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Serum Pentraxin 3 level in Egyptian patients with nonalcoholic fatty liver disease and type 2 diabetes

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Abstract: Background: Nonalcoholic fatty liver disease (NAFLD) is one of the common chronic liver disease causes. For NAFLD detection, liver biopsy is the definitive method, but it has significant restrictions. Pentraxin 3 (PTX3) is an acute phase reactant, and its increased plasma levels are considered indicative of NAFLD. Additionally, individuals with type 2 diabetes mellitus (T2DM) were found to have increased PTX3 serum levels compared to healthy controls. Given that T2DM is a major health concern in Egypt, we intended to investigate the serum PTX3 application as a NAFLD non-invasive diagnostic in T2DM individuals. Methods: A total of 96 participants were evenly distributed into three groups: those with NAFLD and T2DM, those with T2DM but without NAFLD, and a group of healthy controls. Assessments included medical history, clinical exams, lab tests (complete blood count, blood sugar, ALT, AST, creatinine, lipid profile, and PTX3), and imaging (ultrasound and FibroScan). NAFLD diagnosis uses clinical and imaging criteria, with liver biopsies for unclear cases. Results: Among diabetic patients, those with NAFLD had significantly higher PTX3 levels. At a cut-off value of more than 2.3 ng/mL, PTX3 has a positive predictive value of 93.3%, a sensitivity of 87.5%, a specificity of 93.75%, and a negative predictive value of 88.2%, with an accuracy of 87.8%. Conclusion: PTX3 levels were higher in diabetic NAFLD individuals compared to both diabetic ones without NAFLD and healthy controls. Thus, PTX3 is a biomarker for NAFLD with high sensitivity and specificity when suspected in T2DM patients.

Keywords: Noninvasive NAFLD diagnosis, Pentraxin, NAFLD, Diabetes mellitus, MAFLD.

Introduction

NAFLD is the ectopic fat deposit in the liver when there are no other reasons for secondary liver fat infiltration, such as excess alcohol usage, certain medications, and infections. [1] Large-scale population studies have shown that, despite considerable phenotypic variation, most conditions currently diagnosed as NAFLD are associated with metabolic risk factors, including one or more of obesity, insulin resistance (IR), or evidence of metabolic dysregulation. As a result, it has lately been described as metabolic dysfunction-associated fatty liver disease. [2]

NAFLD is closely linked with metabolic syndrome and type 2 diabetes mellitus (T2DM), with studies indicating that up to 70% of T2DM individuals develop NAFLD. [3] With the elevated metabolic and obesity syndrome incidence, NAFLD promptly is becoming the most prevalent hepatic disease globally, and the worldwide incidence in the general population is thought to be about 30%. [4]

Liver biopsy is the conventional gold standard for NAFLD staging and diagnosis. [5] Though, because of its limitations, such as pain, sampling inaccuracy, cost, and patient refusal to undergo invasive tests, [6] the importance of using simple noninvasive diagnostic and prognostic biomarkers has emerged. [7]

The pentraxin superfamily includes pentraxin 3 (PTX3), which is involved in innate immunity and acute and chronic inflammation. Both structurally and functionally, PTX3 is analogous to C-reactive protein. [8] Although hepatocytes do not express PTX3, hepatic progenitor cells from the livers of individuals undergoing fractional hepatectomy show PTX3 expression levels twenty times higher than those of essential hepatocytes, suggesting that PTX3 is produced by various cells within the liver tissue. [9] Pro-inflammatory signals for example; lipopolysaccharides and tumor necrosis factor-alpha are key mediators in the NAFLD pathogenesis and also stimulate PTX3 synthesis. [10] As a result, elevated liver PTX3 may serve as a probable biomarker for local inflammation and significant hepatic histological damage. [11] Considering NAFLD is a chronic inflammatory disorder, plasma PTX3 levels may be used as a disease marker. [12]

According to growing data, inflammatory pathways contribute to the pathogenesis linking obesity with metabolic syndrome and IR. [13] In addition, patients with T2DM showed higher serum PTX3 levels than those with normal levels of blood glucose, implying that PTX3 could have a role in obesity and metabolic syndrome. [14]

Considering the global burden of both NAFLD and T2DM, the study aimed to detect serum PTX3 utility as a non-invasive biomarker for NAFLD in both non-diabetic and diabetic populations.

