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Complement C3 as a potential NAFLD predictor in an Egyptian cohort with diabetes and/or obesity

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Abstract

Complement system is becoming increasingly recognized as being intimately tied to obesity and other various metabolic abnormalities linked to it and may be involved in NAFLD. The goal of this study was to see if complement C3 might be used as a diagnostic and prognostic marker in NAFLD patients. Forty-one NAFLD patients and fourteen age- and gender-matched control individuals were enrolled in this study. All subjects were subjected to abdominal ultrasound examination and clinical assessment with special emphasis on the liver function enzymes, blood glucose levels, lipid profile, and kidney function tests. Non-invasive assessment of hepatic steatosis and fibrosis has evolved using serology-based scoring systems such as the Fibrosis-4 score and NAFLD Fibrosis Score (NFS). Additionally, serum levels of complement C3 were determined by the ELISA method. In this study, BMI, cholesterol, triglyceride levels, and NFS were all substantially higher in NAFLD patients compared to healthy controls. Moreover, complement C3 was considerably higher in NAFLD cases (1.52±0.29 g/L) vs. healthy controls (0.93±0.289 g/L) ($p<0.001$). Compared to lean people (0.93±0.29 g/L), the mean complement C3 levels were significantly higher in obese diabetes (1.69±0.29 g/L), obese non-diabetic (1.48±0.174 g/L), and diabetic non-obese patients (1.36±0.28 g/L). Using a cutoff for complement C3 1.135 (g/L) for distinguishing NAFLD patients from healthy controls has a sensitivity of 90.2% and specificity of 78.6%. In conclusion, serum complement C3 may be useful in the identification of fibrosis in non-alcoholic fatty liver disease. Moreover, complement C3 may be a promising tool for predicting the worsening of liver inflammation.

Highlights

- NAFLD nowadays becomes a challenge due to its growing prevalence, difficulty to diagnose, and complex pathogenesis.
- It is necessary to identify an effective non-invasive and inexpensive biomarker for the early diagnosis, prognosis, and staging of NAFLD to overcome liver biopsy drawbacks such as its invasiveness and high cost.
- Complement C3 may be useful in the identification of fibrosis in NAFLD and it may be a promising tool for predicting the worsening of liver inflammation.

Keywords: NAFLD, Complement C3, NFS, FIB-4

Introduction

Nonalcoholic fatty liver disease (NAFLD) has postulated itself as a serious threat as the number of people with diabetes and obesity rises. It already affects a quarter of all adults globally [1]. NAFLD refers to a variety of diseases

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ranging from simple steatosis to nonalcoholic steatohepatitis (NASH). NAFLD, particularly, NASH, patients are more likely to have adverse outcomes as the disease may progress to serious liver damage such as fibrosis, which can lead to cirrhosis, HCC, and liver-related death [2]. Until now, liver biopsy has been the gold standard for staging and grading the severity of fibrosis but this procedure has numerous drawbacks such as observer variability, post-procedure pain, morbidity, mortality, and sampling bias due to small tissue sample [3].

As a result, we had to find non-invasive markers to avoid biopsy for diagnosing NAFLD.

Several studies have found that the complement system is linked to obesity and related metabolic diseases, and it may have a role in NAFLD. In one of these studies, complement system was observed to be activated in 74% of NAFLD patients [4]. Another study indicated that serum complement C3a was positively associated with liver fat content in individuals with increased risk of type 2 diabetes and cardiovascular diseases [5]. Recently, the association between higher complement C3 levels and NAFLD are observed [6].

The purposes of this study were to (i) explore the relationship between serum complement C3 levels and the prevalence and severity of NAFLD and (ii) develop a recent, efficient, low-cost, and noninvasive biomarker for early-stage recognition of NAFLD.

Material and methods

Between December 2016 and January 2019, 55 subjects (18 to 65 years old) were recruited from persons attending clinics at Cairo University's internal medicine department.

