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Serum Cytokeratin-18 as a Non-invasive Biomarker and its Association with Biochemical Parameters in the Diagnosis of Non-alcoholic Fatty Liver Disease

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Abstract

Objective: Nonalcoholic fatty liver disease (NAFLD) is one of the chronic silent diseases, in which its therapeutic options and noninvasive markers of disease activity and severity remain limited. We aimed in this study to assess cytokeratin-18 (CK18) as a new non-invasive biomarker to distinguish between NAFLD stages and its correlation with some biochemical parameters.

Methods: A case-controlled study was conducted on a sample of 90 subjects aged 12-79 years, categorized into three groups (nonalcoholic steatohepatitis "NASH", steatosis, and controls). CK18, fasting blood glucose (FBG), lipid profile parameters, aspartate aminotransferase (AST), alanine aminotransferase (ALT), urea, and creatinine were determined. Low-density lipoprotein-cholesterol (LDL-C) and body mass index (BMI) were calculated in addition to performing a complete blood count (CBC).

Results: The results indicate that the mean level of serum CK18 in NASH cases was significantly higher than in steatosis and control groups. CK18 has a positive correlation with triglycerides (TG), total cholesterol (TC), ALT, AST, FBG, urea, creatinine, age, BMI, and LDL-C, and a negative correlation with high-density lipoprotein-cholesterol HDL-C. Finally, the ROC curve showed that the sensitivity of the CK18 test was 77.1% and the specificity was 96.6%. The cut-off value for the CK18 test was 161 U/L.

Conclusions: In this study, a significant relationship was observed between CK18, hepatic enzymes, and NAFLD degrees. CK18 has good accuracy, sensitivity, and specificity in diagnosing NASH.

Keywords: Cytokeratin-18, Non-alcoholic fatty liver disease; Non-alcoholic steatohepatitis; Steatosis; lipid profile.

Abbreviations: ALP: Alkaline phosphatase; **ALT:** Alanine aminotransferase; **AST:** Aspartate aminotransferase; **BMI:** Body mass index; **CBC:** Complete blood count; **CK18:** Cytokeratin-18; **FBG:** Fasting blood glucose; **GGT:** Gamma-glutamyl transferase; **HDL-C:** High-density lipoprotein-cholesterol; **HOMA-IR:** Homeostatic Model Assessment for Insulin Resistance; **IR:** Insulin resistance; **LDL-C:** Low-destiny lipoprotein-cholesterol; **MAFLD:** Metabolic dysfunction associated-liver disease; **NAFLD:** Nonalcoholic fatty liver disease; **NASH:** Non-alcoholic Steatohepatitis; **NPV:** Negative predictive value; PPV: Positive predictive value; **ROC:** Receiver operating characteristic curve; **T2DM:** Type 2 diabetes mellitus; **TC:** cholesterol; **χ^2:**Chi-square

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INTRODUCTION

Steatosis (fatty liver) is a buildup of adipose tissue in the liver cells and an increase of fat amounts to over 5% of total liver weight. Non-alcoholic Steatohepatitis (NASH) develops when fat accumulation leads to liver inflammation. NASH can cause serious outcomes like cirrhosis and hepatocellular carcinoma (1). The prevalence of fatty liver disease differs from one place to another due to nutritional habits and sedentary lifestyles (2). Estimates about the prevalence of fatty liver disease are 13.5% in Africa, 23.7% in Europe,

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24.1% in North America, 27.4% in Asia, 30.5% in South America, and 31.8%, which is the highest number, in the Middle East (3).

Four approaches are needed for NAFLD diagnosis. First, liver steatosis is identified using radiation or histopathology. Then, alcohol consumption, any viral etiologies, and other causes of chronic liver disease are ruled out, such as chronic hepatitis B and C, drugs, parenteral feeding, Wilson's syndrome,biliary disorders, autoimmune hepatitis, and malnutrition (4).

Serum signs of inflammation, oxidative stress, apoptosis, and fibrosis have hardly been identified in patients suffering from NAFLD (5,6). Screening of NAFLD with liver biopsy is impractical. There should be noninvasive alternatives to tackle this issue and to distinguish between steatosis, steatohepatitis, and fibrosis. Hepatic enzymes, which are aspartate aminotransferase (AST) and alanine aminotransferase (ALT), rise in 90% of patients suffering from NASH (7,8). Slightly high serum aminotransferase levels are the major abnormal findings in patients with NAFLD. However, liver enzymes may be at normal levels in up to 78% of patients with NAFLD (9).

Other studies concluded that the enzyme Gamma-glutamyl transferase (GGT) in the blood is often elevated in a person suffering from NAFLD (10,11). Alkaline phosphatase (ALP) also rises occasionally in NAFLD; therefore, hepatic function tests cannot give clear results for diagnosing purposes (12). Additional blood tests are useful for ruling out other causes of liver disease. These usually include tests for viral hepatitis (hepatitis A, B, or C) and may include tests for less common causes of liver disease.

