

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

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ABSTRACT

INTRODUCTION: Nonalcoholic fatty liver disease (NAFLD) is a prevalent cause of chronic liver impairment and is significantly correlated with type 2 diabetes mellitus (T2DM). A liver biopsy is the definitive method for diagnosing NAFLD, but it has substantial restrictions. Pentraxin 3 (PTX3) is an acute phase reactant, and elevated plasma PTX3 levels are considered a sign of NAFLD. Furthermore, T2DM patients exhibited higher Pentraxin 3 serum levels than healthy people. Given that T2DM is a major health concern in Egypt, we intended to investigate the utility of serum Pentraxin 3 as a non-invasive diagnostic of NAFLD in T2DM patients.

METHODS: Ninety-six subjects were divided into three equal groups: T2DM with NAFLD, T2DM without NAFLD, and healthy controls. Evaluations included medical history, clinical exams, lab tests (CBC, blood sugar, ALT, AST, creatinine, lipid profile, and Pentraxin), and imaging (ultrasound and Fibroscan). NAFLD diagnosis uses clinical and imaging criteria, with biopsies for unclear cases.

RESULTS: When comparing diabetic patients with NAFLD to people with diabetes without NAFLD, at a cut-off value of more than 2.3 ng/mL, Pentraxin 3 has a sensitivity of 87.5%, specificity of 93.75%, positive predictive value of 93.3%, and negative predictive value of 88.2%, with an accuracy of 87.8%.

CONCLUSION: This study revealed increased PTX3 levels in diabetic patients with NAFLD compared to people with diabetes without NAFLD and controls. Thus, we showed that Pentraxin 3 is a biomarker for NAFLD with high sensitivity and specificity when suspected in T2DM patients.

Keywords: Pentraxin, NAFLD, Diabetes mellitus, MAFLD, biomarker, liver disease

INTRODUCTION

NAFLD is known as hepatic steatosis, or the ectopic deposit of fat 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 the presence of one or more of obesity, insulin resistance, or evidence of metabolic dysregulation. As a result, it has recently been referred to as metabolic dysfunction-associated fatty liver disease (MAFLD) [2].

NAFLD is closely associated with type 2 diabetes

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Received: 14th February 2025; **Initial decision given:** 21st February 2025; **Revised manuscript received:** 20th April 2025; **Accepted:** 11th September 2025.

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Citation for this article: A. I. Elshafie; H. E. Abdel Aziz; T. G. Michael et al. Serum Pentraxin 3 level in Egyptian patients with nonalcoholic fatty liver disease and type 2 diabetes. Rwanda Medical Journal, Vol. 82, no. 3, p. 36-43, 2025. <https://dx.doi.org/10.4314/rmj.v82i3.4>

mellitus and metabolic syndrome, with studies indicating that up to 70% of individuals with T2DM have NAFLD [3]. With the increased incidence of obesity and metabolic syndrome, NAFLD is rapidly becoming the most prevalent liver disease globally, and the worldwide incidence in the general population is thought to be about 30% [4].

A liver biopsy is the traditional gold standard for diagnosing and staging NAFLD [5]. However, due to the limitations of liver biopsies, 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].

Pentraxin 3 is an acute phase reactant and an important part of innate immunity. PTX3 exhibits structural and functional similarities with C-reactive protein [8]. Although hepatocytes do not express PTX3, hepatic progenitor cells obtained from the livers of human individuals undergoing fractional hepatectomy express Pentraxin 3 at levels twenty times greater than essential hepatocytes, indicating that PTX3 is produced by many cells in the liver tissue [9]. Thus, increased liver PTX3 is a possible biomarker of initial local inflammation and severe histological hepatic destruction [10]. Because NAFLD is a chronic inflammatory condition, plasma PTX3 levels could serve as a marker for the disease [11].