Materials and Methods

This study included a prospective cohort of T2DM cases, both with and without NAFLD, and also involved a cross-sectional comparison with a healthy control group. The study included 96 male and female participants, aged 25 to 55, who attended the GIT and liver university clinics from June 2021 to

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June 2022. Evaluations of the participants included medical history, clinical exams, lab tests, and imaging. All cases submitted written informed consent before their inclusion in the study. To ensure balanced group sizes and enable meaningful comparisons, participants were evenly divided into three groups: (1) 32 individuals with NAFLD and T2DM, (2) 32 individuals with T2DM but without NAFLD, and (3) 32 healthy individuals without T2DM or NAFLD and with normal liver enzyme levels. This grouping strategy helped reduce variability and enhance the statistical power of group-wise analyses.

The exclusion criteria were if the participants had a history of alcohol use, were taking steatogenic medications (such as valproate, doxycycline, or tetracycline), had decompensated liver disease, or were using medications that affect serum PTX3 levels, like statins. Additionally, patients with conditions known to elevate plasma PTX3 levels—such as heart failure, asthma, life-threatening illnesses, vasculitis, autoimmune rheumatic diseases, or any inflammatory or infectious disorders—were also excluded.

Control Group Selection:

The control group consisted of age- and sex-matched individuals without a history of NAFLD or T2DM. They were enrolled from the same hospital throughout the same study time and were screened to meet the same general inclusion and exclusion criteria, except for the NAFLD or T2DM.

Data Collection and Measurements:

Data were collected using standardized forms by trained personnel to ensure consistency. Medication utilization, physical activity levels, medical history, dietary habits, laboratory values, and imaging results were reviewed and recorded. While we attempted to control for major confounders, residual confounding cannot be entirely excluded. In cases of missing or unclear information, participants were contacted for clarification or follow-up during subsequent clinic visits. If critical data could not be retrieved, those cases were omitted from the final analysis to ensure consistency and data integrity.

All individuals underwent a comprehensive assessment, including anthropometric measurements, a detailed medical history, and a clinical examination. While wearing light clothing and no shoes, weight and height were measured, and waist circumference was assessed using standardized procedures. Laboratory tests included blood sugar levels, a complete blood count, ALT, AST, serum creatinine, lipid profile, viral markers (HBsAg, anti-HCV Ab), and serum PTX3 levels.

NAFLD patients were diagnosed through a combination of personal history, physical examination, abdominal ultrasonography, and FibroScan with a controlled attenuation parameter (CAP). A liver biopsy was conducted when the diagnosis was unclear.

For every participant, one expert operator performed transient elastography (FibroScan) with CAPs to assess liver status, and patients with hepatic steatosis were categorized into three grades based on the steatosis degree. [15] Further assessment of liver condition was performed using the TOSHIBA SSA-700A (Aplio 5) ultrasound device.

US-guided liver biopsies were done utilizing a 16-gauge Hepafix needle. An experienced hepatopathologist who was not aware of the participants' details assessed biopsy specimens for inflammation, ballooning, and steatosis. [16]

Along with the diagnostic guidelines established by the American Diabetes Association T2DM was detected based on one or more of the subsequent criteria: a fasting plasma glucose (FPG) level of ≥126 mg/dL, a 2-hour plasma glucose level of ≥200 mg/dL through an oral glucose tolerance test (OGTT) utilizing a 75-gram anhydrous glucose solution, or a glycated hemoglobin (HbA1c) value of ≥6.5%. [17] Every diabetes patient was diagnosed after the age of 25, and they are all receiving solely oral medication.