Histopathology can assess the severity of inflammation, discover hepatic scarring (fibrosis or, when severe, cirrhosis), and predict any future complications. The test is conducted after collecting a minor sample of hepatic tissue and delivering it to the laboratory for microscopic examination and biochemical analysis. Still, a liver biopsy is the best way to identify early hepatic injury. Nevertheless, the invasive check technique remains partially inefficient because of sample errors and the risk of medical complications. Thus, examining a biopsy is not an easy process (8,13).

Exploring new biomarkers in NAFLD has been a topic of great interest and research. Several possible biomarkers have been examined and investigated. For instance, the presence of CK18 fragments was studied in patients with NAFLD, who were diagnosed by hepatic histopathology after a biopsy (14,15).

CK18 is classified as a class I cytokeratin. With partner keratin 8, it makes a filament, which is the most frequent product of the intermediate filament gene family. Therefore, these products can be found in a single layer of epithelial tissues of the human body (16).

CK18 fragments found in the plasma showed a significant (P < 0.001) and marked increase in patients with NASH when compared with those having steatosis or normal findings (17). Others conducted further studies on these results. for instance, in a meta-analysis study, the findings showed that the CK18 fragment test has a sensitivity and specificity of 78% and 87%, respectively, for steatohepatitis and NAFLD (18). Aida *et al*. were able to differentiate between NAFLD stages by using the plasma CK18 fragment, which was considered a medically valuable biomarker (19).

In another study, serum CK18 has shown a great specificity for NAFLD and fibrosis; nevertheless, its narrow sensitivity made screening examination for NAFLD staging inadequate. Whether or not performing CK18 tests with additional biomarkers or laboratory tests may demonstrate beneficial results requires additional research (20). It has been reported that hepatocellular carcinoma can be tested through CK18 biomarkers instead of alpha-fetoprotein (21).

Another study was performed on 46 subjects with biopsy-proven NASH (NASH group), 54 subjects with borderline NASH, simple steatosis, and normal liver tissue (non-NASH group), and 30 age-matched healthy volunteers. The results showed that the serum level of CK18 was significantly higher in the NASH group when compared to the non-NASH group or controls. According to the ROC curve, the optimal value of CK18 was 487 U/L, with a sensitivity of 69 % and a specificity of 84.5 % in detecting NASH. The conclusions that came out from this study recommended that serum CK18 could be a potential non-invasive diagnostic serum marker for NAFLD and NASH patients (22).

MATERIALS & METHODS

Study Design

A retrospective case-control study was conducted on a target population comprised of NAFLD patients (case group) in addition to the control group. The patients were categorized into two groups: steatosis and NASH. The cases were: 33 cases of steatosis and 28 cases of NASH registered at the Department of Internal Medicine at Al-Shifa Hospital and AL Quds Hospital in Gaza City. The control group (29 healthy individuals) was randomly chosen. Cases and controls were matched for age and gender. A non-probability convenience sampling method was used.

Sample Collection

Venous blood samples (5 ml) after twelve hours of overnight fasting were collected from all participants. 1 ml was placed in an EDTA tube for CBC, and the remaining was placed into a plain tube for biochemical analysis.

Eligibility Criteria

Inclusion criteria included patients of both sexes with NAFLD, who were diagnosed in the hospital, based on symptoms, biopsy, CT, or Ultrasound. Exclusion criteria eliminate patients with HBV or HCV, patients with any other hepatic disease, and those having any acute or chronic illnesses (severe kidney disease requiring dialysis, thalassemia, hemochromatosis, or malignancy).

Data collection

Questionnaire Interview

A face-to-face interview was conducted to fill in a structured questionnaire designated for cases and controls to meet the study requirements. The researcher also explained the unclear questions to the participants during the interview. Most of the questions were dichotomous. The questionnaire included questions on personal information (age, height, and weight), socioeconomic status, and medical history.

Sample analysis

The biochemical analysis involved the determination of serum glucose, which was performed by using the “GOD-PAP” enzymatic photometric method (Trinder, 1969). TC, TG, and HDL-C were measured by commercial analytical kits (DiaSys, Germany). The "CHOD-PAP" method was used for the determination of TC (23). The determination of TG was done by using a colorimetric enzymatic test using glycerol-3-phosphate-oxidase (24). Serum AST was determined by L-Aspartate and 2-Oxoglutarate method (Expert Panel of Enzymes of the IFCC, Clin. Chem. 24: 497-510, 1986) using AMS, Italy. Serum ALT was determined by L-Alanine and 2-Oxoglutarate method (Tietz, N.W., Fundamentals of Clinical Chemistry, W.B. Saunders Co. Phila., pp 674 & 675,1982). CK18 was determined by using an ELISA kit (Elabscience, 2017). CBC was performed by hematology auto-analyzer CBC [Orphee mythic 18 equipment, Sweden]. Urea was measured according to Burtis assay using Biosystems Reagent Kits (Spain). Serum creatinine was determined using Biosystems Reagent Kits (Spain) and following the manual instructions described by Fabiny and Ertingshausen (25). Serum LDL-C was calculated by using the empirical formula of Friedewald (Friedewald *et al*, 1972). A precipitation method was used for the determination of HDL- HDL-HDL-Cholesterol (27).

