Bull. Pharm. Sci., Assiut University, Vol. 46, Issue 1, 2023, pp. 361-378.

Bulletin of Pharmaceutical Sciences
Assiut University
Website: http://bpsa.journals.ekb.eg/
e-mail: bullpharm@aun.edu.eg

ASSESSMENT OF PENTOXIFYLLINE EFFECTS ON LIVER STEATOSIS UTILIZING DIXON-BASED MRI TECHNIQUE; RANDOMIZED CONTROLLED STUDY

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Background: *Pentoxifylline (PTX) has been proven to reduce hepatic steatosis in animal models; however, data regarding its safety and efficacy in type-2 diabetics (T2D) with nonalcoholic fatty liver disease (NAFLD) are rare.* ***Aim:*** *Determine the effects of PTX in reducing liver fat content (LFC; %) in T2D patients with NAFLD in various disease states.* ***Methods:*** *187 T2D subjects with NAFLD were randomized to receive either Pentoxifylline 800 mg (PTX group) or standard T2D care only (control group) for 24 weeks. The primary outcomes included changes in LFC (%) as measured by magnetic resonance imaging-derived proton density fat-fraction technique (MRI-PDFF) and the calculation of a fibrosis score (NFS).* ***Results:*** *PTX significantly reduced LFC (%) more than the control group (-8.18 vs. -1.87; P< 0.0001). Only the PTX group significantly reduced the NFS score (-1.16; P<0.0001). The PTX group showed significant LFC changes in liver segments II (-9.77; P< 0.0001), IVb (-9.51; P< 0.0001), and VI (-9.13; P< 0.0001); however, the control group achieved significant LFC changes in liver segments III (-2.57; P= 0.02) and VI (-2.22; P= 0.04). In subgroup analysis, PTX showed comparable efficacy in decreasing LFC in different fibrosis scores, gender, and BMI categories. However, Patients with severe steatosis grade (LFC>22.1%) (-10.55%; P=0.001) and HbA1c levels > 7.5% (-8.75%; P= 0.015) achieved significantly higher LFC reductions than other steatosis grades and HbA1c categories.* ***Conclusion:*** *PTX presented a similar efficacy profile in reducing LFC in different fibrosis scores, genders, and BMI categories, while patients with severe steatosis grade and HbA1c > 7.5% achieved higher LFC reductions.*

Keywords: *Pentoxifylline, liver steatosis, Diabetes, MRI-PDFF*

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is the abnormal lipid accumulation in the liver (≥ 5% steatosis) in the absence of alcohol consumption.[1] It is closely associated with obesity and insulin resistance. Consequently, NAFLD and diabetes are distinct conditions connected by diet and metabolic syndrome.[2]

Recently, NAFLD has been recognized as a leading cause of hepatocellular carcinoma and liver transplantation; however, there are limited

Received in 29/11/2022 & Accepted in 9/1/2023

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data on its global statistics. [3] It is regarded as an epidemic disease in the Middle East, with a prevalence of 30% of the population.[4]

Ultrasound classifies NAFLD patients into four grades with low sensitivity. Grade 0 is the absence of steatosis with normal hepatic echotexture, and grade I is the mild steatosis with liver echogenicity that obscures the echogenic walls of portal vein (PV) branches. Moreover, grade II means moderate steatosis with liver echogenicity that masks the diaphragmatic outline, and grade III is severe steatosis with poor visibility of PV, diaphragm, and posterior aspect of the right lobe.[5] The importance of using MRI-PDFF to assess liver fat is emphasized in T2D and NAFLD subjects. As a result, using MRI-PDFF instead of ultrasonography to quantify LFC is a more specific approach.[6]

PTX (3,7-dimethyl-1-(5-oxohexyl)-3,7-dihydro-1H-purine-2,6-dione), a methylxanthine derivative approved by the FDA for treating peripheral vascular diseases and cerebrovascular disorders.[7] It is a non-selective phosphodiesterase inhibitor that can downregulate tumor necrosis factor (TNF-α) and other inflammatory cytokines (e.g., IL-6, IL-8, and IL-10). Overproduction of TNF-α impairs insulin sensitivity and induces hepatic inflammation and, consequently, progression to NASH. [8] In an animal model of combined T2D and NAFLD, PTX treatment effectively alleviated liver steatosis on histology and decreased liver enzymes, insulin resistance, and triglycerides.[9] In a meta-analysis, PTX showed modest decreases in NAS score and lobular inflammation while not improving steatosis or fibrosis on histology.[10]

Aim

This study aims to evaluate the effectiveness of PTX in regressing LFC and fibrosis markers among different disease statuses in type-2 diabetic subjects with NAFLD.

Ethics approval

The study was performed according to the good clinical practices recommended by the Declaration of Helsinki and its amendments. In addition to written informed consent from each participant, ethical approval was provided by Beni-Suef University Research Ethics Committee (REC-H-PhBSU-21005).

METHODS

A randomized (1:1) single-blinded clinical study (registered in clinicaltrials.gov NCT04910178) was conducted at the endocrine clinic of Minia University Hospital. The physicians performing radiology and laboratory analysis were blinded to study groups or participants' data.

Inclusion criteria

Adult subjects (>18 years old) were allowed to participate according to the following criteria: 1- Confirmed diagnosis of T2DM according to ADA guidelines 2021.[11] 2- Using sulfonylurea for at least the previous six months.

Exclusion criteria

1- Normal subjects or patients diagnosed with type-1 diabetes mellitus. 2- Previous history of alcohol intake. 3- Evidence of other liver diseases (e.g., viral hepatitis, drug-induced liver disease, or autoimmune hepatitis). 4- Pregnant or lactating females. 5- Young participants aged ≤ 18 years. 6- Patients with eating disorders or previous bariatric surgery 7- Immunocompromised patients with a history of inflammatory, immunological, or malignant diseases. 8- History of cardiac disease (especially NYHA classes III/ IV) or chronic kidney disease (estimated eGFR below 60ml/min/1.73m^2, CrCl below 60ml/min, or on dialysis). 9- History of recurrent attacks of ketoacidosis in diabetic patients. 10- History of recurrent UTI or Genital infection in females. 11- History of recurrent foot injuries or infections. 12- History of biliary disease or hepatobiliary disease (ascites or jaundice). 13- Evidence of liver cirrhosis or HCC based on ultrasound or MRI. 14- History of hepatic encephalopathy or gallstone pancreatitis. 15- History of hypersensitivity to either drug. 16- Known contraindication to MRI examination (cardiac pacemakers or implanted devices with ferromagnetic field). 17- History of thyroid disease. 18- History of administered drugs interacting with PTX.

Study groups

Before the study, all type-2 diabetic subjects presented to the endocrine clinic were evaluated for eligibility. Then, eligible subjects were divided into three groups based on ultrasound grading: mild (n= 57), moderate (n=

58), and severe fatty liver patients (n= 55), and then randomly assigned to either group. Pentoxifylline 400 mg twice daily (Trental 400mg SR; Sanofi Egypt under the license of Sanofi-Aventis, Germany; Batch No. BEG009) was combined with sulfonylurea (PTX group). The other group (control) received only standard T2DM treatment (sulfonylurea).

Study Outcomes

Primary outcome measures

The primary outcome was evaluating the changes in fatty liver grading using ultrasound and changes in LFC (%) using the MRI-PDFF technique (mDixon Quant.). The ultrasound was performed using Toshiba Xario Aplio 500 US system with a convex probe (2-5 μHz).