All subjects were screened regarding T2DM and obesity without a prior diagnosis of NAFLD. Participants were selected regarding to their medical history, physical examination, and routine blood chemistries.

The participants were divided into 4 groups:

Group (I): Healthy subjects act as controls
Group (II): Obese diabetic NAFLD patients
Group (III): Diabetic non-obese NAFLD patients
Group (IV): Obese non-diabetic NAFLD.

Volunteers having a history of any chronic liver disease including HBV or HCV, autoimmune hepatitis, hemochromatosis, drug-induced disease, or those with self-reported acute infection within two weeks) were excluded, as were those with a BMI less than 18.0 kg/m^2. The Medical Research Ethical Committee, National research center, Cairo, Egypt accepted the study protocol (Approval No.16-118). An informed consent was signed by all participants.

Methods

The subjects' body height and weight were recorded and BMI was calculated. Ultrasonography, conducted by skilled examiners, was used to identify NAFLD. Besides, the NAFLD fibrosis score [7] and FIB-4 score [7] were used for the categorization of the severity of NAFLD.

$$\begin{aligned}\text{NFS} = &-1.675 + 0.037 \times \text{age}\ [\text{y}] + 0.094 \times \text{BMI}\ [\text{kg/m}^2] \\ &+ 1.13 \times \text{IFG/diabetes}\ [\text{yes} = 1, \text{no} = 0] + 0.99 \\ &\times \text{AST/ALT ratio} - 0.013 \times \text{platelet count}\ [\times 10^9/\text{L}] \\ &- 0.66 \times \text{albumin}\ [\text{g/dL}]\end{aligned}$$

$$\text{FIB} - 4\ \text{score} = \text{Age}\ [\text{y}] \times \text{AST}\ [\text{U/L}]/\text{platelet}\ [\times 10^9/\text{L}] \times \sqrt{\text{ALT}\ [\text{U/L}]}$$

Blood sampling

Five milliliters of venous blood were collected on plain tubes from all subjects under complete aseptic conditions, left for 10 min at room temperature to clot, and after that centrifuged at 3000 rpm for 10 min and the separated serum was divided into three separate parts: One aliquot used for hepatitis (HBV, HCV) serological markers assay, one for routine biochemical laboratory tests and the last one used for determination of serum complement C3.

Detection of complement C3 levels in serum of studied cases by ELISA

Serum Complement C3 was assessed in all of the participants using an ELISA kit provided by (NOVA, Beijing, China). For the quantitative analysis of complement C3, the assay uses a double-antibody sandwich ELISA method. The test was performed according to the manufacturer's instructions, and the findings were expressed in grams per liter.

Statistical analysis

SPSS version 21 for Windows was used to analyze the data (SPSS Inc., Chicago IL, USA). The mean ±standard deviation was used to express quantitative data.

Also, The *t*-test was used to compare groups. While the chi-square test or Fischer's exact test were used for categorical data.

Spearman's correlation coefficient was used to determine the correlations between complement C3 levels and the other biomarkers.

The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of serum complement C3 levels were calculated for evaluating

the efficacy of complement C3 in distinguishing subjects with NAFLD and the severity of NAFLD.

Significant was defined as a *P* value of less than 0.05.

Results

Overall, 41 NAFLD patients were included in the present study (2 male and 39 female); these cases were divided into 3 groups according to the presence of diabetes mellitus or obesity as a risk factor for NAFLD. The mean age of diabetic obese cases, diabetic cases, and obese cases were 47.4 ± 13.69, 47.29 ± 14, and 48.42 ± 4.7 years (Y), respectively, and 14 matched healthy controls with mean age 48.86 ± 10.08 years.

The present study showed that the mean BMI was significantly higher in NAFLD cases compared to healthy control (32 ±7.7 kg/m^2 *vs.* 23.8±1.5 kg/m^2) (*P*<0.001).

Hemoglobin a1c was higher in NAFLD cases compared to healthy control (6.42±1.1 vs. 5.76±1.16 %) but without a significant difference (*P*=0.09).