According to growing data, inflammatory pathways play a role in the pathogenesis linking obesity with insulin resistance and metabolic syndrome [12]. In addition, patients with type 2 diabetes 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 [13].

We sought to evaluate the value of blood Pentraxin 3 levels as a non-invasive biomarker of NAFLD in patients with type II DM as in non-diabetics, given both NAFLD and type 2 diabetes are serious health issues around the world.

METHODS

Study design and participants

This study included a prospective cohort of T2DM patients, both with and without NAFLD, and also involved a cross-sectional comparison with a healthy control group. The study included 96 participants, aged 25 to 55, who attended the GIT and liver university clinics from June 2021 to June 2022. Evaluations of the participants included

medical history, clinical exams, lab tests, and imaging. All participants provided written informed consent prior to enrollment. To ensure balanced group sizes and enable meaningful comparisons, participants were evenly divided into three groups: (1) 32 individuals with T2DM and NAFLD, (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.

Participants were excluded from the study if they 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.

The control group consisted of age- and sex-matched individuals without a history of nonalcoholic fatty liver disease or type 2 diabetes. They were recruited from the same hospital during the same study period and were screened to meet the same general inclusion and exclusion criteria, except for the presence of NAFLD or T2DM.

Data collection

Data were collected using standardized forms by trained personnel to ensure consistency. Medical history, medication use, dietary habits, physical activity levels, 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 essential data could not be obtained, those cases were excluded from the final analysis to maintain consistency and data integrity.

Participants' and laboratory examination

All participants underwent a comprehensive assessment, including a detailed medical history, clinical examination, and anthropometric measurements. Weight and height were measured with participants wearing light clothing and no shoes, and waist circumference was assessed using standardized procedures. Body mass index

(BMI) was calculated as weight divided by the square of height (kg/m^2). Laboratory tests included a complete blood count (CBC), blood sugar levels, ALT, AST, serum creatinine, lipid profile, and viral markers (HBsAg, anti-HCV Ab), which were analyzed using an enzyme immunoassay (EIA) kit (Abbott, Axyam, USA). Serum Pentraxin 3 levels were assessed from a venous blood sample.

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 performed if the diagnosis was uncertain.

For every participant, one expert operator performed transient elastography (Fibroscan) with controlled attenuation parameters to assess liver status, and patients with hepatic steatosis were categorized into three grades based on the steatosis degree [14]. The liver status was further assessed using TOSHIBA SSA-700A (Apilo 5) ultrasound.

US-guided liver biopsies were performed using a 16-gauge Hepafix needle. An experienced hepatopathologist who was not aware of the subjects' details assessed biopsy specimens for steatosis, inflammation, and ballooning [15].

A diagnosis of type 2 diabetes mellitus was made based on the American Diabetes Association's diagnostic criteria, which include a fasting plasma glucose (FPG) of 126 mg/dl or higher, or two-hour blood glucose of 200 mg/dl or higher during an oral glucose tolerance test (OGTT) that uses a glucose load that is equivalent to 75 grams of anhydrous glucose dissolved in water, or a HA1C of 6.5% or higher [16]. Every diabetes patient was diagnosed after the age of 25, and they are all receiving solely oral medication.

All blood samples for Pentraxin 3 were drawn from an antecubital vein. The blood was emptied into a tube containing ethylene diamine tetraacetate, and the samples were centrifuged for 15 minutes at 1000g. The plasma was immediately extracted and refrigerated at 80 degrees Celsius until analysis. The Human Pentraxin ELISA Kit (Aviscera Bioscience Inc.) used a quantitative sandwich enzyme immunoassay approach to assess plasma PTX3 levels. The intra-assay and inter-assay coefficients of variation were 4%-6% and 8%-10%, respectively. The lowest detected quantity of PTX3 was 0.02 ng/ml.