Quantifying liver steatosis

MRI-PDFF was performed using a 1.5-T MRI system (Philips MR system Ingenia). Multiple images were acquired at various echo times to separate fat and water signals (in-phase (IP) and out-phase (OP)). On the MRI-PDFF maps, an experienced radiologist set a circular region of interest (ROI) of the same size (140-170 mm2) corresponding to each liver segment (Segment I, II, III, IVa, IVb, V, VI, VII, and VIII) and spleen, avoiding blood vessels, organ margins, bile ducts, and visual artifacts. The radiologist was blinded to the patient's clinical details. LFC was determined using the following formula: $[(SI_{IP} - SI_{OP})/2SI_{IP}] \times 100$.

SIIP and SIOP are the hepatic to splenic SI ratios in the IP and OP images. In both phases, SI is the mean ROIs measured. Furthermore, grading of NAFLD using MRI-PDFF maps was done according to the following cut-offs; Normal liver (< 6.5%), Grade I (> 6.5 and < 17.4%), Grade II fatty liver (> 17.4 and < 22.1%), Grade III (> 22.1%). [12]

Fibrosis scores

NFS score was calculated as: (-1.675 + 0.037 × age (years) + 0.094 × BMI (kg/m2) + 1.13 × IFG/diabetes (yes= 1, no= 0) + 0.99 × AST/ALT ratio – 0.013 × platelet ($\times 10^9$/l) – 0.66 × serum albumin (g/dl). [13] According to the results, NFS values less than -1.455 indicate a low likelihood of fibrosis; NFS values between -1.455 and 0.675 indicate an indeterminate fibrosis probability, and NFS values greater than 0.675 indicate a high possibility of fibrosis. 4.4.2. Secondary outcome measures:

Liver function tests

Changes in serum albumin (g/dl), alanine aminotransferase (ALT; mg/dl), aspartate aminotransferase (AST; mg/dl), serum bilirubin (mg/dl), ALP (IU/L), and GGT (U/ml).

Glycemic parameters

Changes in glycosylated hemoglobin (HbA1c; %), (fasting glucose (FG; mg/dl), 2-hr postprandial glucose (2-hr PPG; mg/dl), and fasting serum insulin level (μU/ml).Furthermore, changes in insulin resistance (HOMA-IR) were calculated using the following equation:

$$\frac{\text{FG } \left(\frac{\text{mg}}{\text{dl}}\right) \text{X fasting insulin(IU/L)}}{405} \quad [14]$$

Changes in B-cell function (HOMA-B) was estimated as follows:

$$\frac{\text{fasting insulin (IU/L)X360}}{\text{FG } (\frac{\text{mg}}{\text{dl}}) - 63} \quad [15]$$

Lipid profile

Changes in LDL cholesterol (mg/dl), triglycerides (mg/dl), HDL cholesterol (mg/dl), and total cholesterol (mg/dl).

Anthropometric measures

Weight (Kg), body mass index (BMI), and waist-to-hip ratio changes.

All outcomes were collected at baseline and after 24 weeks. Safety was assessed through vital signs, adverse events, physical examination, and blood chemistry.

Sample size calculation

Based on the previous clinical studies,[16&17] we assumed a baseline LFC value of 16 ± 6 %, and an anticipated 5% decrease would be clinically acceptable and relevant. Upon these assumptions, 46 patients were required to achieve a power of 80% at a significance level of 0.05. As a result, we randomized 85 patients per group to have adequate study power accounting for dropouts.

Statistical analysis

We used the statistical package SPSS software (Version 25.0, SPSS Inc., Chicago, Ill., USA) for data entry and analysis. Categorical data were expressed as n (%), and the χ 2 test was used to compare the baseline and posttreatment data. However, a paired

student's t-test was used for continuous variables and reported as mean ± SD and 95% confidence interval of the difference (95% CI). A one-way ANOVA test was used to compare the statistical significance of baseline values across study groups. Bivariate correlation analysis was performed using Pearson correlation. A two-tailed P value < 0.05 was regarded as statistically significant.

RESULTS AND DISCUSSION

Results

Description of study cohort

From December 2020 to December 2021, 187 subjects with T2DM and NAFLD were randomly assigned to either study group. Finally, 170 subjects completed the trial and were analyzed (Figure 1). The subjects were 59 (69.4%) females and 26 (30.6%) males in the PTX group and 58 (68.2%) females and 27 (31.8%) males in the control group.

The mean age in the PTX group was 49.49 ± 6.66, and the control group was 47.36 ± 8.55. The two groups exhibited similar baseline parameters (supplementary table 1). According to direct interviews on follow-up, the compliance rate for PTX exceeded 95%; this may be due to using a low dose of the drug (800 mg/day instead of 1200mg/day). Only 12 (14.1%) subjects experienced gastrointestinal disturbances (flatulence, gases, abdominal cramps, and nausea). Higher rates of side effects were reported in previous studies. [18]

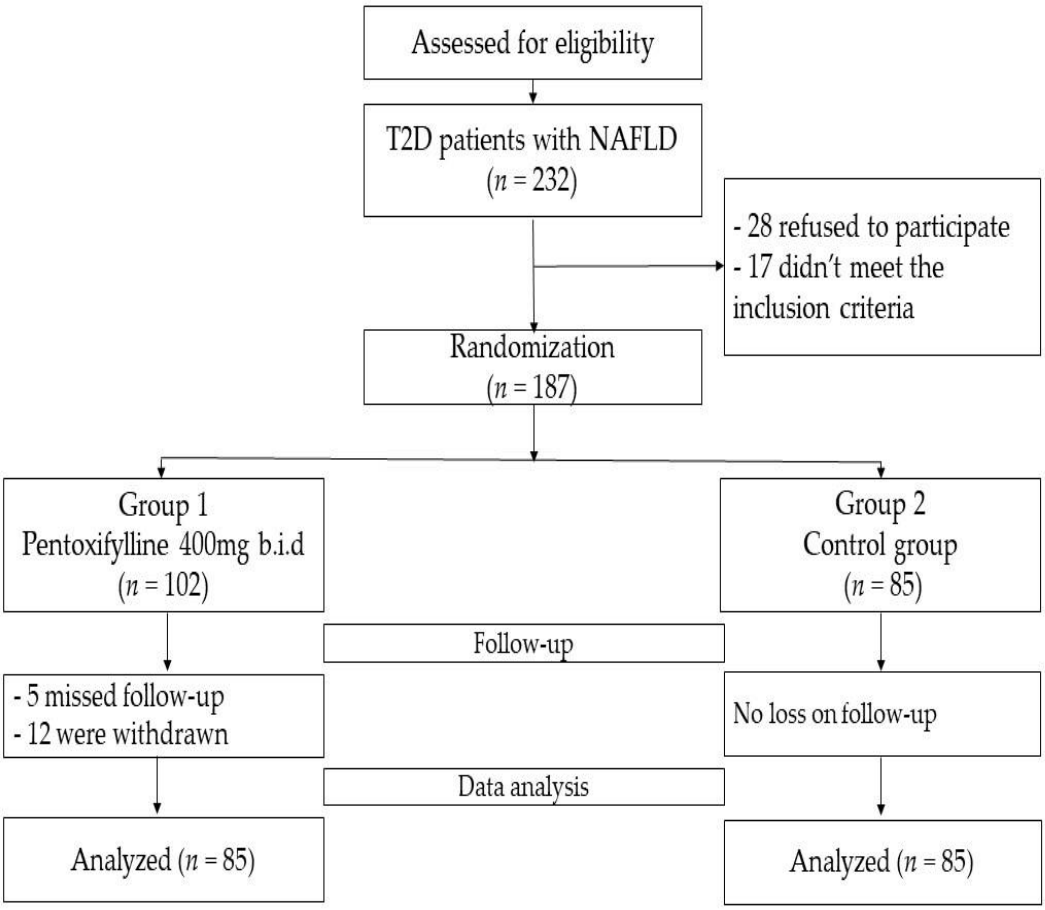

Fig. 1: Flow chart of the study cohort.