Body mass index

The BMI is defined as the body mass (kg) divided by the square body height (m^2) of an individual. Height and weight were measured for each subject, then the BMIwas calculated for each subject as follows: BMI = body weight in Kg/height in square meters (unit kg/ m^2).

Statistical analysis

Statistical Package for the Social Sciences (SPSS, version 22) was used for data processing and analysis. The cross-tabulation and simple distribution of the study variables were analyzed. To detect the associations, significance, interactions, and relations between different qualitative variables, the Chi-square (χ^2) test was used, and means of quantitative variables were compared by an independent sample t-test and one-way ANOVA test. Pearson correlation test and ROC with PPV and NPV were performed. The results were agreeable in all the above-mentioned procedures and statistically significant when the p-value was less than 5% ($P < 0.05$)

RESULTS

General characteristics of the study participants

Table 1 shows that 86.9% of the cases are smokers compared to 62.1% for the controls; the difference was statistically significant ($P = 0.007$). On the other hand, 72.4% of controls are physically active compared to 27.9% of cases; the difference was also statistically significant ($P < 0.001$).

Regarding the mean age of the study participants, the mean age of cases was 48.1±15.0, and that of controls was 41.6±13.6. There was no statistically significant difference between the cases and controls regarding age (Table 1)

Table 1: General characteristics of the study participants.

Items	Cases (61) No (%)	Controls (29) No (%)	Total (90) No (%)	Test	*P*-value
Gender					
Male	42(68.8)	18(62.1)	60(66.7)	χ^2	0.523
Female	19(31.2)	11(37.9)	30(33.3)		
Smoking					
Yes	53 (86.9)	18 (62.1)	71 (78.9)	χ^2	0.007
No	8 (13.1)	11 (37.9)	19 (21.1)		
Physical Activity					
Yes	17 (27.9)	21 (72.4)	38 (42.2)	χ^2	<0.001
No	44 (72.1)	8 (27.6)	52 (57.8)		
Age (mean±SD)	48.1±15.0	41.6±13.6	46.0±14.9	T	0.051

T: Student test; **χ^2:**Chi-square

Clinical characteristics of the study population

Figure 1 shows that the majority of the cases (93.4%) have hyperlipidemia compared to 10.3% of the controls; the difference was statistically significant ($P < 0.001$). 12.9% of the cases have Diabetes Mellitus (DM) compared to 6.9% for controls, with no statistically significant difference. Moreover, 42.6% of the cases have hypertension compared to 10.3% for controls, and the difference was statistically significant ($P = 0.004$). On the other hand, the percentage of cases with a family history of NAFLD was 31.1% in cases and 10.4% in controls, with a statistically significant difference ($P = 0.032$) (Table 2).

Table 2: Clinical characteristics of the study participants.

Items	Cases (61) No (%)	Controls (29) No (%)	Test	*P*-value
Hyperlipidemia				
Yes	57(93.4)	3(10.3)	χ^2	**< 0.001**
No	4(6.6)	26(89.7)		
DM				
Yes	14(12.9)	2(6.9)	Y	0.117
No	47(77.1)	27(93.1)		
Hypertension				
Yes	26(42.6)	3(10.3)	χ^2	**0.004**
No	35(57.4)	26(89.7)		
Family history of NAFLD				
Yes	19(31.1)	3(10.4)	χ^2	**0.032**
No	42(68.9)	26(89.6)		

DM: Diabetes Mellitus; **NAFLD:** Non-alcoholic fatty liver disease; **χ^2:**chi-square

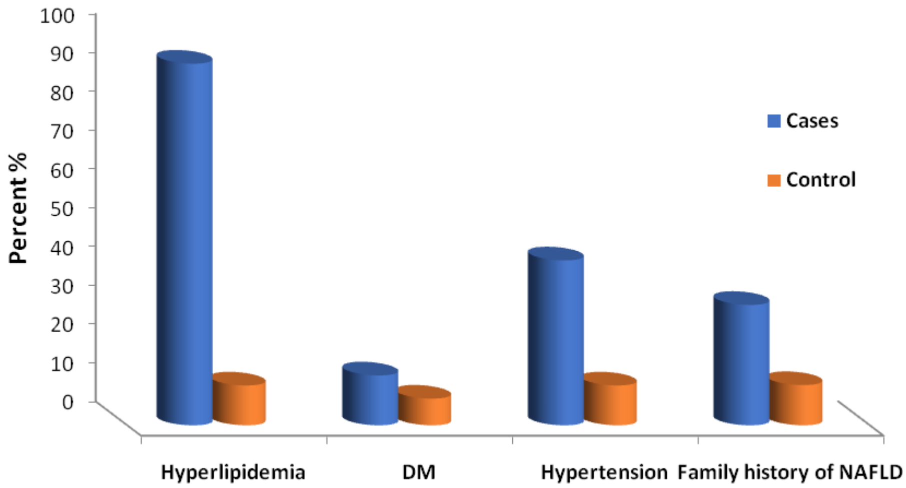

Figure 1: Clinical characteristics of the study participants.