By considering the hematological characteristics of the studied groups; there were no significant differences in red blood cell count (RBCs), hemoglobin, and platelet count in NAFLD patients compared to healthy controls (*P* >0.05). However, there was a significant difference in the mean value of WBCs between both studied groups (*P*=0.038).

The variation in routine clinical investigations of liver function among different groups was shown in Fig. 1. Patients with NAFLD had similar ALT and AST levels compared to healthy controls (*P*=0.75 and *P*=0.54, respectively). Additionally, there was a significant increase in AST levels in obese non-diabetic patients (25.5 ±5.52 U/L) compared to obese diabetic patients (19.7±6.69 U/L) (*P*<0.05).

In addition, albumin levels was similar in NAFLD patients (3.71 ±0.5 g/dL) and healthy controls (3.9±0.33g/dL) (*P*=0.122).

As regards to lipid profile, both total cholesterol and triglyceride were significantly higher in NAFLD cases compared to healthy controls as shown in Fig. 2 (*P*=0.004 and 0.03, respectively). However, both HDL and LDL were similar in both studied groups. It was (49.2 ±7.5 and 93.5±14 mg/dL in control group *vs.* 49.76 ± 14.76 and 101.1±35.6 mg/dL in NAFLD group) (*P*=0.868 and *P*=0.298, respectively) (Fig. 2).

As regards Fib-4 score and NFS, there was a non-significant elevation in Fib-4 score in NAFLD cases (1.9±3.6) compared to healthy controls (0.6±0.4) (*P*=0.169) (Fig. 3). In contrast, NFS was significantly elevated in NAFLD cases compared to healthy controls (−1.04±2.87 vs. −2.7±0.9) (*P*=0.036) (Fig. 3). Furthermore, diabetic cases showed significantly higher Fib-4 score and

