyl peptidase 4 inhibitors (DPP4i)	67%
Sulphonylureas (SU)	61%
Sodium-glucose cotransporter-2 inhibitors (SGLT-2i)	35%
Voglibose	13%
Insulin	28%

Table 1: Baseline Characteristics.

After a follow-up period of 90 to 150 days from baseline, a significant overall reduction in HbA1c levels was observed, decreasing from 8.93% to 7.58% (p<0.01) (Figure 2).

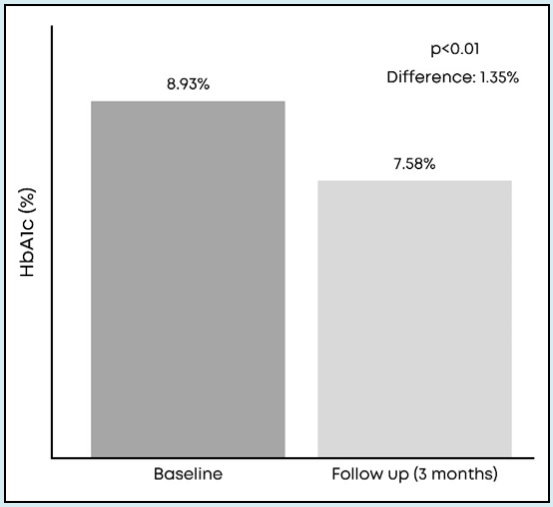

Figure 2: Change in HbA1c from baseline to follow-up.

Additionally, a notable decrease in HbA1c percentages was detected across all FIB-4 groups (p<0.05). (Table 2) The findings also show no significant differences in BMI (25.75 vs. 25.89, p=0.5).

FIB-4 Groupings	HbA1c at Baseline	HbA1c at Follow-up	P-value
Low risk (<1.3)	10.02	8.53	0.01
Indeterminate risk (1.3 to 2.67)	7.96	7.08	0.017
High risk (>2.67)	8.35	6.71	0.01

Table 2: HbA1c across FIB-4 groupings.

A significant reduction in the mean FIB-4 scores (1.99 to 1.54) was noted at follow-up (p<0.01). The reduction in FIB-4 scores, categorized by FIB-4 groupings from baseline, is as follows (Figure 3):

- Low Risk (<1.3, n=22): No significant change in FIB-4 score (0.90 vs. 0.87, p=0.3).
- Indeterminate Risk (1.3 to 2.67, n=18): Significant reduction in FIB-4 score (2.07 vs. 1.64, p<0.01).
- High Risk (>2.67, n=14): Significant reduction in FIB-4 score (3.59 vs. 2.48, p<0.01).

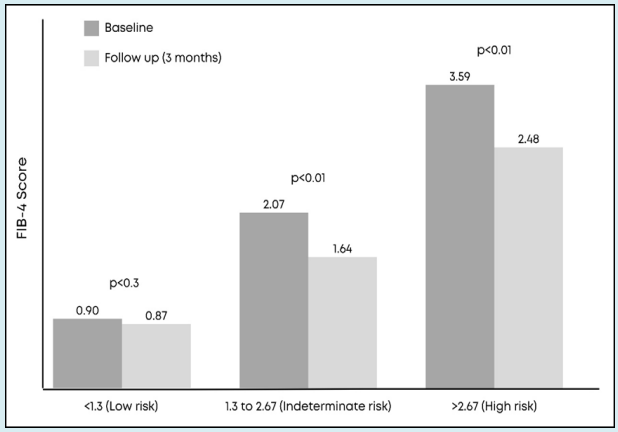

Figure 3: Change in FIB-4 groupings from baseline to follow-up.

Discussion

We aimed to evaluate the effectiveness of Pioglitazone on fibrosis progression among individuals with T2D, utilizing the FIB-4 index as the primary outcome measure. Our findings demonstrate that Pioglitazone was associated with a reduction in FIB-4 scores from baseline, particularly among patients classified as having indeterminate or high risk of fibrosis. These results underscore the importance of considering fibrosis risk when managing T2D and suggest a possible role for Pioglitazone in a broader, risk-stratified therapeutic strategy.