The mean levels of height, weight, and BMI among the study groups

The cases were classified into two groups according to the stage of NAFLD,namely steatosis and NASH. 33 (54%) of the cases were diagnosed with steatosis, and 28 (46%) of the patients were diagnosed with NASH. Table 4.3 represents the mean levels of BMI and weight in steatosis cases (32.1±4.5 Kg/m^2 & 89.4±14.8 Kg), NASH cases (36.9±7.0 Kg/m^2 & 106.9±21.7 Kg), and controls (25.7±3.8 Kg/m^2 & 75.1±15.1 Kg), respectively. The difference was statistically significant (P < 0.001). Furthermore, there was no statistically significantdifference in height between the different groups.

Table 3: The mean levels of height, weight, and BMI among the study groups.

Variables	Mean ± SD			F	Overall *P*-value
	Controls (n=29)	Steatosis (n=33)	NASH (n=28)		
BMI (Kg/m^2)	25.7±3.8	32.1±4.5*	36.9±7.0$^{*\#}$	32.962	<0.001
Height (Cm)	170.0 ±11.3	166.3 ±14.3	170.0 ± 8.7	1.047	0.355
Weight (Kg)	75.1 ± 15.1	89.4 ±14.8*	106.9 ±21.7$^{*\#}$	23.944	<0.001

BMI: Body mass index; *****Significant difference with the control group; $^{\#}$Significant difference with steatosis.

Different biochemical parameters among the study groups

Table 4 shows that the mean level of serum CK18 in NASH cases was (247.7±66.3 U/L), which was higher compared to the mean in steatosis cases (168.7±51.1 U/L) and the controls (94.9±43.1 U/L). The difference was statistically significant (P < 0.001) (Figure 2).

Moreover, the levels of ALT, AST and FBG in NASH cases (51.6±53.7 U/L, 61.1±75.0 U/L and 136.8±68.4 mg/dl) were higher when compared to steatosis cases (29.3±16.9 U/L, 32.5±13.3 U/L and 121.7±33.7 mg/dl) and controls (17.7±7.0 U/L, 20.7±10.4 U/L and 92.7±17.9 mg/dl) and the difference was statistically significant (P = 0.001, 0.002 and 0.001), respectively (Table 4).

Table 4 also presents the levels of urea and creatinine in the different groups. The mean levels of urea in steatosis cases (34.8±7.9 mg/dl), NASH cases (40.4±10.9 mg/dl), and controls (29.0±6.6 mg/dl) were statistically significant (P < 0.001). The mean levels of creatinine in steatosis cases (0.95±0.2 mg/dl), NASH cases (1.07±0.3 mg/dl), and controls (0.81± 0.2 mg/dl) were also statistically significant (P < 0.001).

Table 4: Different biochemical parameters among the study groups.

Variables	Mean ± SD			F	Overall *P*-value
	Controls (n=29)	Steatosis (n=33)	NASH (n=28)		
CK18U/L	94.9±43.1	168.7±51.1*	247.7±66.3*#	56.940	**<0.001**
ALT U/L	17.7±7.0	29.3±16.9	51.6±53.7*#	8.294	**0.001**
AST U/L	20.7±10.4	32.5±13.3	61.1±75.0*#	6.677	**0.002**
FBG mg/dl	92.7±17.9	121.7±33.7*	136.8±68.4*	7.313	**0.001**
Urea mg/dl	29.0±6.6	34.8±7.9*	40.4±10.9*#	12.467	**<0.001**
Creatinine (mg/dl)	0.81±0.2	0.95±0.2*	1.07±0.3*	10.449	**<0.001**

ALT: Alanine transaminase; **AST:** Aspartate aminotransferase; **CK18:** Cytokeratin 18; **FBG:** Fasting blood glucose; **NASH:** Non-alcoholic steatohepatitis; *****significant difference with control; #Significant difference with steatosis.

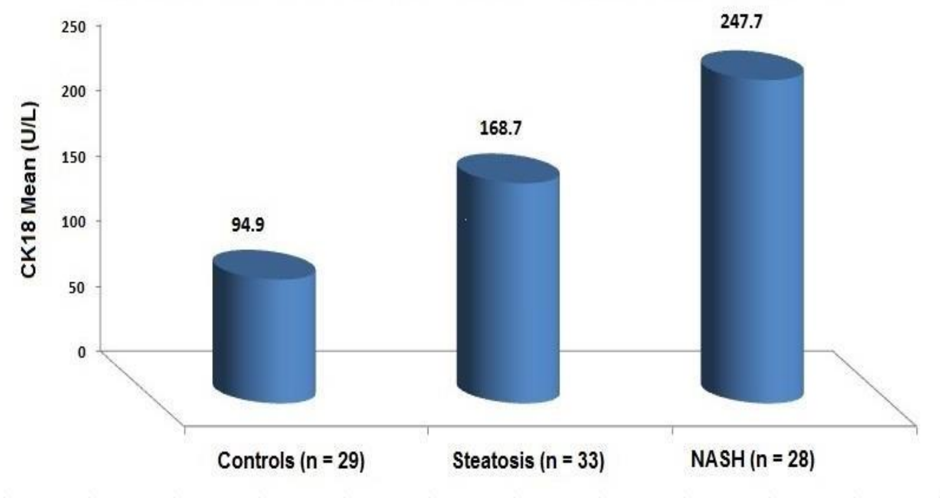

Figure 2: The mean levels of CK18 among the study categories.