Sample size

A sample size of 32 per group is consistent with similar observational studies, and it meets the minimum requirement for detecting medium effect sizes (Cohen's $d \approx 0.5$) with a power of 0.80 and an alpha level of 0.05, particularly when using ANOVA or t-tests. Moreover, the recruitment period of one year provided adequate opportunity to enroll a representative and homogeneous sample from the target population while also remaining feasible in terms of resources and clinic patient flow.

Statistical analysis

Data was collected, coded, and analyzed using the Statistical Package for Social Sciences (SPSS) version 25. The normality of the data distribution was assessed using the Shapiro-Wilk test. Continuous variables that followed a normal distribution were analyzed using parametric tests, such as the independent samples t-test and one-way ANOVA. For variables that did not meet the assumption of normality, non-parametric alternatives, including the Mann-Whitney U test and Kruskal-Wallis test, were applied. For categorical data, frequencies (counts) and relative frequencies (percentages) were used to summarize it. Standard diagnostic indices, including sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and overall diagnostic efficacy, were assessed in the manner described by Galen [17]. To compare categorical data, the Chi-square (χ^2) test was used. The exact test was employed instead when the predicted frequency was less than 5, and a statistically significant result was defined as a probability (p) value of less than 0.05 [18].

RESULTS

The study included 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 Pentraxin 3 levels in patients with T2DM and

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

Pentraxin 3 (ng/ml)	Groups									ANOVA	
	T2DM with NAFLD			T2DM without NAFLD			Controls			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*				

Tukey's test was used for pairwise comparisons between all groups (Group I vs Group II, Group I vs Group III, and Group II vs Group III); *P < 0.05 was considered statistically significant.;SD: standard deviation; NAFLD: Nonalcoholic fatty liver disease; T2DM: Type 2 diabetes mellitus

NAFLD as compared to diabetic individuals without NAFLD and controls (Table 1 and Figure 1). Our study indicated no correlation between serum Pentraxin 3 levels and the degree of steatosis in NAFLD patients (Table 2). However, a significant positive correlation was found between Pentraxin 3 levels and LDL, triglycerides, and ALT. The study also found a strong negative correlation between Pentraxin 3 and HDL. No other laboratory or clinical variables showed a significant correlation with Pentraxin 3 (Table 3).

In the receiver operating curve (ROC) analysis between T2DM with NAFLD and controls, Pentraxin 3 at the cut-off value above 2.05 ng/mL demonstrated a sensitivity of 87.5%, specificity of 96.8%, PPV of 96.6%, and NPV of 88.6% with an accuracy of 92.9%. When comparing T2DM patients with and without NAFLD, a Pentraxin 3 cut-off above 2.3 ng/mL predicted NAFLD with a sensitivity of 87.5%, specificity of 93.7%, PPV of

93.3%, NPV of 88.2%, and an accuracy of 87.8% (Table 4; Figures 2 and 3).

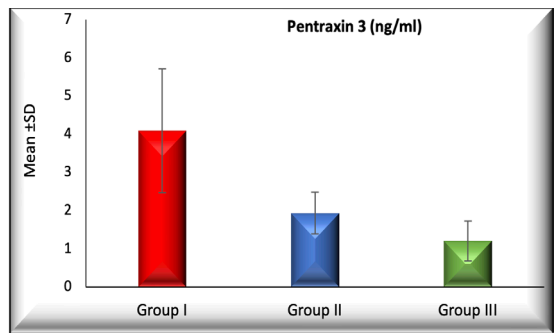


Figure 1: Serum Pentraxin 3 (PTX3) levels (ng/mL) in the study groups

Group I (red bar) represents patients with both nonalcoholic fatty liver disease (NAFLD) and type 2 diabetes mellitus (T2DM); Group II (blue bar) includes patients with T2DM only; and Group III (green bar) represents healthy control participants.