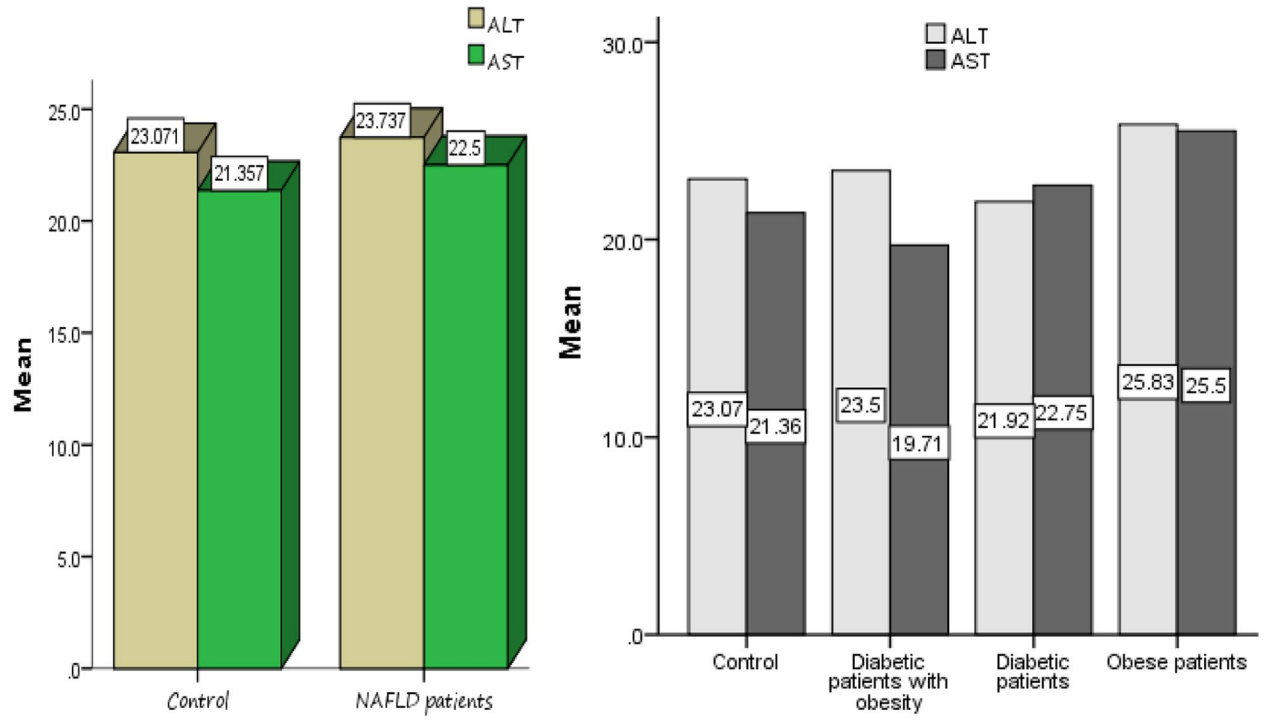

Fig. 1 Comparison between ALT and AST levels in all studied groups

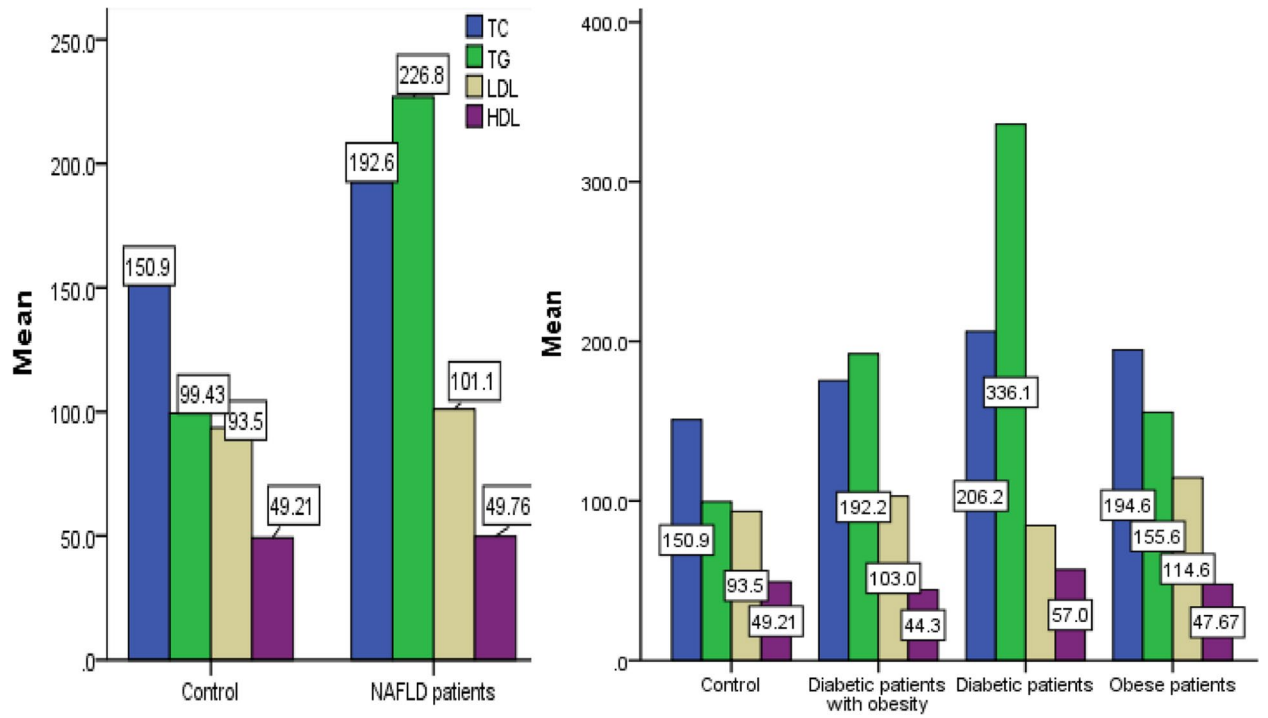

Fig. 2 Comparison between all studied groups as regard to lipid profile

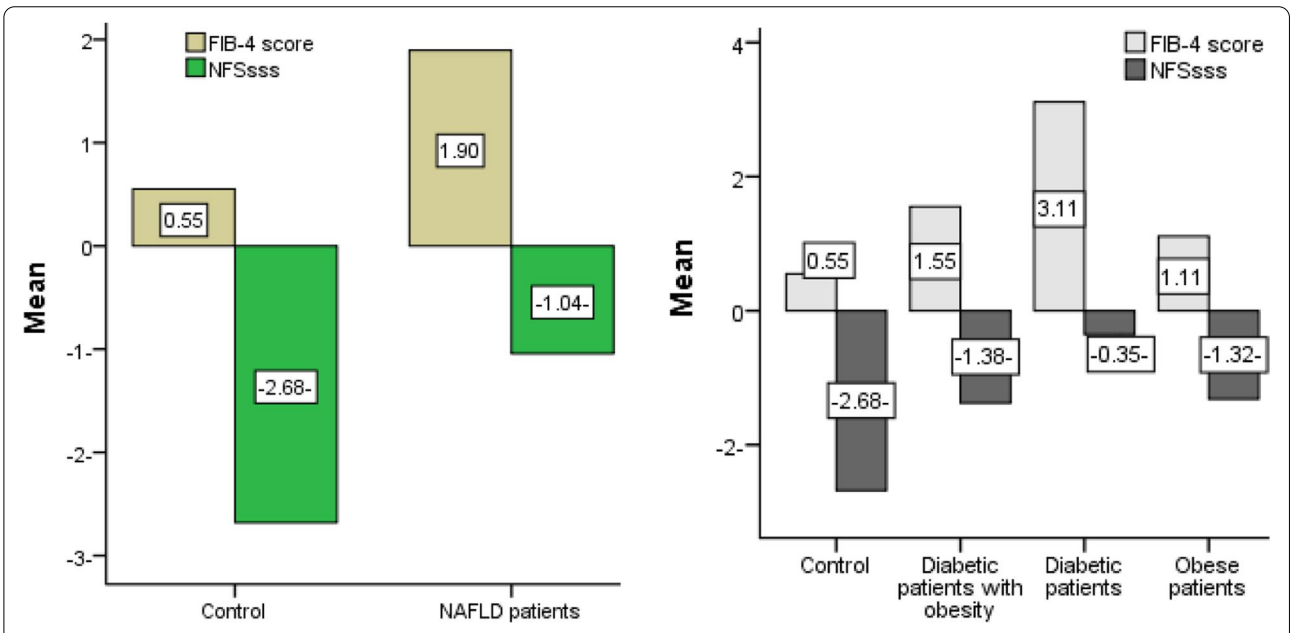

Fig. 3 Comparison between all studied groups as regard to NFS and FIB-4 score

NFS compared to the control group as shown in Fig. 3 (P<0.05).

According to complement C3, the present study showed that the mean serum level of complement C3 was 1.52±0.29 g/L in NAFLD cases vs. 0.93±0.289 g/L in controls. Overall, there was a statistically significant increase in serum complement C3 levels in NAFLD cases compared to healthy controls (p<0.001) (Table 1).

Table 1 Complement C3 levels in NAFLD and control group

Parameters	Group (I) Control group (*N*=14)	Total NAFLD group *N*=41	*P* value
Complement C3 (g/L)	**0.927±0.289**	**1.52±0.29**	**<0.001*****

***: $P \leq 0.001$

Furthermore, this study indicated that serum levels of complement C3 were considerably greater in groups II, III, and IV compared with the lean healthy subjects (1.69±0.29 g/l, 1.48±0.174 g/L, and 1.36±0.28 g/L vs. 0.93±0.29 g/l) (P<0.001) (Table 2).The present study demonstrated that serum complement C3 3 is positively correlated with BMI, NFS, creatinine, and Cholesterol (r=0.478, P<0.001; r=0.323, P=0.018; r=0.327, P=0.018; and r=0.339, P=0.018, respectively). On the other hand, no correlation was found between complement C3 and all other studied parameters (P>0.05) (Table 3).