All blood samples for measuring PTX3 were collected from the antecubital vein. The blood was emptied into a tube containing ethylene diamine tetraacetate, and the samples were centrifuged for 15 minutes at 1000g. Plasma was promptly separated and stored at –80°C until further analysis. Plasma PTX3 concentrations were calculated using the Human Pentraxin ELISA Kit (Aviscera Bioscience Inc.), which utilizes a quantitative sandwich enzyme-linked immunosorbent assay (ELISA) technique. The variation intra-assay coefficient ranged from 4% to 6%, while the variation inter-assay coefficient ranged from 8% to 10%. The PTX3 lowest detected quantity was 0.02 ng/ml.

Sample Size Calculation:

A sample size of 32 participants per group aligns with that of comparable observational studies and satisfies the minimum threshold needed to distinguish medium effect sizes (Cohen's d ≈ 0.5) with 80% statistical power at a significance level of 0.05, particularly when employing ANOVA or t-test analyses. Additionally, the one-year recruitment period was sufficient to enroll a representative and homogeneous sample from the target population while ensuring feasibility with respect to available resources and clinic patient throughput.

Statistical analysis:

All data was collected, processed, and analyzed with the Statistical Package for Social Sciences (SPSS) version 25. In order to ascertain the normality of the data distribution, the Shapiro-Wilk test was implemented.

We employed parametric statistical methods, such as the one-way analysis of variance (ANOVA) and the independent samples t-test, to analyze continuous variables that exhibited a normal distribution. Non-parametric test alternatives, for example; the Kruskal-Wallis test and Mann-Whitney U test, were implemented for variables that failed to satisfy the assumption of normality. Categorical variables were summarized using frequencies (counts) and relative frequencies (percentages). Diagnostic performance measures—involving specificity, sensitivity, negative predictive value (NPV), positive predictive value (PPV), and overall diagnostic accuracy—were calculated following the method described by Galen. [18] Comparisons between categorical variables were performed using the Chi-square (χ^2) test. When predicted cell counts were less than five, the exact test was utilized instead. A p-value of <0.05 was judged statistically significant. [19]

Results

The study consisted of 96 participants divided into three equal groups, matched for age and gender.

- **Group 1** (patients with T2DM and NAFLD) consisted of individuals aged 30 to 55 years (mean age 46 ± 6), with 62.5% males and 37.5% females.

- **Group 2** (patients with T2DM without NAFLD) included individuals aged 30 to 55 years (mean age 45 ± 9), comprising 59% males and 41% females.
- **Group 3** (control group) consisted of participants aged 25 to 55 years (mean age 43 ± 8), with 59% males and 41% females.

Our results demonstrated a significant rise in PTX3 levels in T2DM and NAFLD cases as compared to diabetic individuals not having NAFLD and controls (Table 1 and Figure 1). Our study indicated no correlation between serum PTX3 levels and the steatosis degree in NAFLD patients (Table 2). However, between PTX3 levels and LDL, triglycerides, and ALT, a significant positive correlation was found. The study also discovered a considerable negative relation between PTX3 and HDL. No other laboratory or clinical factors demonstrated a significant connection with PTX3 (Table 3). Our findings revealed no association between gender distribution in the studied groups and PTX3 levels (Table 4).

In the receiver operating curve (ROC) analysis between T2DM with NAFLD and controls, PTX3 at the cut-off value above 2.05 ng/mL established a sensitivity of 87.5%, a PPV of 96.6%, a specificity of 96.8%, and an NPV of 88.6% with an accuracy of 92.9%. When comparing T2DM patients with and without NAFLD, a PTX3 cut-off above 2.3 ng/mL predicted NAFLD with 88.2% as NPV, PPV of 93.3%, 87.5% as sensitivity, 93.7% as specificity, and an accuracy of 87.8% (Table 5; Figures 2 & 3).