Supplementary Table 1: Baseline characteristics of study patients.

Parameters			PTX	CONTROL	P-value
T2D comorbidities	Hypertension	N (%)	16 (18.8%)	25 (28.2%)	0.145
	Dyslipidemia	N (%)	25 (29.4%)	22 (25.9%)	0.496
	Neuropathy	N (%)	29 (34.1%)	41 (48.2%)	0.087
Medications	Statins	N (%)	14 (16.5%)	22 (25.9%)	0.583
	B-blockers	N (%)	5 (5.9%)	7 (8.2%)	0.803
	ACEI's/ARBs	N (%)	15 (17.6%)	25 (29.4%)	0.052
	Diuretics	N (%)	9 (10.6%)	7 (8.2%)	0.731
	NSAID's	N (%)	30 (35.3%)	24 (28.2%)	0.310
	Pregabalin/ Gabapentin	N (%)	22 (25.9%)	12 (14.1%)	0.193
	Vitamin B12 injections	N (%)	27 (31.8%)	50 (58.8%)	0.020
SBP (mmHg)		Mean ± SD	121.53 ± 7.20	130.18 ± 14.03	0.0001*
DBP (mmHg)		Mean ± SD	76.06 ± 6.08	83.35 ± 8.84	0.0001*
Weight (Kg)		Mean ± SD	87.02 ± 9.37	85.34 ± 12.36	0.74
Height (meter)		Mean ± SD	1.64 ± 0.07	1.59 ± 0.07	0.0001*
BMI (Kg/m2)		Mean ± SD	32.36 ± 3.70	34.02 ± 5.68	0.09
Waist-to-hip ratio		Mean ± SD	0.963 ± 0.07	0.969 ± 0.05	0.96
FG (mg/dl)		Mean ± SD	146.75 ± 31.58	153.92 ± 41.30	0.67
2hr-PPG (mg/dl)		Mean ± SD	264.91 ± 67.82	252.29 ± 67.42	0.61
HbA1c (%)		Mean ± SD	8.37 ± 1.04	8.34 ± 1.05	0.99
HOMA-B		Mean ± SD	78.40 ± 69.88	84.24 ± 53.17	0.91
HOMA-IR		Mean ± SD	6.00 ± 4.32	6.45 ± 3.62	0.94
Insulin (μIU/L)		Mean ± SD	16.20 ± 11.24	17.36 ± 9.33	0.92
LFC (%)		Mean ± SD	21.05 ± 7.01	19.87 ± 7.11	0.68
NFS		Mean ± SD	-0.88 ± 0.92	-1.21 ± 1.20	0.23
AST (U/L)		Mean ± SD	28.24 ± 12.66	26.88 ± 10.58	0.92
ALT (U/L)		Mean ± SD	27.73 ± 12.50	26.24 ± 10.58	0.91
Total Bilirubin (mg/dl)		Mean ± SD	0.55 ± 0.25	0.48 ± 0.22	0.12
ALP (U/L)		Mean ± SD	110.18 ± 30.52	80.27 ± 23.29	0.0001*
GGT (U/L)		Mean ± SD	46.05 ± 17.06	47.70 ± 12.66	0.89
Total cholesterol (mg/dl)		Mean ± SD	240.67 ± 39.66	239.02 ± 39.98	0.99
Triglycerides (mg/dl)		Mean ± SD	164.82 ± 37.42	140.68 ± 31.13	0.06
LDL (mg/dl)		Mean ± SD	150.20 ± 37.73	160.55 ± 26.66	0.15
HDL (mg/dl)		Mean ± SD	47.07 ± 11.49	45.40 ± 7.92	0.62

**Significant if P-value < 0.05.

* ACEI's = angiotensin competitive enzyme inhibitors, ARB= angiotensin receptor blocker, NSAID= nonsteroidal anti-inflammatory drug, T2D= type-2 diabetes, DBP= diastolic blood pressure, SBP= systolic blood pressure, BMI=body mass index, HbA1c=glycosylated hemoglobin, HOMA-B=hemostatic model assessment for β-cell function, HOMA-IR= hemostatic model assessment for insulin resistance, LFC= liver fat content, NFS= NAFLD fibrosis score, AST=serum aspartate transaminase, ALT=serum alanine transaminase, ALP= alkaline phosphatase, GGT= gamma glutamyl transferase, LDL=low density lipoprotein, HDL= high density lipoprotein, eGFR= estimated glomerular filtration rate, SD= standard deviation.

Effects on anthropometric parameters and blood pressure

The PTX and control groups showed a significant reduction in systolic blood pressure (SBP) (P= 0.018 and 0.011, respectively) and an insignificant decrease in diastolic blood pressure (DBP). Weight, BMI, and waist-to-hip ratio were all significantly lowered by PTX. Surprisingly, all the patients in this study had a BMI above 25 Kg/m^2. Surprisingly, all the patients in this study had a BMI above 25 Kg/m^2.

Effects on liver steatosis

In supplementary table 2, Ultrasound images and MRI-PDFF maps ruled out fatty liver in five (5.9%) subjects in the PTX group. Furthermore, there was a statistically significant difference in changing MRI-PDFF grades in the PTX (P< 0.0001) and control groups (P< 0.0001). End-of-treatment MRI-PDFF (%) was found to be significantly lower in the PTX group (-8.18 %; P< 0.0001) and in the control group (-1.87 %; P< 0.0001). Changes in LFC in each liver segment are summarized in Table 2.

Only the PTX had a significant decrease in NFS (P<0.0001); moreover, after treatment, the PTX group reduced NFS from high to low fibrosis probability (<-1.45) in 5 (5.9%) subjects. (Figure 2)

Supplementary Table 2: Changes in Ultrasonography and MRI- PDFF grading after 24 weeks.

		PTX	Control	P-value
		N (%)	N (%)	
Ultrasonography				
Baseline	Grade 1	26(30.6%)	26(30.6%)	0.995
	Grade 2	29(34.1%)	30(35.3%)	
	Grade 3	30(35.3%)	29(34.1%)	
Posttreatment	Grade 0	5(5.9%)	---	0.0001*
	Grade 1	50(58.8%)	26(30.6%)	
	Grade 2	30(35.3%)	34(40%)	
	Grade 3	---	25(29.4%)	
P-value		0.0001*	0.0001*	
MRI-PDFF (%)				
Baseline	Grade 1	26(30.6%)	34(40%)	0.626
	Grade 2	21(24.7%)	18(21.2%)	
	Grade 3	38(44.7%)	33(38.8%)	
Posttreatment	Grade 0	5(5.9%)	---	0.0001*
	Grade 1	66(77.6%)	48(56.5%)	
	Grade 2	14(16.5%)	4(4.7%)	
	Grade 3	---	33(38.8%)	
P-value		0.0001*	0.0001*	

*Chi-Square test.
*Significant if P-value < 0.05.
* Data are presented as; number (percentage).
*MRI-PDFF= magnetic resonance imaging-proton density fat fraction.