The optimal cutoff value of complement C3 was 1.135 (g/L) for distinguishing patients with NAFLD from healthy control with a sensitivity of 90.2% and specificity of 78.6%; an area under the ROC curve (AUROC) 0.929 (Fig. 4).

Complement C3's sensitivity and specificity for discriminating patients with NFS less than −1.455 from those with NFS> − 1.455 were 73.3% and 77.8%, respectively, at a cut-off value of 1.365 (g/L). The AUROC was 0.752 (95% confidence interval: 0.584–0.920), with a P value of 0.023 (Fig. 5).

The difference between patients with a Fibrosis-4 score of more than or equal to 1.30 and those with a Fibrosis-4 score of less than 1.30 was not significant (P=0.693).

At cutoff value of 1.345 (g/L) the sensitivity and specificity of complement C3 were 85.7% and 40% respectively for discriminating patients with Fibrosis-4 score less than 1.30 from those with Fibrosis-4 score ≥1.30. The AUROC was 0.539(95% CI: 0.352–0.725) (Fig. 6).

Table 3 correlation between complement C3 and other studied parameters

Parameters	Concentration of complement C3 (g/L)	
	R	*P* value
Age (years)	− 0.115	0.403
Body mass index (kg/m^2)	0.478	<0.001***
Fibrosis-4 score	0.234	0.092
NAFLD fibrosis score	0.323	0.018*
Hemoglobin A1c (per gm %)	− 0.138	0.389
Alanine aminotransferase (U/L)	− 0.012	0.934
Aspartate aminotransferase (U/L)	− 0.006	0.966
Albumin (g/dL)	− 0.224	0.107
Urea (mg/dL)	0.169	0.246
Creatinine (mg/dL)	0.327	0.018*
Cholesterol (mg/dL)	0.339	0.018*
Triglycerides (mg/dL)	0.251	0.085
Low-density lipoprotein (mg/dL)	0.055	0.713
High-density lipoproteins (mg/dL)	− 0.129	0.389
White blood cell count (x10^3/μL)	0.01	0.94
Red blood cell count (× 10^6/μL)	− 0.057	0.68
Hemoglobin (g/dL)	0.121	0.378
Platelet counts (×10^3/μL)	− 0.076	0.582

*: $P \leq 0.05$, ***: $P \leq 0.001$

Discussion

During recent years, several studies have investigated the role of complement system in metabolic disorders [8, 9] and showed that serum complement C3 levels are linked to dyslipidemia [10], coronary heart disease [11], diabetes [12], and hypertension [13]. Obesity and insulin resistance, both risk factors for NAFLD, impaired numerous complement system components. C3 plasma levels, for example, are increased in obesity and insulin resistance [14] while C1q expression in adipose tissue is upregulated in obese insulin-resistant rodents [15]. These findings show that the complement system may play a vital role in the initiation and maintenance of chronic hepatitis in NAFLD patients with steatosis.

Table 2 Complement C3 levels in the all studied cases

Parameters	Group 1 Control group (*N*=14)	Group II Obese-diabetic (*N*=15)	Group III Diabetic Non-obese group (*N*=14)	Group IV Obese Non-diabetic group (*N*=12)
Complement C3 (g/l)	**0.927±0.289**	**1.698±0.29**	**1.36±0.28**	**1.48±0.174**
***P* value between each group and group I**		***P*<0.001****	***P*<0.001****	***P*<0.001****
***P* value between each group and group II**			***P*<0.001****	***P*=0.036***
***P* value between each group and group III**				***P*=0.260**