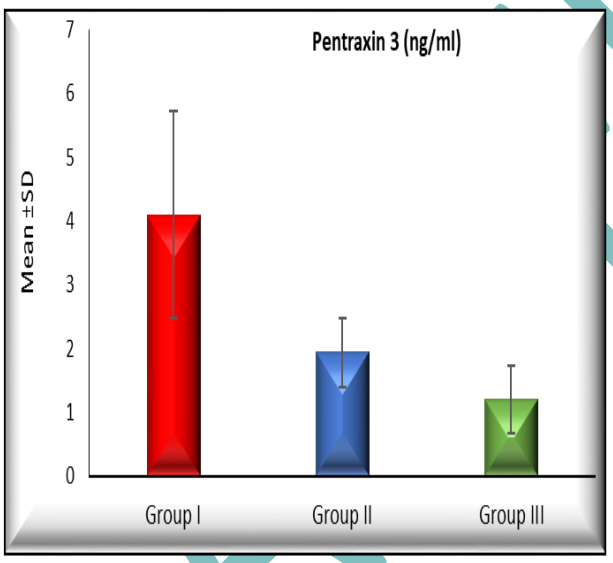

Figure (1): Serum Pentraxin 3 (PTX3) levels (ng/mL) in the study groups.The figure illustrates the mean ± standard deviation of serum PTX3 levels in three groups: Group I (red bar) represents patients with both NAFLD and T2DM; Group II (blue bar) includes patients with T2DM only; and Group III (green bar) represents healthy control participants. Group I exhibited substantially higher serum PTX3 levels than Groups II and III. One-way ANOVA was implemented to detect statistical significance, which was then subsequently post-hoc analysis (TUKEY'S test).

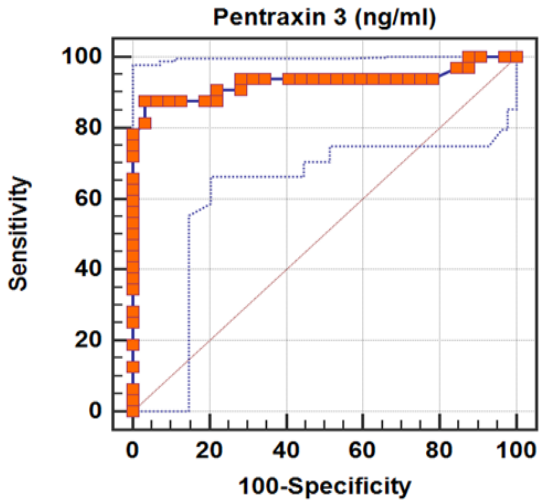

Figure (2): ROC curve analysis of serum (PTX3) levels (ng/mL) for distinguishing patients with NAFLD. The y-axis represents sensitivity, while the x-axis shows 100–specificity. The orange squares denote observed data points. The solid ROC curve demonstrates high diagnostic accuracy, with the area under the curve (AUC) demonstrating strong discriminative capability. The dotted blue lines represent the 95% confidence interval of the ROC curve. The diagonal red line represents the line of no discrimination. This analysis shows that PTX3 at the cutoff value > 2.05 ng/mL (that predicts NAFLD patients) shows 87.5% as sensitivity, specificity of 96.87%, PPV of 96.6%, and NPV of 88.6% with an accuracy of 92.9%.