Table 2: Full liver fat fraction mapping by MRI-PDFF in study groups

Liver segments	PTX			Control			
	Baseline	Posttreatment	P-value	Baseline	Posttreatment	P-value	P-value
I	20.56±8.41	12.31±5.79	0.0001	19.91±8.87	19.18±9.39	0.572	0.0001
II	21.94±8.50	12.17±4.30	0.0001	19.47±8.72	17.34±7.54	0.074	0.0001
III	23.45±7.56	14.98±6.30	0.0001	20.29±8.19	17.72±8.91	0.026	0.001
IVa	20.87±8.44	13.74±6.27	0.0001	18.61±8.83	17.58±8.97	0.294	0.0001
IVb	22.85±9.54	13.34±5.74	0.0001	19.49±7.81	16.86±7.78	0.051	0.0001
V	19.50±9.15	11.91±6.74	0.0001	19.52±8.44	17.58±9.04	0.099	0.0001
VI	19.84±8.90	10.72±5.10	0.0001	19.47±7.07	17.26±7.11	0.04	0.0001
VII	21.13±9.23	13.52±6.57	0.0001	20.73±6.49	19.11±6.49	0.112	0.0001
VIII	20.70±8.84	13.06±6.31	0.0001	19.59±7.93	17.59±7.57	0.003	0.007
Total LFC (%)	21.10±1.32	12.92±1.24	0.0001	19.67±0.60	17.80±0.80	0.0001	0.0001

*Paired T-test.
*Significant if P-value < 0.05.
*LFC= liver fat content, MRI-PDFF= magnetic resonance imaging-proton density fat fraction
* Data are presented as; mean ± standard deviation.
Table 3: Subgroup analysis of primary outcomes based on LFC and NFS grades, gender, BMI, and HbA1c:

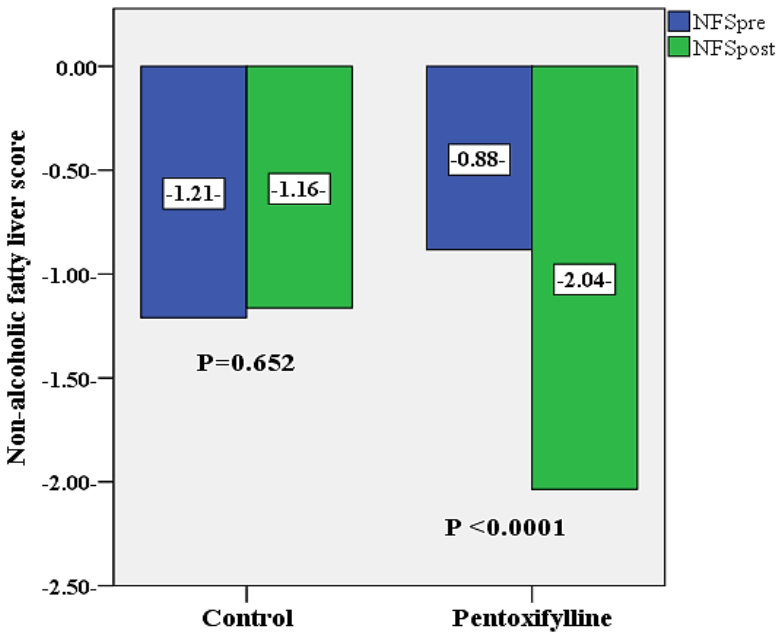

Fig.2: Changes in the nonalcoholic fatty liver score (NFS) in the PTX and control groups after 24 weeks.

Effects on biochemical tests

Table 1 summarizes the changes in different biochemical parameters in study groups.

Effects on lipid profile

The PTX group showed significantly lower levels of serum triglycerides (P< 0.0001), total cholesterol (P< 0.0001), and LDL (P< 0.0001). (Figure 3)

Table 1: Changes in anthropometric parameters, blood pressure, and biochemical characteristics after 24 weeks.

	PTX				Control			
	Baseline	posttreatment	Difference (95% CI)	P-value	Baseline	posttreatment	Difference (95% CI)	P-value
SBP (mmHg)	121.75 ± 7.30	117.50 ± 5.50	-4.25 (-7.67,-0.83)	0.018	129.75±14.19	121.75 ± 4.67	-8.00 (-13.90,-2.10)	0.011
DBP (mmHg)	76.25 ± 6.26	74.25 ± 4.67	-2.00 (-5.26,1.26)	0.214	83.00±8.94	80.25 ± 3.43	-2.75 (-6.01,0.51)	0.094
Weight (Kg)	86.0(10.8)	80.3(7.4)	-5.7 (-8.3,-3.2)	0.0001	84.95 ± 12.50	85.35 ± 10.53	0.40 (-1.68,2.48)	0.692
BMI (Kg/m2)	31.97±3.72	29.91 ± 3.34	-2.06 (-2.98,-1.14)	0.0001	33.90 ± 5.82	34.10 ± 5.41	0.19 (-0.66,1.04)	0.633
Waist-to-hip ratio	0.955±0.71	0.935 ± 0.73	-0.020 (-0.029,-0.010)	0.0001	0.969 ± 0.04	0.966 ± 0.05	-0.004 (-0.156,0.008)	0.527
FG (mg/dl)	146.75±31.58	107.85 ± 17.09	-38.91 (-44.86,-32.95)	0.0001	153.92±41.30	118.57 ± 20.40	-35.35 (-43.67,-27.03)	0.0001
2-hr PPG (mg/dl)	264.91±67.82	162.55 ± 32.33	-102.08 (-120.67,-89.49)	0.0001	252.29±67.42	185.15 ± 38.29	-67.14 (-79.75,-54.53)	0.0001
HbA1c (%)	8.37±1.04	7.31 ± 0.39	-1.06 (-1.26,-0.89)	0.0001	8.34 ± 1.05	7.52 ± 0.49	-0.83 (-1.02,-0.64)	0.0001
HOMA-B	78.40±69.88	126.25 ± 116.88	47.86 (28.05,67.66)	0.0001	84.24 ± 57.16	116.92 ± 53.17	32.68 (22.63,42.73)	0.0001
HOMA-IR	6.00±4.32	3.26±2.12	-2.74 (-3.47,-2.01)	0.0001	6.45 ± 3.62	4.88±2.39	-1.56 (-2.27,-0.85)	0.002
Insulin (μIU/L)	16.20±11.24	12.67 ± 8.72	-3.53 (-5.34,-1.72)	0.0001	17.36 ± 9.33	16.58 ± 7.46	-0.78 (-2.31,0.77)	0.320
AST (U/L)	28.24±12.66	20.95 ± 6.15	-7.28 (-9.48,-5.08)	0.0001	26.88 ± 10.58	29.48 ± 11.55	2.60 (0.47,4.73)	0.017
ALT (U/L)	27.73±12.50	19.45 ± 7.28	-8.28 (-10.58,-5.99)	0.0001	26.24 ± 10.58	31.92 ± 11.23	5.68 (3.64,7.73)	0.0001
Total Bilirubin (mg/dl)	0.55±0.25	0.46 ± 0.09	-0.09 (-0.14,-0.03)	0.002	0.48 ± 0.22	0.59 ± 0.26	0.11 (0.06,0.15)	0.0001
Total Bilirubin (mg/dl)	0.14±0.11	0.18 ± 0.14	0.03 (-0.02,0.08)	0.226	0.14 ± 0.06	0.19 ± 0.12	0.05 (0.03,0.08)	0.0001
Albumin (gm/dl)	4.22±0.46	4.75 ± 0.38	0.53 (0.40,0.65)	0.0001	4.36 ± 0.37	4.22 ± 0.39	-0.14 (-0.27,-0.01)	0.029
ALP (U/L)	110.18±30.52	78.38 ± 42.31	-31.80 (-21.39,-6.08)	0.0001	80.27 ± 23.29	80.58 ± 30.32	0.31 (-5.05,5.66)	0.912
GGT (U/L)	46.05±17.06	31.49 ± 8.93	-14.56 (-18.28,-10.84)	0.0001	47.70 ± 12.66	44.61 ± 10.97	-3.09 (-6.11,-0.07)	0.045

*Paired T-test

*Data are presented as mean ± standard deviation, Significant if P-value < 0.05.