*: $P \leq 0.05$, **: $P \leq 0.01$

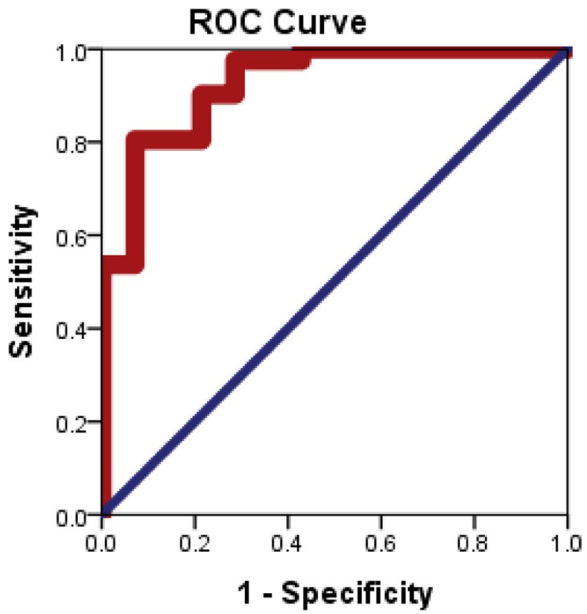

Fig. 4 ROC curve of complement C3 to discriminate NAFLD patients from control subjects

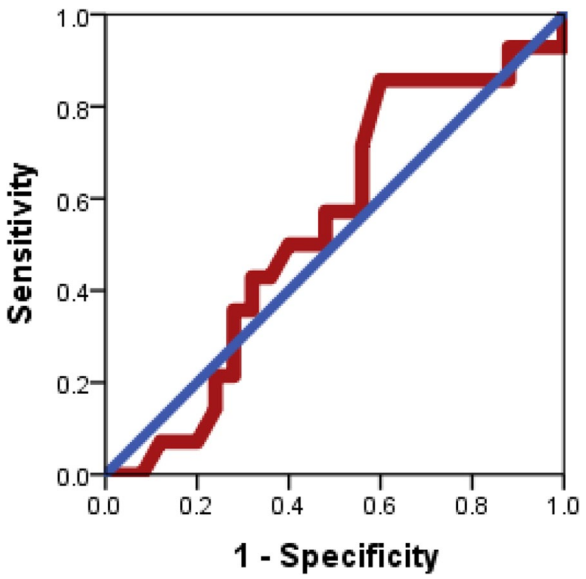

Fig. 6 ROC curve of complement C3 to discriminate patients with Fibrosis-4 score of less than 1.30 from patients with a Fibrosis-4 score of more than 1.30

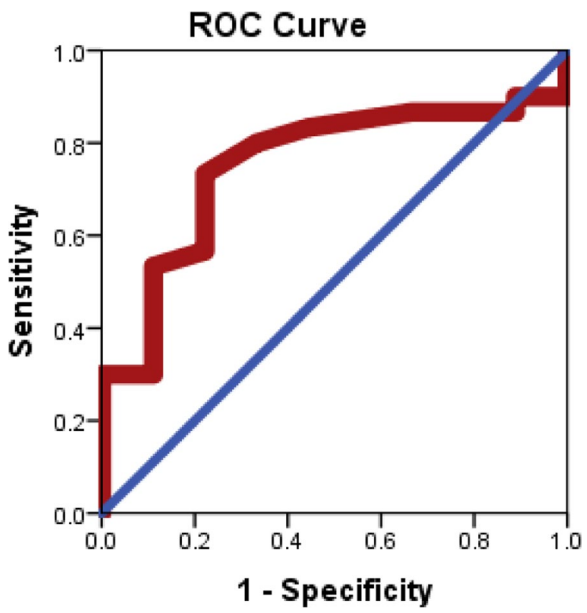

Fig. 5 ROC curve of complement C3 to distinguish between patients with NAFLD fibrosis score less than −1.455 from patients with NAFLD fibrosis score > − 1.455

The goal of this study was to see if complement C3 might be used as a predictor of NAFLD in a group of Egyptians who had diabetes and/or obesity.