Lipid profile among the study groups

The results show that steatosis and NASH groups have higher TC (286.8±62.8 & 368.2±123.5 mg/dl), TG (186.9±37.8 & 250.9±69.7 mg/dl), and LDL-C (122.7±30.6 & 254.6±107.9 mg/dl), respectively compared to the control group, and these differences were statistically significant (P < 0.001) (Table 5). HDL-C mean levels are lower in steatosis (47.3±10.4 mg/dl) and NASH (45.3±15.9 mg/dl) groups compared to controls (62.1±13.3 mg/dl) with a statistically significant difference (P < 0.001) (Table 5).

Table 5: The mean levels of lipid profile among the study participants.

Variables(mg/dl)	Mean ± SD			F	P-value
	Controls (n=29)	Steatosis (n=33)	NASH (n=28)		
TC (mg/dl)	185.8±31.3	286.8±62.8*	368.2±123.5*#	36.630	**<0.001**
TG (mg/dl)	135.7±25.9	186.9±37.8*	250.9±69.7*#	42.133	**<0.001**
LDL-C (mg/dl)	122.7±30.6	199.1±67.4*	254.6±107.9*#	22.453	**<0.001**
HDL-C (mg/dl)	62.1±13.3	47.3±10.4*	45.3±15.9*	14.129	**<0.001**

HDL-C: High-density lipoprotein cholesterol; **LDL-C:** Low-density lipoprotein cholesterol; **TC:** Total cholesterol; **TG:** Triglycerides. *****Significant difference with control; # Significant difference with steatosis.

WBC, Hb, and PLTs counts among study groups

Table 6 illustrates that there is no statistical difference in WBC count (6.8±2.9, 6.7±1.9 & 6.7±2.1 x 10^3/µl); Hb concentration (11.9±1.5, 11.8±2.0 & and 12.3±1.9 g/dl) and PLTs count (214.6±77.4, 211.1±79.3 & 218.7±72.4 x 10^3/µl), between NASH, steatosis, and control groups, respectively.

Table 6: The mean levels of WBCs, Hb, and PLTs among study groups.

Variables	Mean ± SD			F	P-value
	Controls (n=29)	Steatosis (n=33)	NASH (n=28)		
WBCs (10^3/µl)	6.7±2.1	6.7±1.9	6.8±2.9	0.020	0.980
Hb(g/dl)	12.3±1.9	11.8±2.0	11.9±1.5	0.624	0.538
PLTs (10^3/µl)	218.7±72.4	211.1±79.3	214.6±77.4	0.075	0.927

Hb: Hemoglobin; **NASH:** Non-alcoholic steatohepatitis; **PLTs:** Platelets; **WBCs:** White blood cells.

Correlation between CK18 and the different studied parameters

Table 7 shows the correlation between CK18 and different clinical parameters. There was a weak positive correlation between CK18 and age, ALT, AST, and FBG. The correlation was positive and moderately strong between CK18 and BMI, TC, TG, LDL-C, urea, and creatinine. On the other hand, there was a weak negative correlation between CK18 and HDL-C.

Table 7: Correlation between CK18 and the different clinical parameters.

Variables	CK18	
	r	**P-Value**
Age	0.235	**0.026**
Body mass index (BMI)	0.589	**<0.001**
Triglycerides	0.541	**<0.001**
Total Cholesterol	0.543	**<0.001**
ALT	0.246	**0.020**
AST	0.247	**0.019**
FBG	0.355	**0.001**
HDL-C	-0.326	**0.002**
LDL-C	0.444	**<0.001**
Urea	0.419	**<0.001**
Creatinine	0.422	**<0.001**

ALT: Alanine transaminase; **AST:** Aspartate aminotransferase; **CK18:** Cytokeratin 18; **FBG:** Fasting blood glucose; **LDL-C:** Low-density lipoprotein cholesterol; **HDL-C:** High density lipoprotein cholesterol.

The mean CK18 levels according to different parameters

The following Table 8 shows the mean difference in CK18 levels according to physical activity and NAFLD family history. The mean level of CK18 was higher in participants with a lifestyle involving no physical activity (195.0 ± 77.0 U/L) compared to those with a lifestyle involving physical activity (134.6±74.3 U/L), and the difference was statistically significant (P < 0.001). The mean CK18 level of participants with NAFLD family history was 191.2 ± 79.9 U/L compared to 162.1± 80.9 U/L in those with no NAFLD family history, with no statistically significant difference.

Table 8: The mean CK18 levels according to different parameters.

Variable	CK18 (U/L) mean ± SD	t-Test	P-value
Physical activity			
Yes (38)	134.6±74.3	3.735	<0.001
No (52)	195.0±77.0		
NAFLD Family history			
Yes (23)	191.2 ± 79.9	1.494	0.139
No (67)	162.1 ± 80.9		

CK18: Cytokeratin 18; NAFLD: Non-alcoholic fatty liver disease.