*DBP= diastolic blood pressure, SBP= systolic blood pressure, BMI=body mass index, FG= fasting glucose, 2-hr PPG= 2hr postprandial glucose, HbA1c=glycosylated hemoglobin, HOMA-B=hemostatic model assessment for β-cell function, HOMA-IR= hemostatic model assessment for insulin resistance, AST=serum aspartate transaminase, ALT=serum alanine transaminase, ALP= alkaline phosphatase, GGT= gamma glutamyl transferase, C.I= confidence interval.

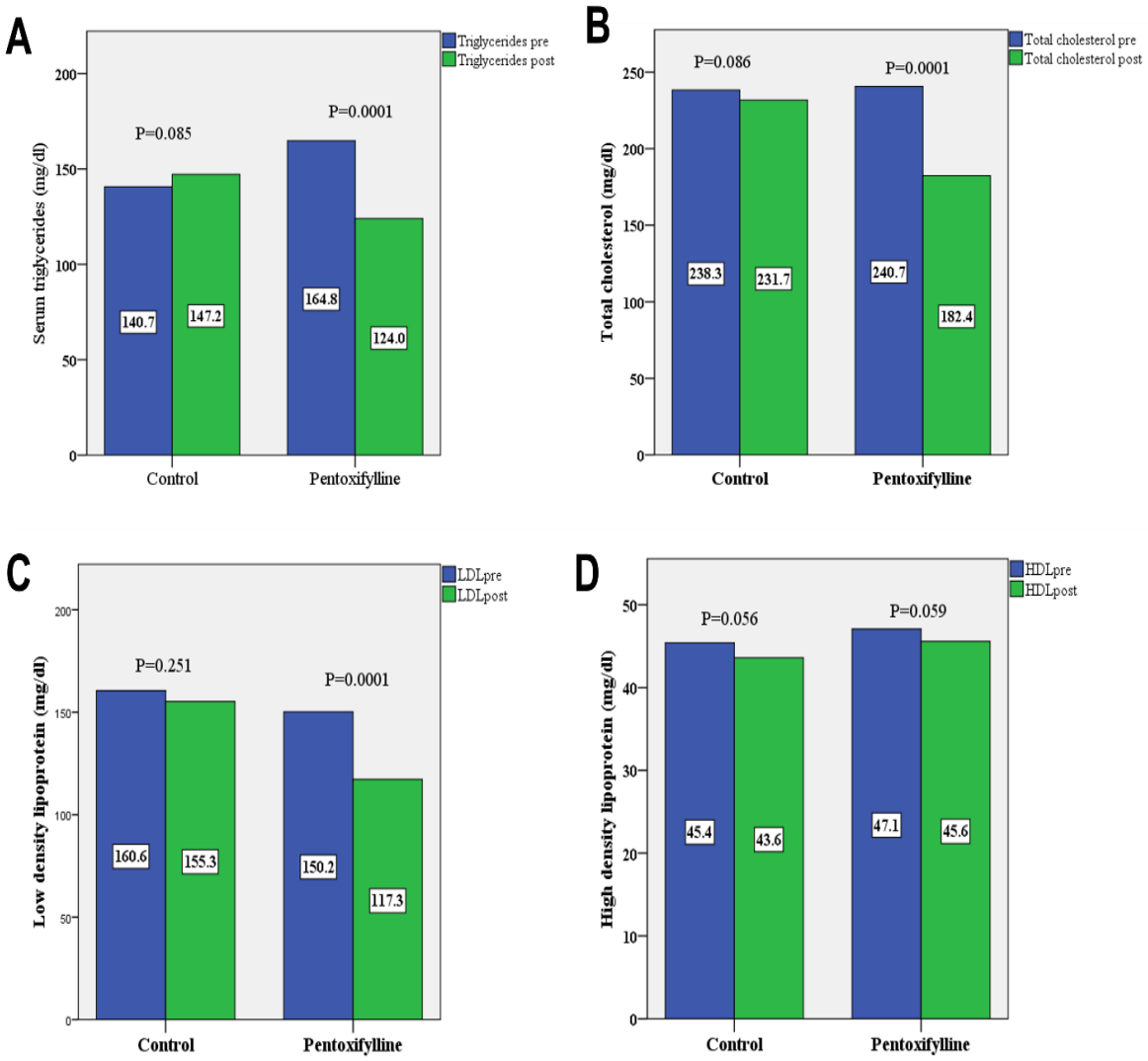

Fig. 3: Changes in Lipid profile after 24 weeks.

a) Changes in serum triglycerides in study groups, b) Changes in total cholesterol in study groups, c) Changes in serum low-density lipoprotein in study groups, d) Changes in high-density lipoprotein in study groups

Correlation analysis

In the PTX group, a correlation study between changes in LFC and changes in some selected parameters revealed a significant positive correlation with FG (r= 0.516; P<0.0001), 2-hrs PPG (r= 0.476; P< 0.0001), HbA1c (r=0.601; P< 0.0001), and LDL (r= 0.435; P<0.0001), and a significant negative correlation with HOMA-B (r= -0.335; P< 0.0001) and fasting insulin (r= -0.305; P= 0.004). In the control group, the correlation study revealed a significant positive correlation with weight (r= 0.482; P<0.0001), BMI (r= 0.475; P< 0.0001), and 2-hrs PPG (r= 0.387; P<0.0001), and a significant negative correlation with AST (r= -0.579; P< 0.0001) and ALT (r= -0.300; P= 0.005). (Supplementary table 3)

Supplementary Table 3: A correlation between changes in MRI-PDFF values and changes in selected measured parameters after 24 weeks of treatment in study groups.

Δ MRI-PDFF / Parameters	PTX		Control	
	r	P value	r	P value
ΔWeight	0.143	0.192	0.482	0.0001
Δ BMI	0.150	0.170	0.475	0.0001
Δ Waist-to-hip ratio	0.211	0.051	0.180	0.100
Δ FG	0.516	0.0001	0.185	0.091
Δ 2-hr PPG	0.476	0.0001	0.387	0.0001
Δ HbA1c	0.601	0.0001	0.077	0.527
Δ HOMA-IR	-0.105	0.337	0.213	0.050
Δ HOMA-B	-0.335	0.002	0.206	0.051
Δ Fasting Insulin	-0.305	0.004	0.201	0.080
Δ AST	-0.068	0.539	-0.579	0.0001
Δ ALT	0.125	0.256	-0.300	0.005
Δ GGT	0.075	0.498	-0.185	0.090
Δ ALP	0.0188	0.084	-0.084	0.445
Δ Triglycerides	-0.052	0.634	0.193	0.086
Δ TC	0.157	0.151	0.128	0.242
Δ LDL	0.435	0.0001	-0.01	0.537
Δ HDL	-0.191	0.079	-0.271	0.012

* Pearson correlation
* Significant if P-value < 0.05.
* r=correlation coefficient, BMI= body mass index, FG= fasting glucose, 2-hr PPG= 2hr postprandial glucose, HbA1c=glycosylated hemoglobin, HOMA-B=hemostatic model assessment for β-cell function, HOMA-IR= hemostatic model assessment for insulin resistance AST=serum aspartate transaminase, ALT=serum alanine transaminase, ALP= alkaline phosphatase, GGT= gamma-glutamyl transferase, TC=total cholesterol, LDL=low density lipoprotein, HDL= high density lipoprotein.