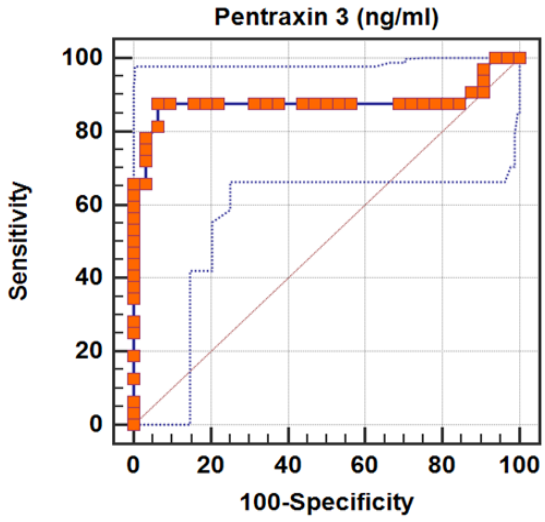

Figure (3): The ROC curve illustrates the diagnostic performance of serum PTX3 (ng/mL) levels in identifying NAFLD patients in T2DM cases. The y-axis represents sensitivity, while the x-axis shows 100–specificity. The orange squares denote observed data points. The solid ROC curve demonstrates high diagnostic accuracy, with the area under the curve (AUC) demonstrating strong discriminative ability. The dotted blue lines represent the 95% confidence interval of the ROC curve. The diagonal red line represents the line of no discrimination. This analysis show that PTX3 level at the cutoff value >2.3 ng/mL shows a sensitivity of 87.5%, PPV of 93.3%, specificity of 93.75%, and NPV of 88.2% with an accuracy 87.8% to predict NAFLD in T2DM patients

Table (1): Comparison of the examined groups for serum Pentraxin 3

Pentraxin 3 (ng/ml)	Groups			ANOVA	
	T2DM with NAFLD (Group I)	T2DM without NAFLD (Group II)	Controls (Group III)	F	P-value
Range	0.7 - 6.6	0.54 - 3.7	0.5 - 2.5	67.381	<0.001*
Mean ±SD	4.092 ± 1.625	1.934 ± 0.550	1.202 ± 0.525		
	TUKEY'S Test				
	I&II	I&III	II&III		
Pentraxin 3	<0.001*	<0.001*	0.016*		

(SD, standard deviation) *P < 0.05 was considered statistically significant.

Table (2): Comparison between different steatosis grade groups regarding Pentraxin 3 in NAFLD patients (group 1)

		Pentraxin 3				ANOVA	
		N	Mean	±	SD	F	P-value
FibroScan Steatosis Grade Grade 1: Mild steatosis	G1	8	3.955	±	1.551	3.603	0.148
Grade 2: Moderate steatosis Grade 3: Severe steatosis	G2	12	3.334	±	1.978		
	G3	12	4.691	±	1.345		

(G, Grade)

Table (3): Correlation of Pentraxin 3 to investigations.

Correlations	Pentraxin 3	
	R	P-value
Age	0.160	0.205
BMI (kg/m²)	0.147	0.246
Waist circumference	0.048	0.705
Total Leucocyte Count	0.080	0.529
Hemoglobin	-0.015	0.909
Platelets	-0.058	0.651
Random blood sugar	0.030	0.816
Fasting blood sugar	0.212	0.092
HbA1c	0.003	0.979
Cholesterol	0.247	0.052
HDL	-0.352	0.004*
LDL	0.353	0.004*
Triglycerides	0.254	0.043*
PT	0.014	0.912
INR	0.003	0.979
Albumin	0.085	0.506
AST	0.021	0.869
ALT	0.278	0.026*
GGT	0.269	0.053
T. Bilirubin	0.160	0.206
D. Bilirubin	0.233	0.063
Creatinine	0.100	0.430

(BMI, Body mass index; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; GGT, Gamma-glutamyl transferase; HDL, High-density lipoprotein; LDL, Low-density lipoprotein)

Table (4): Correlation of Pentraxin 3 according to gender

Groups	Sex	Pentraxin 3 (ng/ml)				T-Test	
		N	Mean	±	SD	t	P-value
T2DM with NAFLD (Group I)	Male	20	4.100	±	1.669	0.035	0.973
	Female	12	4.079	±	1.622		
T2DM without NAFLD (Group II)	Male	19	1.871	±	0.462	-0.786	0.438
	Female	13	2.027	±	0.667		
Controls	Male	19	1.314	±	0.464	0.004	0.996
	Female	13	1.012	±	0.588		