Youden index cut-off points, sensitivity, specificity, NPV, and AUC of CK18 for predicting NAFLD

Table 9 shows the cut-off points of CK18 for diagnosing NAFLD. The cut-off value for CK18 was 161 U/L, the area under the curve (AUC) was 0.921 (P< 0.0001), and sensitivity and specificity were 77.1% & 96.6%, respectively. A positive predictive value (PPV) was 97.7%, while a negative predictive value (NPV) was 66.7%, and the accuracy was 83.3%.

Table 9: Youden index cut-off points, sensitivity, specificity, NPV, and AUC of CK18 for predicting NAFLD.

Biomarker	NAFLD (n=61)	Controls (n=29)	Cut-off point (U/L) of steatosis	Cut-off point (U/L) of NASH	Sensitivity %	Specificity %	PPV %	NPV %	Accuracy %	AUC (95% CI)	P-value
CK 18 (U/L)	14	28	<161	< 195	77.1	96.6	97.9	66.7	83.3	0.921 (0.84-0.97)	<0.0001
	47	1	>161	> 195							

DISCUSSION

NAFLD is a complex metabolic condition that has been around for a while and has been linked to other metabolic illnesses, including obesity and type 2 diabetes (T2DM) (28). Generally, insulin resistance-induced hepatic lipogenesis is thought to be the precursor of NAFLD. The risk of consequences such as cardiovascular disease (CVD), chronic kidney disease (CKD), and an increase in overall mortality rises as NAFLD worsens from simple steatosis to NASH, cirrhosis, and hepatocellular carcinoma (HCC) (29).

Because of the observed relation between metabolic dysfunction and NAFLD, some researchers suggested that NAFLD should be renamed as "metabolic dysfunction-associated liver disease" (NAFLD). MAFLD can be diagnosed by the presence of hepatic steatosis, obesity, DM, and metabolic dysfunction, which is characterized by: waist circumference greater than 102 centimeters (cm) in males and 88 cm in females, blood pressure greater than 130/85 mmHg, TG content above 1.70 mmol/L, HDL-C content less than 1 mmol/L in males and less than 1.3 mmol/L in females, prediabetes, insulin resistance scores (HOMA-IR) greater or equal to 2.5, or C-reactive protein levels above 2 mg/L (30).

The mean age of NAFLD cases who participated in the current study was 48.1 ± 15.0 years, with no statistically significant difference compared to the control group. The age of 65.5% of the cases was more than 40 years. This is consistent with the study showing that the prevalence of NAFLD increases with age, and the peak prevalence of NAFLD is between 40–60 years old (31). Our results do not agree with those of (32) who showed that most patients were young (30-41 years old), and the least frequent cases were witnessed among individuals 50 years of age. This may be explained by the lifestyles of different populations.

Lack of physical activity may be a risk factor for NAFLD, which is illustrated in this study by the high number of cases who did not participate in any physical activities. This agrees with the results of two studies, which showed that NAFLD patients had low levels of physical activity (33,34). Increased physical activity is highly helpful in the management of NAFLD (35,36). The study also demonstrates that smoking may be a significant risk factor for NAFLD, which is consistent with other studies (37,38).

A statistically significant positive relationship between hypertension and NAFLD has been shown previously (39), in addition to other studies that showed that the percentage of cases with hypertension was greater in patients with NAFLD than those without NAFLD (40–42). Those outcomes are consistent with our results, which revealed that the percentage of cases with hypertension is significantly higher than the controls.

Despite that the percentage of cases with DM is higher compared to the control group, the difference was not statistically significant ($P = 0.117$). A cohort study confirmed that NAFLD is a strong risk factor for developing DM in middle-aged healthy Japanese men (43). Furthermore, others found that the highest prevalence of NAFLD in Iranian adults was among patients with T2DM, which was as high as 55.8% (44). NAFLD can be viewed as a good predictor for the clustering of risk factors for metabolic syndrome, and T2DM patients have an increased risk of progression to NAFLD (45). In a study done by Zheng *et al*., it was shown that NAFLD was an independent risk factor for the development of DM among Japanese, and the study demonstrated that the risk of developing DM in the NAFLD participants was higher than that of the non-NAFLD participants (46).

A common feature of NAFLD is the presence of insulin resistance (IR). The mechanism by which IR can affect NAFLD is not completely understood. One hypothesis suggested that NAFLD decreases the level of adiponectin, which is known to enhance insulin sensitivity. Adiponectin decreases IR by inhibiting the secretion of inflammatory cytokines like TNF-α and IL-18 (47). IL-18 is involved in hepatic cell injury, and its inhibition will prevent the destruction and dysfunction of liver cells.

Moreover, the present study demonstrated a statistically significant increase in the level of FBG in the two case groups compared to the control group. This is compatible with another research, in which a total of 66 individuals out of the 100 had insulin resistance, and there was a significant correlation between insulin resistance and raised fasting blood sugar or fasting plasma insulin values. The chance of developing NAFLD is high if the participants have insulin resistance, or vice versa. There was an increased prevalence of prediabetes and diabetes in the subjects with NAFLD (48,49).