A systematic review by Kaur S, et al. [18] (18 articles) demonstrated that pioglitazone effectively enhances liver fat content, improves histological features, and positively influences metabolic parameters. A meta-analysis by Wang Z, et al. [14] (7 articles, n=614) and Lian J, et al. [15] (4 studies) revealed that in individuals on Pioglitazone, no significant differences in weight and BMI were noted. Even in the present study there is no significant change in the BMI from baseline. Many studies have revealed an increase in body weight in individuals on Pioglitazone [13,19,20]. The increase in weight caused by pioglitazone (may be dose-dependent, less with lower doses) may be due to water–sodium retention and increased fat content [21]. In the present study, Pioglitazone has significantly reduced HbA1c across all FIB-4 groups. Lian J, et al. [15] also reported a significant reduction in HbA1c from baseline in the Pioglitazone group [HbA1c SMD -0.77(95%CI -0.99 -0.55, p<0.00001)]. Similar results for a decrease in HbA1c were also seen in studies by Ito D, et al. [22] (8.3±1.4 vs. 7.07±0.89), Yoneda M, et al. [13] (7.09±0.19 vs. 6.40±0.18), and Asakawa M, et al. [2] (8.18 ± 1.24 vs. 7.36 ± 1.08%).

In the present study, FIB-4 scores significantly decreased from 1.99 at baseline to 1.54 at follow-up (p<0.01) which can be compared to a study by Aghajanpoor M, et al. [23] in which Pioglitazone reduced FIB-4 scores (1.33 to 1.17) after 24 weeks in adults with T2D and fatty liver. According to a study by Mino M, et al. [20] pioglitazone reported a reduction in FIB-4 scores in individuals with baseline levels of ALT >30 IU/L. Pioglitazone demonstrated reduction in FIB-4 scores in adults with NAFLD (1.84±1.13 vs. 1.71±1.19) and NASH or advanced fibrosis (2.06±1.24 vs. 1.70±1.19, p≤0.05) [22]. Yoneda M, et al. [13] conducted a randomized controlled trial (RCT) and reported a reduction in FIB-4 scores in people with NAFLD and T2D on Pioglitazone (2.12±1.82 vs.1.74±0.96). Asakawa M, et al. [2] also observed in individuals with NAFLD and T2D that, supplementary Pioglitazone medication significantly decreased FIB-4 scores (1.95 ± 1.46 to 1.35 ± 0.82, p<0.01). The findings from the present study contrast with Cho K, et al. [24] findings, which reported no significant alteration in FIB-4 scores after 24 weeks on Pioglitazone (1.32±0.50 to 1.35±0.52). The current study reported that Pioglitazone reduced FIB-4 scores in the indeterminate (2.07 vs. 1.64, p<0.01) and high-risk (3.59 vs. 2.48, p<0.01) groups. While a study by Chehrehgosha H, et al. [25] indicated no significant change in the total FIB-4 score (1.06±0.52 vs. 1.09±0.64) and among the three FIB-4 groups after 24 weeks. Various factors, like the patient's age and disease duration, influence the severity of fibrosis, as shown by the FIB-4 scores. According to a meta-analysis by Mozes F, et al. [26] higher FIB-4 scores signify more advanced fibrosis and are associated with an increased risk of adverse events (all-cause mortality, HCC, need for liver transplantation, and cirrhosis-related complications).

Strengths and Limitations

The present study analyzed data from 54 individuals who met the inclusion criteria, with significant reductions in HbA1c and FIB-4 scores observed during the follow-up. This real-world study suggests that Pioglitazone helps in reducing fibrosis progression in adults with T2D, a protective benefit, beyond glycemic control. The results add to the increasing body of data demonstrating its ability to reduce chronic complications. Compared to RCTs, this real-world study offers a comprehensive representation of clinical practice, enhancing its applicability to everyday care.

However, to address the topics not explored in this study, future research can expand on this foundation. To confirm these results and offer a more comprehensive understanding of pioglitazone's effectiveness, prospective trials with a larger sample, longer follow-up period, and control or comparison group inclusion would be crucial. Furthermore, more studies on potential adverse events will contribute to a fair assessment of its effectiveness and safety. Through these initiatives, the effect of Pioglitazone in reducing the advancement of fibrosis in T2D will be better understood.

Conclusion

In individuals with T2D and NAFLD, early screening and diagnosis of fibrosis improves the prognosis and management. Early detection of fibrosis lowers the risk of serious sequelae by timely management that can reduce or even stop its progression. The results of this study indicate that Pioglitazone has protective benefits against the advancement of fibrosis, especially in individuals who are more susceptible, in addition to glycemic control.

Conflict of Interest

No potential conflicts of interest relevant to this article were reported

Data Availability

Data is available upon request from the corresponding author.

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