Table (5): Diagnostic performance of Pentraxin 3 in differentiation of patients with NAFLD and without NAFLD

ROC curve between T2DM and NAFLD and T2DM without NAFLD (predict NAFLD in DM patients)						
	Cutoff	Sensitivity	Specificity	PPV	NPV	Accuracy
Pentraxin 3 (ng/ml)	>2.3	87.50	93.75	93.3	88.2	87.8%
ROC curve between T2DM and NAFLD and controls (predict NAFLD patients in healthy individuals)						
	Cutoff	Sensitivity	Specificity	PPV	NPV	Accuracy
Pentraxin 3 (ng/ml)	>2.05	87.50	96.87	96.6	88.6	92.9%

(ROC, Receiver operating characteristic; PPV, positive predictive value; NPV, negative predictive value)

Discussion

Globally, NAFLD is the most prevalent chronic liver disease cause, and its prevalence is elevating at a rate that is comparable to that of obesity. [20] NAFLD is significantly linked to metabolic syndrome and T2DM. [4] The gold standard for diagnosing NAFLD is a liver biopsy. [5] Nonetheless, liver biopsies have serious limits. [6] PTX3 is an acute-phase reactant that plays a crucial role in innate immunity. [8] High plasma PTX3 is regarded as a sign of NAFLD. [12] In addition, T2DM cases had higher PTX3 serum levels than individuals with normal blood sugar. [14]

The study indicated that diabetics with NAFLD had significantly higher PTX3 levels in comparison to diabetics without NAFLD and healthy controls (4.1 ± 1.62 vs. 1.93± 0.55 vs. 1.2 ± 0.52 ng/mL, P < 0.001), and this was consistent with *Boga et al*. (2015), who reported that NAFLD patients had greater PTX3 levels than controls (4.1 ± 2.3 vs. 1.3 ± 0.8 ng/mL, P < 0.001), [12] and in agreement with *Trojak et al.* (2019), who reported the median PTX3 level was 4.26 ng/ml in diabetic patients with NAFLD and 3.77 ng/ml in diabetic cases without NAFLD (P = 0.93). [21] Also, PTX3 levels were higher in diabetic cases without NAFLD than in healthy participants (1.93 ± 0.55 vs. 1.2 ± 0.52 ng/mL, *P* = 0.016), and this was comparable to *Karamfilova et al. (2022),* who reported greater serum PTX3 levels in T2DM patients contrasted with those with normal blood sugar (2.32 ± 0.93 vs. 1.88 ± 0.90 ng/mL, *P* = 0.028). [14]

In this study there were significantly elevated PTX3 levels in NAFLD patients, but we could not establish a definitive relationship between PTX3 and disease severity, including steatosis grade, which is consistent with Maleki et al. (2014), who evaluated PTX3 in 32 biopsy-confirmed NAFLD patients and 34 controls. They found that PTX3 was ineffective in discriminating different degrees of NAFLD. [22] Future research should incorporate exploring the PTX3 potential as a disease progression marker.

Our findings indicated a substantial positive relationship between PTX3 and LDL, triglycerides, and ALT (P = 0.004, 0.043, and 0.026), but a significant negative correlation with HDL (P = 0.004). Nevertheless, no obvious relationship was found between Pentraxin3 and the other laboratory. *Hussein et al.* (2022) detected a positive correlation between PTX3 levels and weight, body mass index, waist circumference, total bilirubin, GGT, ALT, AST, cholesterol, triglycerides, and LDL (P < 0.001). [23] *Albitar et al.* (2019) found no link between PTX3 and many indicators in NAFLD patients, including anthropometric measurements. [24] Our findings indicated that gender distribution within the studied groups did not influence PTX3 levels, as there were no significant differences in PTX3 concentrations between males and females. This conclusion is consistent with the results of *Albitar et al.* (2019), who also found no notable difference in PTX3 levels between male and female participants in the NAFLD group. [24]