In the etiology of NASH, excess dietary carbohydrates and fatty acids from adipose tissue or de novo lipogenesis in the presence of IR play a key role (50). Through a multi-enzyme mechanism, excess carbohydrates are transformed into fatty acids. The high levels of fatty acids can cause the production of lipotoxic agents, which lead to endoplasmic reticulum stress, mitochondrial dysfunction, hepatocellular injury, inflammation, and apoptosis. Several factors regulate the response of hepatic cells to lipotoxic stress, like gut microbiome, cholesterol, uric acid, and periodic hypoxia (51). One of the important factors in the pathogenesis of NAFLD is visceral adiposity. The adipose tissue secretes TNF-α and IL-6, which are pro-inflammatory cytokines. Several studies proved that a high level of TNF-α is positively associated with the severity of steatohepatitis and fibrosis. It was shown that increased lipolysis of visceral fat can be caused by insulin resistance through reducing glucose uptake into muscle cells (52).

Hyperlipidemia cases in our study were higher compared to the control group, with a significant difference ($P < 0.001$). The findings of Sen and his researchers are in agreement with our results, as their study stated that an abnormal lipid profile was prevalent among patients with NAFLD (53). In addition, another study showed that the prevalence of hyperlipidemia in the non-NAFLD group was significantly lower than in the NAFLD group (54). Family history of NAFLD might be a significant risk factor in causing NAFLD, as it is shown by the results of our study. Benedict and his colleagues found a link between the disease and the presence of genes causing an increase in the level of TG in the body (55).

Here, the levels of TC, TG, and LDL-C were higher in steatosis and NASH cases compared with the control group, and the differences were statistically significant. Moreover, the levels in the NASH group were significantly higher than in the steatosis one. On the other hand, HDL-C values decreased in steatosis and NASH cases compared to controls, with statistically significant differences. The same results were observed in studies conducted by (49). These findings recognize dyslipidemia as a risk factor for NAFLD.

Obesity is an independent risk factor for NAFLD occurrence. A previous research showed that obesity increased the risk of NAFLD by 3.5 folds (56). The obesity-mediated NAFLD risk is caused by increased IR and inflammation. Obesity is directly linked to inflammation via TNF-α, which increases IR. The multiplication of M1 macrophages, which secrete pro-inflammatory biomarkers such as IL-6 and TNF-α, is one mechanism by which increasing adipose tissue in the liver causes increased inflammation and IR. Downstream signaling cascades have been connected to IR, and these biomarkers trigger them (57).

Kosasih and his colleagues presented consistent results with our findings, in which the body mass index and weight values in NASH cases were significantly higher than those in steatosis and controls. In a recent study, high BMI was found as an independent risk factor for the incidence of NAFLD, and also the researchers found that high TG levels were a risk factor in the high-BMI group. They concluded that TG contributes about 25% to the appearance of NAFLD in obese individuals (58).

CK18 is considered the most widely used indicator for NAFLD. Several scientists used CK18 as a direct indicator of NAFLD and for adverse effects on health (59,60). Our work revealed that the mean level of CK18 increases significantly with the progression of the disease. Levels in NASH cases (247.7±66.3 U/L) were higher than those in steatosis cases (168.7±51.1 U/L) and those of controls (94.9±43.1 U/L). These findings were compatible with those reported by others (61). In another study, the researchers concluded that CK18 is a suitable non-invasive indicator for NAFLD (62). It was noted that, CK18 serum levels increased in the high fructose drinking group, and the reliability of CK18 as a biomarker for noninvasive evaluation of liver cell death in metabolic syndrome was suggested (63).

An increase in ALT and AST levels with significant differences for NASH compared to steatosis and control groups is shown in our work. Two studies have found that AST and ALT were raised in 90% of patients suffering from NASH (7,8), while a significant relationship was observed between hepatic enzymes ALT, AST, and NAFLD degrees (49). However, the repetitive determination of transaminases (ALT/AST) is not suitable for evaluating fibrosis and first-stage steatosis or for differentiating between simple steatosis and steatohepatitis (9,11).

Creatinine and urea levels were generally within normal range in this study, but significantly higher in NASH compared to steatosis and control participants. In addition, steatosis had a significant increase in these parameters compared to controls. The association of NAFLD with renal function was determined by other studies (64), as cases with fibrotic NAFLD are at high risk of kidney function impairment.

Levels of serum creatinine were analyzed in 1412 Chinese adults. NAFLD was associated with impairment of kidney function. The most striking finding of this study is that NAFLD is inversely associated with kidney function (65).

A weak positive correlation between CK18 and age, ALT, AST, and FBG was observed, while the correlation was positive and moderately strong between CK18 and BMI, TC, TG, LDL-C, urea, and creatinine. On the other hand, there was a negative weak correlation between CK18 and HDL-C. The same results wereindicated for lipid profile tests, BMI, AST, and ALT (8).