Subgroup analysis

Table 3 summarizes subgroup analysis in primary outcome parameters for both groups. In the PTX group, severe NAFL cases exhibited higher LFC (%) (P= 0.001) and ALP changes (P< 0.0001) compared to mild and moderate NAFL cases; however, in all NAFL grades, PTX showed comparable efficacy in decreasing NFS scores, AST, ALT, and GGT levels. PTX presented similar LFC changes in patients with different fibrosis probabilities. Also, PTX had similar effects in both males and females in decreasing LFC (%) (P= 0.132), NFS scores (P= 0.410), AST (P= 0.755), ALT (P= 0.838), ALP (P=0.236), and GGT (P= 0.279). In different HbA1c categories, PTX showed comparable reductions in NFS scores (P=568), AST (P=0.058), GGT (P= 0.089), and ALP (P=0.273). Patients with HbA1c >7.5% showed a higher reduction in LFC (%) (P= 0.015) and ALT (P= 0.027) than lower HbA1c (≤7.5%) in the PTX group. Finally, PTX exhibited comparable changes in LFC (%) (P= 0.471), NFS (P= 0.841), AST (P= 0.169), ALT (P= 0.449), GGT (P= 0.137), ALP (P= 0.828) in different BMI categories.

Table 3: Subgroup analysis of primary outcomes based on LFC and NFS grades, gender, BMI, and HbA1c.

Parameters			PTX			Control			P-value
			Baseline	Posttreatment	P-value	Baseline	Posttreatment	P-value	
LFC (%)	Fatty liver grades	Mild	12.88±3.64	8.02±2.15	0.0001	12.86±3.52	11.26±4.42	0.038	0.001
		Moderate	21.39±2.42	12.78±3.35	0.0001	18.64±4.73	15.54±4.54	0.0001	0.0001
		Severe	27.80±4.29	17.25±3.04	0.0001	27.44±3.32	26.11±3.26	0.006	0.0001
	NFS grades	Low	19.92±4.11	10.99±3.77	0.0001	21.44±7.90	20.10±8.69	0.001	0.0001
		Intermediate	21.50±8.12	13.71±5.07	0.0001	19.71±6.04	16.75±6.33	0.0001	0.0001
		High	21.18±2.61	12.54±1.14	0.0001	13.86±6.05	13.61±2.96	0.842	0.0001
	Gender	Male	19,86 ±8.25	12.94±4.19	0.0001	18.92±5.84	16.60±5.83	0.0001	0.0001
		Female	21.58±6.40	12.88±4.99	0.0001	20.29±7.62	18.38±8.03	0.0001	0.0001
	HbA1c	HbA1c≤7.5	18,99±4,90	12,67±3,99	0.0001	15,00±5,67	13,38±7,02	0,036	0.0001
		HbA1c>7.5	21.73±7.49	12.98±4.97	0.0001	21.47±6.84	19.30±7.03	0.0001	0.0001
	BMI	BMI≤30	21.02±6.56	13.48±3.90	0.0001	17.94±6.35	16.50±8.33	0.006	0.0001
		BMI>30	21.06±7.25	12.66±5.05	0.0001	20.67±7.31	18.40±7.03	0.0001	0.0001
NFS	Fatty liver grades	Mild	-1.19±0.96	-2.40±0.79	0.0001	-0.86±1.00	-0.129±0.83	0.004	0.002
		Moderate	-0.91±1.29	-1.77±0.73	0.0001	-1.01±1.20	-0.83±0.99	0.147	0.0001
		Severe	-0.63±0.53	-1.97±1.08	0.0001	-1.72±0.99	-1.40±1.22	0.164	0.0001
	NFS grades	Low	-2.00±0.27	-2.26±0.75	0.179	-2.39±0.71	-1.78±0.85	0.002	0.002
		Intermediate	-0.61±0.49	-2.10±0.85	0.0001	-0.59±0.46	-0.92±0.67	0.001	0.0001
		High	1.18±0.55	-0.31±0.04	0.005	0.73±0.03	0.23±0.81	0.116	0.034
	Gender	Male	-0.71±0.73	-1.99±0.73	0.0001	-1.11±1.28	-1.00±1.10	0.414	0.0001
		Female	-0.96±0.98	-2.06±0.98	0.0001	-1.25±1.17	-1.24±0.90	0.898	0.0001
	HbA1c	HbA1c≤7.5	-٠,٩٣±٠,٨٤	-2.19±0.86	0.0001	-0.86±0.97	-1.08±0.77	0,203	0.0001
		HbA1c>7.5	-0.87±0.94	-1.99±0.92	0.0001	-1.32±1.25	-1.19±1.02	0,290	0.0001
	BMI	BMI≤30	-0.92±0.68	-2.04±0.91	0.0001	-1.93±0.97	-2.00±0.68	0.529	0.0001
		BMI>30	-0.87±1.00	-2.03±0.92	0.0001	-0.91±1.16	-0.81±0.85	0.497	0.0001
AST (IU/L)	Fatty liver grades	Mild	25.29±14.85	21.00±9.12	0.068	22.31±11.76	23.23±5.15	0.613	0.069
		Moderate	25.17±3.84	20.97±1.83	0.0001	26.00±10.12	34.70±14.26	0.0001	0.0001
		Severe	33.20±14.84	20.90±5.89	0.0001	31.90±7.73	39.69±10.01	0.184	0.0001
	NFS grades	Low	25.74±3.00	22.83±6.97	0.078	27.14±8.91	29.40±9.78	0.098	0.016
		Intermediate	29.18±15.16	20.23±5.91	0.0001	24.86±10.45	29.36±13.92	0.006	0.0001
		High	29.00±6.71	20.60±3.13	0.006	36.38±3.77	30.50±0.54	0.250	0.689
	Gender	Male	28.65±14.61	20.85±5.56	0.002	21.65±6.01	26.19±6.89	0.0001	0.0001
		Female	28.05±11.23	21.00±6.44	0.0001	29.19±11.35	30.93±12.87	0.238	0.0001
	HbA1c	HbA1c≤7.5	23.62±9.37	18.52±6.61	0,005	22.52±8.09	23.57±6.92	0,559	0.014
		HbA1c>7.5	29.75±13.28	21.75±5.99	0.0001	28.31±10.96	31.42±12.13	0,020	0.0001
	BMI	BMI≤30	27.20±12.60	22.28±8.33	0.060	26.00±7.92	29.24±5.27	0.021	0.006
		BMI>30	28.67±12.76	20.40±4.96	0.0001	27.25±11.55	29.58±13.36	0.106	0.0001
ALT (IU/L)	Fatty liver grades	Mild	26.50±12.15	18.95±5.43	0.0001	17.50±6.49	29.04±3.14	0.0001	0.0001
		Moderate	27.52±14.09	16.07±3.98	0.0001	25.43±7.07	33.13±11.99	0.0001	0.0001
		Severe	29.00±11.40	23.17±9.32	0.003	34.90±11.23	33.24±13.90	0.314	0.091
	NFS grades	Low	31.57±7.23	20.57±3.81	0.0001	30.14±11.95	30.23±12.10	0.956	0.0001
		Intermediate	27.35±13.84	19.19±8.31	0.0001	23.50±9.10	31.98±11.17	0.0001	0.0001
		High	14.40±0.89	17.20±7.16	0.347	23.50±5.88	39.00±1.07	0.0001	0.002
	Gender	Male	24.62±8.85	16.69±6.58	0.0001	22.42±7.82	26.62±11.80	0.009	0.0001
		Female	29.10±13.64	20.66±7.29	0.0001	27.92±34.25	34.25±10.23	0.0001	0.0001
	HbA1c	HbA1c≤7.5	21.76±9.56	17.71±7.22	0.011	21.00±8.26	27.38±7.49	0,010	0.0001
		HbA1c>7.5	29.69±12.78	20.02±7.26	0.0001	27.95±10.75	33.41±11.89	0.0001	0.0001
	BMI	BMI≤30	24.32±6.05	17.40±5.66	0.0001	27.28±6.55	30.88±8.55	0.050	0.0001
		BMI>30	29.15±14.16	20.30±7.74	0.0001	25.80±11.88	32.35±12.22	0.0001	0.0001
ALP (U/L)	Fatty liver grades	Mild	98.46±51.43	114.54±33.07	0.060	77.08±28.10	69.69±24.50	0.271	0.029
		Moderate	110.97±21.85	71.67±30.67	0.0001	77.63±21.09	82.97±31.75	0.170	0.0001
		Severe	119.86±33.15	52.89±9.93	0.0001	85.86±20.30	87.86±31.90	0.548	0.0003
	NFS grades	Low	118.87±26.65	79.04±31.67	0.0001	95.71±25.50	94.09±37.43	0.778	0.007
		Intermediate	107.96±31.75	78.11±47.08	0.0001	68.31±14.15	72.10±21.20	0.125	0.0001
		High	95.40±27.73	78.40±32.20	0.001	75.50±10.16	66.00±3.21	0.084	0.257