Table 2: Comparison between different steatosis grade groups regarding Pentraxin 3 in NAFLD patients

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

N: Frequency; SD: standard deviation

Table 3: Correlation of Pentraxin to investigations

Correlations	Pentraxin	
	r	P-value
Age	0.160	0.205
BMI	0.147	0.246
WC	0.048	0.705
TLC	0.080	0.529
HB	-0.015	0.909
PLT	-0.058	0.651
RBS	0.030	0.816
FBS	0.212	0.092
HbA1c	0.003	0.979
Cholesterol	0.247	0.052
HDL	-0.352	0.004*
LDL	0.353	0.004*
Trig	0.254	0.043*
PT	0.014	0.912
INR	0.003	0.979
S.ALB	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
Creat	0.100	0.430

BMI: Body mass index; WC: Waist circumference; TLC: Total Leucocyte Count; RBS: Random blood sugar; FBS: Fasting blood sugar; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; GGT, Gamma-glutamyl transferase; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; *P < 0.05 was considered statistically significant.

Table 4: ROC Curve Analysis for Pentraxin 3 (ng/ml) in Predicting NAFLD

Comparison Group	Cutoff (ng/ml)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
T2DM with NAFLD vs. T2DM without NAFLD	>2.3	87.5	93.75	93.3	88.2	87.8
T2DM with NAFLD vs. Healthy Controls	>2.05	87.5	96.87	96.6	88.6	92.9

ROC: Receiver operating characteristic; PPV: positive predictive value; NPV: negative predictive value

DISCUSSION

NAFLD is the leading cause of chronic liver disease globally. Its incidence is rising at about the same rate as obesity [19].

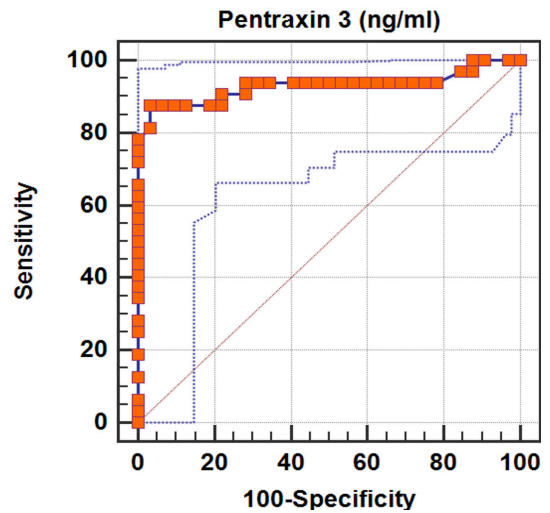


Figure 2: Receiver Operating Characteristic (ROC) curve analysis of serum Pentraxin 3 (PTX3) levels (ng/ml) for distinguishing patients with nonalcoholic fatty liver disease (NAFLD)

The orange squares denote observed data points. The solid ROC curve demonstrates high diagnostic accuracy, with the area under the curve (AUC) indicating 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.

NAFLD is significantly linked to metabolic syndrome and type 2 diabetes [4]. Liver biopsy The definitive method for diagnosing NAFLD [5]. However, liver biopsies have serious limits [6]. Pentraxin 3 is an acute-phase reactant that plays a crucial role in innate immunity [8]. High plasma PTX3 is regarded as a sign of NAFLD [11]. In addition, patients with T2DM had increased PTX3 serum levels compared to those with normal blood glucose [13].

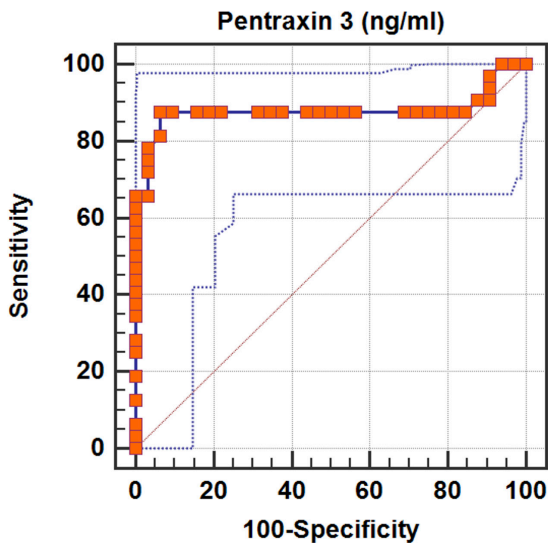


Figure 2: The ROC curve illustrates the diagnostic performance of serum PTX3 (ng/mL) levels in identifying patients with NAFLD in T2DM patients