Our data indicated that the mean of CK18 in individuals who do physical activity was significantly lower compared to those who do not. In a study conducted in 2012, they concluded that physical activity reduces a circulatory marker of hepatocyte apoptosis in individuals with NAFLD (66). Recently, it has been found that simple resistance exercise decreased CK18 and FGF21 levels in NAFLD patients (67).

ROC curve results showed that the sensitivity of the CK18 test is 77.1% and specificity is 96.6%, and the cut-off value for the CK18 test is 161 U/L. This result agrees with those indicated by a study conducted by Maher et al, which showed that the ROC curve diagnostic performance of CK18 in diagnosing NASH had a cutoff value of >240 U/L, with sensitivity of 76.7% and specificity of 95.0%. CK18 was found to correlate with disease severity assessed by the NAS scoring system with $P = 0.001$ (68). Also, pooled sensitivity and specificity values for chosen serum markers for diagnosing NASH are as follows: CK18 (M30), 0.75 and 0.77; CK18 (M65), 0.71 and 0.77, respectively (15). Others indicated that, for diagnosis of NASH, CK18 levels should be more than 395 U/L with sensitivity, specificity, PPV, and NPV values of 85.7, 99.9, 99.9, and 85.7, respectively (17).

CONCLUSIONS:

In the present study, we proposed that CK18 is a suitable biomarker for NAFLD diagnosis. Therefore, it is very important to understand and identify novel biomarkers specific to different stages of NAFLD. Genetic markers, such as circulating noncoding RNAs and extracellular vesicles, might be promising alternative biomarkers for NAFLD. Therefore, these potential new biomarkers should be further improved and validated in diverse populations. A significant relationship was observed between CK18 with hepatic enzymes and NAFLD degrees. CK18 has good accuracy, sensitivity, and specificity in diagnosing NASH. More research is needed to combine biochemical markers in the diagnosis of NAFLD and staging.

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سيتوكيراتين–18 كعلامة بيولوجية غير جراحية وارتباطه بالمعلمات البيوكيميائية في تشخيص مرض الكبد الدهني غير الكحولي

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الملخص

الهدف: مرض الكبد الدهني غير الكحولي هو أحد الأمراض المزمنة الصامتة والتي مازالت خياراته العلاجية والعلامات غير الجراحية التي يمكن استخدامها للكشف عن نشاط المرض وشدته محدودة. لقد هدفنا في هذه الدراسة إلى تقييم السيتوكيراتين–18 كمؤشر حيوي جديد غير جراحي للتمييز بين مراحل مرض الكبد الدهني غير الكحولي وارتباطه ببعض المعلمات الكيميائية الحيوية.

الطرق: أجريت هذه الدراسة من نوع دِراسَةُ الحالاَتِ و الشَّواهِد على عينة تتألف من 90 فردًا يتراوح أعمارهم بين 12 و 79 سنة، وتم تصنيفهم إلى ثلاث مجموعات مرضى بالتهاب الكبد الدهني غير الكحولي، مرضى عندهم تَنَكُّسٌ دُهْنِيّ ، والمجموعة الضابطة. تم قياس مستويات السيتوكيراتين–18، الجلوكوز في الدم صائم، الدهون المختلفة، إنزيم ناقلة الأمين الأسبارتية، إنزيم ناقِلَةُ أَمينِ الأَلانين، اليوريا والكرياتينين. تم حساب مستوى الليبوبروتين منخفض الكثافة ومؤشر كتلة الجسم بالإضافة إلى إجراء فحص الدم الكامل.

النتائج: تشير النتائج إلى أن متوسط مستوى السيتوكيراتين–18 في مصل الدم في حالات التهاب الكبد الدهني غير الكحولي كان أعلى بكثير من التنكس الدهني والمجموعة الضابطة. يوجد علاقة إيجابية بين السيتوكيراتين–18 مع الكوليسترول الكلي، إنزيم ناقلة الأمين الأسبارتية، إنزيم ناقِلَةُ أَمينِ الأَلانين، الجلوكوز في الدم صائم، اليوريا والكرياتينين، العمر، مؤشر كتلة الجسم والليبوبروتين منخفض الكثافة، وعلاقة سلبية مع الليبوبروتين عالي الكثافة. أخيرًا ، أظهر منحنى مميز التشغيل أن حساسية فحص السيتوكيراتين–18 تبلغ 77.1٪ والنوعية 96.6٪. القيمة الفاصلة لاختبار السيتوكيراتين–18 هي 161 وحدة / لتر.

الاستنتاجات: لوحظ في هذه الدراسة وجود علاقة معنوية بين السيتوكيراتين–18 والإنزيمات الكبدية ودرجات مرض الكبد الدهني غير الكحولي. يتمتع فحص السيتوكيراتين–18 بدقة وحساسية وخصوصية جيدة في تشخيص مرض التهاب الكبد الدهني غير الكحولي.

الكلمات الدالة: سيتوكراتين–18، مرض الكبد الدهني غير الكحولي، إلتهاب الكبد الدهني غير الكحولي، تنكس دهني، مستوى الدهون.