Table 3: Continued.

	Gender	Male	97.27±33.59	74.04±38.24	0.030	92.04±24.99	86.12±26.82	0.374	0.156
		Female	115.86±27.48	80.29±44.16	0.0001	75.08±20.66	78.14±31.65	0.238	0.0001
	HbA1c	HbA1c≤7.5	103.33±38.82	67.81±28.73	0,004	77.00±30.17	69.19±23.08	0,280	0.040
		HbA1c>7.5	112.42±27.26	81.84±45.55	0,0001	81.34±20.73	84.31±31.62	0.273	0.0001
	BMI	BMI≤30	112.84±34.72	79.36±39.93	0.001	89.72±31.65	91.40±33.07	0.831	0.004
		BMI>30	109.07±28.84	77.97±43.58	0.0001	76.33±17.65	76.07±28.18	0.898	0.0001
GGT (U/L)	Fatty liver grades	Mild	41.54±16.15	27.04±11.37	0.0001	48.07±17.06	47.31±13.39	0.848	0.012
		Moderate	41.38±9.78	30.17±6.65	0.0001	41.47±7.15	38.40±6.47	0.199	0.016
		Severe	54.47±20.31	36.62±5.48	0.0001	53.82±9.37	48.62±9.62	0.0001	0.003
	NFS grades	Low	33.74±8.42	29.59±6.45	0.066	52.91±10.05	43.66±12.93	0.0001	0.117
		Intermediate	50.77±17.35	32.10±9.99	0.0001	43.67±13.85	45.05±10.18	0.537	0.0001
		High	48.80±17.44	33.20±4.02	0.179	46.05±8.61	46.50±3.71	0.801	0.061
	Gender	Male	48.00±13.13	30.65±8.28	0.0001	49.81±8.32	38.35±9.19	0.001	0.211
		Female	45.19±18.56	31.85±9.24	0.0001	46.77±14.12	47.37±10.60	0.684	0.0001
	HbA1c	HbA1c≤7.5	40.24±12.83	32.21±8.28	0,.35	41.53±14.66	43.43±13.37	0,671	0.087
		HbA1c>7.5	47.95±17.91	31.25±9.18	0.0001	49.73±11.34	45.00±10.14	0.001	0.0001
	BMI	BMI≤30	45.96±14.56	26.98±8.12	0.0001	52.92±11.56	42.20±14.53	0.001	0.063
		BMI>30	46.08±18.11	33.36±8.63	0.0001	45.53±12.55	45.62±9.05	0.958	0.0001

*Paired T-test.

*Significant if P-value < 0.05.

* Data are presented as; mean ± standard deviation.

*LFC= liver fat content, NFS= NAFLD fibrosis score, AST=serum aspartate transaminase, ALT=serum alanine transaminase, ALP= alkaline phosphatase, GGT= gamma glutamyl transferase, HbA1c=Glycosylated hemoglobin, BMI=body mass index.

* This cohort was classified according to BMI into; 25 patients with BMI ≤ 30kg/m2 (overweight) and 60 patients with BMI>30kg/m2 (obese) in both groups. According to NFS values into; low probability (35 patients in the control group and 23 patients in the PTX group), intermediate probability (42 patients in the control group and 57 patients in the PTX group), and high probability (eight patients in the control group and five patients in the PTX group) of fibrosis. According to HbA1c, 21 patients with HbA1c ≤ 7.5 and 64 patients with BMI>7.5 were in both groups.

Discussion

The rising prevalence of NAFLD, and the knowledge that medical treatment would be long-term, underlined the need for cost-effective treatment.[18] Currently, there is no approved treatment for NAFLD other than dietary modifications and regular exercise, which are frequently recommended but hard to accomplish.[19]

Previous studies have demonstrated the biochemical and histological improvements following the administration of PTX to subjects with NASH; however, we are the first study to assess the changes in LFC in T2DM subjects with NAFLD using the Dixon-based MRI-PDFF method in different disease conditions.

PTX and control groups achieved significant decreases in SBP with no effects on DBP. A previous study on diabetic subjects found that PTX 800mg daily significantly reduced SBP (P=0.001) and DBP (P= 0.001).[20]

We set a target value for glycemic parameters in all subjects based on the ADA 2021 guidelines (FG 80–130 mg/dL, 2-hrs PPG ≤ 200 mg/dL, and HbA1c≤ 7.5 %).[11] This glycemic equipoise was achieved by optimizing the sulfonylurea dose and requiring all subjects to adhere to the same diet and exercise regimen to minimize the effects of changes in glycemic parameters on liver steatosis. The further improvements in the glycemic profile seen in the PTX group were owing to the fact that PTX can improve insulin receptor signaling and sensitivity.[21]

The current study used the MRI-PDFF technique to estimate LFC, which is more sensitive than liver histology to detect LFC changes and treatment response in clinical trials.[16, 22]

There was a significant regression in liver steatosis on ultrasonography and MRI maps. PTX (800mg daily), when combined with sulfonylurea, significantly reduced LFC and improved glycemic parameters compared to the sulfonylurea alone**.** The declines in the control group can be judged clinically unacceptable based on the predefined value of –5% for the clinically relevant decrease in LFC. PTX reduced LFC in all liver segments, but the control group demonstrated significant reductions in segments III, VI, and VIII.

PTX effectively alleviated liver steatosis on histology, liver enzymes, insulin resistance, and triglycerides in an animal model of

combined T2DM and NAFLD.[9] Satapathy et al. reported that 55% of subjects administered PTX (800mg) achieved lower AST and ALT levels and improved hepatic steatosis on histology results.[23]

Obesity increases the risk of losing glycemic control and the progression of NAFLD to NASH. As a result, losing weight can improve glycemic control, lower cardiovascular risk, and alleviate liver steatosis. Moreover, a 5% reduction in BMI is associated with a 25% relative reduction in LFC. [24] The PTX group showed a significant 6.63 % reduction in weight and 6.44% in BMI.

Improvements in BMI and weight are linked to a regression in NAFLD grading, which is evident from changes in triglyceride metabolism and insulin resistance. [25] However, unlike the control group, we found no correlation between LFC reduction and changes in weight, waist-to-hip ratio, and BMI in the PTX group. As a result, weight loss and the improvements in abdominal obesity in the PTX group had a minor impact on LFC changes.