This study showed that certain NAFLD cases who suffer from diabetes and obesity had higher urea levels. Previous results recommended that NAFLD may accelerate the development and progression of CKD as it is particularly frequent among NAFLD patients, ranging from 20 to 50%. A meta-analysis study that evaluates the incidence and prevalence of CKD in patients with simple fatty liver, NASH, and advanced fibrosis concluded that the severity of NAFLD was directly associated with CKD [16].

This case-control study revealed that NAFLD patients had considerably greater C3 levels than healthy controls, and C3 activity was linked to disease severity.

In agreement with our results, a previous cross-sectional study noticed that complement C3 levels are linked to the prevalence and severity of NAFLD in the Chinese population and that this link is independent of obesity and metabolic syndrome [5].

Also compared to lean healthy people, complement C3 levels were significantly greater in obese cases, whether or not they had diabetes, as well as diabetic-non obese patients.

BMI, NAFLD fibrosis score, creatinine, and cholesterol levels are all positively linked with serum complement C3.

This is in line with a previous study that found serum complement C3 to be an independent factor linked to the risk of NAFLD (OR = 5.231; 95% CI: 3.169–8.635), and this indicated that elevated serum complement C3 can be considered one of the important risk factor of NAFLD [5].

Although the role of complement C3 in the development of NAFLD is unknown, but numerous hypotheses have been postulated. First of all, complement components, especially C3, play a key role in lipid metabolism [10]. Hepatocytes are the primary sites of C3 synthesis, but other cells such as adipose tissue can also secrete it. Recently, it has also been identified in lipoprotein particles, such as high-density lipoprotein and chylomicron [17].

Several animal studies attempted to elucidate the precise role of complement in lipid metabolism regulation. One of these studies tried to disrupt complement C3 gene to study the effect of lacking this gene in mice. They detected that mice which lack C3 gene had approximately 58% higher triglyceride levels as well as marked elevation in both low-density lipoprotein (LDL) cholesterol and very-low-density lipoprotein (VLDL) triglycerides [18].

Secondly, innate immune response plays an important role in the progression of NAFLD, "two-hit model". The first hit is linked to insulin resistance (IR) and fat storage in the liver (hepatic steatosis), and oxidative stress subsequently up-regulates a variety of inflammatory cytokines and adipokines, resulting in the second hit [19].

The complement system, which has a key role in innate immunity, may be triggered by the first hit, contributing in the second hit in NAFLD pathogenesis [20].

The third, hepatocyte apoptosis is a major morphologic and pathogenic feature of human NAFLD and NASH and is triggered by intracellular stress of membrane-bound organelles and molecular cascades including caspases 3 and 7 [21]. Apoptosis activates the complement system, which can aid in the detection and clearance of apoptotic cells [22]. As a result, the increase of serum complement C3 may have a protective effect against NAFLD mediated by apoptosis.

Conclusion

We found that serum complement C3 levels increased considerably in NAFLD patients especially in those with increasing NAFLD fibrosis score (NFS).

Thus, serum complement C3 could be a viable tool for predicting the progression of liver inflammation, as well as a possible biomarker for assessing therapy outcomes in NAFLD.

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Authors' contributions
HMR, MAA, and NAE conceptualized the study; HMR, NAE, and WAE helped design the experiments and analyzed the data. MAA examined and diagnosed the patients and revised the manuscript; HMR, NAE, and WAE performed the experiments and drafted the manuscript. The final version has been read, revised, and edited by all authors to be submitted for publication. The author(s) read and approved the final manuscript.

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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request

Declarations

Ethics approval and consent to participate
The study protocol was approved by the Medical Research Ethical Committee - National research center, Cairo, Egypt at 8/11/2016 (Approval No.16-118). Written informed consent was obtained from all participants.

Consent for publication
The consents of publication are available from the corresponding author on reasonable request

Competing interests
The authors declare that they have no competing interests

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