The orange squares denote observed data points. The solid ROC curve demonstrates high diagnostic accuracy, with the area under the curve (AUC) indicating 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 was consistent with Boga et al. [11], who reported that NAFLD patients had greater PTX3 levels than controls (4.1 ± 2.3 vs. 1.3 ± 0.8 ng/mL, $P < 0.001$), and in agreement with Trojak et al. [20], who reported the median Pentraxin 3 level was 4.26 ng/ml in diabetic patients with NAFLD and 3.77 ng/ml in diabetic patients without NAFLD ($P = 0.93$). Also, PTX 3 levels were higher in diabetic patients without NAFLD than in healthy subjects (1.9 ± 0.6 vs. 1.2 ± 0.5 ng/mL, $P = 0.016$), and that was in agreement with Karamfilova et al. (2022), who reported greater serum Pentraxin 3 levels in patients with T2DM compared with those with normal blood sugar (2.32 ± 0.93 vs. 1.88 ± 0.90 ng/mL, $P = 0.028$) [13].

We found no relation between serum PTX 3 levels and degree of steatosis, which is consistent with Maleki et al. [21], who evaluated Pentraxin 3 in 32 NAFLD cases and 34 controls, with liver biopsy conducted in all cases. They found that Pentraxin 3 was ineffective in discriminating different degrees of NAFLD. Future research should incorporate exploring the potential of PTX3 as a marker of disease progression.

Our findings indicated a substantial positive

relationship between Pentraxin 3 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. [22] found a positive correlation between Pentraxin 3 levels and weight, body mass index, waist circumference, total bilirubin, GGT, ALT, AST, cholesterol, triglycerides, and LDL ($P < 0.001$). Albitar et al. [23] found no association between PTX3 and numerous indicators in NAFLD patients, including anthropometric measures. 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% negative predictive value, with an accuracy of 87.8%. The ROC curve analysis of Pentraxin 3 between patients with T2DM and NAFLD and controls revealed that the cut-off value over 2.05 ng/mL (which predicts NAFLD patients) has a sensitivity of 87.5%, specificity of 96.87%, PPV of 96.6%, NPV of 88.6%, and accuracy of 92.9%. These results were close to those reported by Boga et al. [11], who showed that the best cutoff value for the diagnosis of NAFLD was 2.45 ng/mL with a sensitivity of 91.1%, specificity of 71.4%, PPV of 76.1%, 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%.

Compared to existing non-invasive markers such as FIB-4 and the NAFLD Fibrosis Score (NFS), PTX3 offers a unique perspective by reflecting inflammatory activity, which may provide additional insight into the fibrotic process. For FIB-4, a threshold of 1.45 yields a sensitivity of approximately 90% but with a specificity of 35%. Conversely, at a higher threshold of 2.67, the specificity improves to 90%, but the sensitivity decreases to around 52% [24]. The NAFLD Fibrosis Score, using a cutoff of -1.45, demonstrates a sensitivity of 70% and a specificity of 55% for detecting advanced fibrosis [25].

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, for now, be viewed as a supplementary marker. Further large-scale, prospective studies 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 can be influenced by genetic, environmental, and inflammatory differences across ethnic groups. Broader, multi-ethnic studies are needed to confirm these findings.

CONCLUSION

Our findings suggest that plasma Pentraxin 3 could serve 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 potential 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.

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