The findings of this study are consistent with previous trials. Earlier studies suggested that PTX improves plasma TNF-α and IL-6, ALT, and AST levels and improves NAFLD activity score (NAS) and fibrosis score in NASH subjects.[10&26] CIOBOATĂ et al. reported that PTX revealed significant improvements in NAS scores, especially necroinflammation. Also, there was a significant reduction in liver enzymes, ALP, and GGT.[21]

A meta-analysis published in 2014 emphasized the beneficial effects of PTX on body weight, serum glucose, liver enzymes, serum TNF-α, NAS scores, and lobular inflammation in NAFLD subjects.[10] Another research reported significant liver enzyme reduction and steatosis regression on ultrasound imaging.[27] This study agreed with previous studies, as PTX demonstrated improvements in serum liver enzymes, GGT, and ALP.

Liver fibrosis is a marker of NAFLD progression. NFS is among the most widely recommended tests to identify advanced fibrosis (F3-F4) and rule out significant fibrosis in subjects with NAFLD.[28–30] PTX therapy showed a significant reduction in the risk of developing advanced fibrosis compared to the control group.

Despite finding a correlation between LFC reduction and improvements in fasting, 2-hrs PPG, and HbA1c, the changes in LFC in the PTX group were higher than in the control group.

According to Zein et al., the changes in the fatty liver with PTX treatment were unrelated to the improvements in insulin resistance.[18] The current study approves the previous result.

This study reported significant reductions in triglycerides, total cholesterol, and LDL with PTX therapy, while other researchers reported that PTX did not affect serum LDL and triglyceride levels.[10&21]

The results of the subgroup analysis highlighted the effectiveness of PTX in different disease stages. In the PTX group, severe NAFL had the greatest LFC (%) changes, followed by moderate and mild NAFL. Also, The PTX group exhibited a similar regression in the fibrosis probability in different NAFL grades. In all NAFL grades, PTX was more beneficial than the control group in reducing LFC (%), NFS score, GGT, and ALP. In mild NAFL, PTX had significantly more ALT reductions ($P< 0.0001$) and statistically insignificant AST lowering effects ($P=0.069$) than the control group. However, in moderate NAFL patients, PTX showed higher AST ($P< 0.0001$) and ALT reductions ($P< 0.0001$) than the control group, while in severe NAFL patients, PTX exhibited significantly higher AST reductions ($P< 0.0001$) and insignificantly higher ALT reductions ($P= 0.091$) than the control group.

By classifying patients according to fibrosis score, the control group failed to decrease LFC in patients with high NFS scores but successfully reduced fibrosis probability in intermediate and low NFS scores. The control group only showed significant regression in fibrosis probability in patients with intermediate NFS scores. The PTX group showed a comparable decrease in LFC in all patients with different NFS scores. PTX failed to improve fibrosis probability in patients with low NFS scores; however, it showed equal efficacy in patients with intermediate and high NFS scores. Based on gender, PTX showed no difference between males and females in alleviating liver steatosis indices (LFC, NFS, and liver function tests).

In Obese patients, PTX had comparable LFC (%), NFS score, AST, and ALT reductions compared to overweight patients. Patients with uncontrolled diabetes in terms of; HbA1c values > 7.5% at baseline showed similar NFS

score regression and higher LFC (%) and ALT reductions than patients with HbA1c ≤ 7.5%.

Despite the encouraging results observed in our study regarding the effects of PTX on liver steatosis, we acknowledge some limitations. We did not use a placebo in the control group because this study was performed in a real-world setting, and the subjects had already received standard T2DM care. We could not include a liver biopsy due to the low acceptance rate in subjects with simple steatosis and the procedure's invasiveness. Moreover, a liver biopsy could have several limitations, like interobserver variability and sampling errors.[19] Although all medications impacting liver fat were omitted, potential drug interactions for co-prescribed drugs on NAFLD cannot be ruled out.

Conclusion

T2D patients with NAFLD who received PTX had lower LFC and fibrosis scores and improved glycemic, weight, and lipid profiles than the control group. PTX showed good efficacy and safety profiles in patients with different fatty liver grades and fibrosis scores. PTX remains effective in reducing LFC and fibrosis scores similarly in both genders, obese and overweight patients, and in varied HbA1c levels.

Acknowledgment

The authors acknowledge internal medicine department members for their support.

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Bull. Pharm. Sci., Assiut University, Vol. 46, Issue 1, 2023, pp. 361-378.

نشرة العلوم الصيدلية
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BULL. PHARM. SCI. Assiut Univ.

تقييم تأثيرات البنتوكسيفيلين على تنكس الكبد الدهنى باستخدام تقنية التصوير بالرنين المغناطيسي القائمة على ديكسون. دراسة معشاة ذات شواهد

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الخلفية: أثبت البنتوكسيفيلين أنه يقلل من الدهون الكبدية في الحيوانات. ومع ذلك ، فإن البيانات المتعلقة بفعاليته وسلامته على مرضى السكري من النوع الثاني الذين يعانون من مرض الكبد الدهني غير الكحولي نادرة.

الهدف: تحديد آثار إضافة البنتوكسيفيللين مع السلفونيل يوريا في تقليل محتوى الدهون الكبدية في مرضى داء السكري من النوع الثاني الذين يعانون من مرض الكبد الدهني في مختلف المستويات المرضية.

الطرق: تم اختيار ١٨٧ مريض داء سكري من النوع الثاني مصابا بمرض الكبد الدهني وتوزيعهم عشوائيا لتلقي إما البنتوكسيفللين أقراص ٨٠٠ ملجم (مجموعة PTX) أو أدوية داء السكري فقط (المجموعة الضابطة) لمدة ٢٤ أسبوعا. تضمنت النتائج الأولية للدراسة تغيرات في نسبة الدهون الكبدية كما تم قياسها بواسطة التصوير بالرنين المغناطيسي المشتق من تقنية فصل الدهون بكثافة البروتون (MRI-PDFF) ومؤشر لقياس درجة التليف بالكبد (NFS).

النتائج: أخفض البنتوكسيفللين نسبة الدهون الكبدية أكثر من المجموعة الضابطة احصائيا (−٨,١٨ مقابل −١,٨٧؛ P<٠,٠٠٠١). أظهرت مجموعة البنتوكسيفللين فقط تراجعا كبيرا إحصائيا في مؤشر التليف الكبدي (−١,١٦؛ P<٠,٠٠٠١). كما أظهرت مجموعة البنتوكسيفللين تغيرات كبيرة إحصائيا في نسبة الدهون الكبدية في الفص الثاني والرابع والسادس ؛ بينما، في المجموعة الضابطة، ظهرت انخفاضات كبيرة إحصائيا في الفص الثالث والسادس فقط. وفي تحليل المجموعات الفرعية ، أظهر

البنتوكسيفيللين فعالية مماثلة في خفض نسبة الدهون الكبدية في ذوي درجات مؤشر التليف الكبدي المختلفة ، والاناث والذكور ، وفئات مؤشر كتلة الجسم. ومع ذلك ، فإن مرضي الكبد الدهني الشديد أو المرضي المصابون بمستويات سكر تراكمي عالية اظهروا انخفاضا كبيرا احصائيا أكثر من ذوي درجات الكبد الدهني والسكر التراكمي الاخري.

الاستنتاج: حافظ البنتوكسيفللين على فعاليته في خفض نسبة الدهون الكبدية LFC في جميع درجات الكبد الدهني، ودرجات التليف ، ومؤشر كتلة الجسم ، وحالات مؤشر السكر التراكمي المختلفة ، مقارنة بالمجموعة الضابطة.