As a method of diagnosis for NAFLD in diabetics, ROC curve analysis revealed that a cut-off value above 2.3 ng/mL had 87.5% sensitivity, 93.75% specificity, 93.3% positive predictive value, and 88.2% NPV, with an accuracy of 87.8%. The ROC curve analysis of PTX3 between patients with NAFLD and T2DM and controls revealed that the cut-off value over 2.05 ng/mL (which predicts NAFLD patients) has a NPV of 88.6%, PPV of 96.6%, sensitivity of 87.5%, specificity of 96.87%, and accuracy of 92.9%. These results align with those reported by *Boga et al.* (2015), who showed that the best cutoff value for the NAFLD diagnosis was 2.45 ng/mL with a specificity of 71.4%, PPV of 76.1%, sensitivity of 91.1%, and NPV of 88.9%, and at the cutoff value of 3.43 ng/mL, the level of specificity was 95% and sensitivity was 68%. [12]

Compared to existing non-invasive markers like the NAFLD Fibrosis Score (NFS) and FIB-4, PTX3 may provide additional insight into the screening method for identifying NAFLD. For FIB-4, a threshold of 1.45 yields a sensitivity of approximately 90% but with a specificity of 35%. At a higher threshold of 2.67, specificity increases to 90%, while sensitivity drops to roughly 52%. [25] The NAFLD Fibrosis Score, using a cutoff of -1.45, demonstrates a specificity of 55% and a sensitivity of 70% for detecting advanced fibrosis. [26]

However, while PTX3 appears to be a promising biomarker, its clinical utility has yet to be firmly established. Given the strong validation and widespread acceptance of markers like FIB-4 and NFS, PTX3 should be considered a secondary marker for now. Further large-scale, prospective investigations are needed to confirm its diagnostic and prognostic value. A limitation of our study is the potential impact of unmeasured or uncontrolled factors, such as differences in medications, diet, and physical activity, that may influence serum PTX3 levels. Furthermore, our study's focus on Egyptian patients may limit its generalizability, as PTX3 levels may be influenced by genetic, environmental, and inflammatory differences across ethnic groups. Further research involving broader and more ethnically diverse populations is necessary to confirm and extend these findings.

Conclusion

The study indicates that plasma PTX3 could be applied as a sensitive and specific screening method for identifying NAFLD in diabetic patients, particularly with the use of a higher cutoff value than in healthy individuals. Given the study's limitations, further research involving larger, more diverse populations and longitudinal studies in varied clinical settings is needed to clarify PTX3's role in NAFLD progression and its probability as a predictive biomarker before considering it for routine screening, both in diabetic and non-diabetic individuals. These studies should ideally include repeated measurements of PTX3 over time and assess its relationship with clinical outcomes such as fibrosis progression and liver-related complications.

Disclosure Statements

Ethics approval and consent to participate

The Research Ethics Committee of the Faculty of medicine, Ain Shams University approved the study (FWA 000017585) in June 2021. All patients enrolled for the validation of this study gave a written informed consent.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author's contribution

The authors confirm contribution to the paper as follows: Ahmed Ibrahim Elshafie: research plan development. HossamEldin Abdel Aziz: supervision of case collection, review of research results, and participation in manuscript writing. Tari George Michael: collection of scientific material, data recording and analysis, and contribution to manuscript writing. Mostafa Attya ElFors: collection of scientific material and data recording and analysis. Ahmed Mohamed Mahmoud: collection of scientific material, data analysis, manuscript writing, and preparation, submission, and follow-up of the publication process. Mohamed Nabil Badawy: case collection, collection of scientific material, data recording and analysis, and contribution to manuscript writing. All authors reviewed the results and approved the final version of the manuscript.

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Conflicts of interest

The authors declare that there is no conflict of interest regarding the publication of this article

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