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Original Article

Performance of serum CD163 as a marker of fibrosis in patients with NAFLD

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ABSTRACT

Background and aims: CD163, a surface hemoglobin-haptoglobin scavenger receptor, is expressed on macrophages and monocytes and up-regulated during macrophage activation. This study aimed to evaluate CD163 in nonalcoholic steatohepatitis patients as a diagnostic and prognostic marker in such patients. **Methods**: Serum samples were collected from 41 NAFLD patients and 14 healthy controls. All cases were subjected to clinical assessment, abdominal ultrasound examination, laboratory assessment including liver function and enzymes, kidney function, and lipid profile. Fib-4 and NAFLD fibrosis score were calculated for all patients. Also, serum levels of CD163 were detected by ELISA technique. **Results:** The present study showed that BMI, NAFLD fibrosis score (NFS), uric acid, cholesterol, and triglyceride levels were significantly elevated in the NAFLD cases compared with healthy controls ($P < 0.05$). The serum level of sCD163 was considerably higher in NAFLD cases (**9.97 ± 9.97** ng/ml) vs. healthy controls (**1.87 ± 0.83** ng/ml) ($p < 0.001$). Circulating level of sCD163 was significantly higher in the obese-diabetic subjects and diabetic non-obese patients as compared with the lean healthy subjects (**11.15 ± 7.69** ng/ml) and **11.46 ± 13.83** ng/ml vs. **1.87 ± 0.83** ng/ml, $P < 0.05$; respectively. The sensitivity and specificity of this marker was 85.4%, and 92.9 for distinguishing patients with NAFLD in obese and/or diabetic subjects from healthy controls. C**onclusion**: serum level of CD163 can be used as a diagnostic marker for individuals with NAFLD. However, it didn't correlate with NAFLD fibrosis score of those patients and thus couldn't predict the severity of disease.

1. Introduction

New noninvasive and conceptually simple, serologic biomarkers-based test is required to detect hepatic inflammation, distinguish simple steatosis seen in Nonalcoholic fatty liver disease (NAFLD) from nonalcoholic steatohepatitis (NASH) non-invasively, and to develop preventive measures. Different immune cells, including macrophages recruited from the circulation and resident liver macrophages (Kupffer cells), are involved in the pathogenesis of NAFLD and NASH [1]. Thus, Macrophages may play a key role in the development of liver inflammation and fibrosis. CD163, a surface hemoglobin-haptoglobin scavenger receptor, is expressed on macrophages and monocytes and up-regulated during macrophage activation [2]. CD163 is shed during macrophages activation as soluble CD163 (sCD163) in the blood [1,3]. A recent study has shown that levels of sCD163 are elevated in HCV-related cirrhosis patients compared with those with minimal or no fibrosis [4]. Also, sCD163 correlates with inflammation, specifically the hepatic activity index, and fibrosis among chronic HBV and HCV patients [5]. So, there is a need to investigate the association of serum CD163 levels with the prevalence and severity of NAFLD.

The objectives of this study were to: (i) investigate the association of serum sCD163 levels with the prevalence and severity of NAFLD; (ii) identify a new, effective, inexpensive and noninvasive biomarker for the early diagnosis, prognosis, and staging of the disease that can support clinicians in their daily routine.

2. Material and methods

This study was conducted on 55 individuals; their ages ranged from 18 to 65 years. Abdominal ultrasonography was used to diagnose NAFLD. They were recruited from inpatients and clinics of

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the internal medicine department at Cairo University during the period from December 2016 to January 2019. Subjects were divided into 4 groups: healthy control, obese diabetic NAFLD, diabetic non-obese NAFLD, and obese non-diabetic NAFLD patients.

Patients with history of viral hepatitis, autoimmune hepatitis, or other forms of chronic liver disease, those with self-reported acute infection within 2 weeks, and those with body mass index less than 18.0 kg/m^2 were excluded from the study.

The study protocol was approved by the Medical Research Ethical Committee, National research center, Cairo, Egypt (Approval No.16–118). Written informed consent was obtained from all participants.

2.1. Methods

All participants underwent detailed history and physical examination. The subjects' body weight and height were recorded. Body mass index (BMI) was calculated. NAFLD was diagnosed by ultrasonography performed by an experienced operator, and the severity of the disease was categorized according to the NAFLD fibrosis score [6] and FIB-4 score [7].

2.1.1. Blood sampling

5 ml of venous blood samples were collected from patients and control cases. Within 30 min, sera were separated by centrifugation at 3000 rpm for 10 min after a minimum time span of 30 min, and then aliquoted, and stored at −80 °C until further processing. Biochemical analysis including aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin, serum albumin, creatinine, urea, CBC, cholesterol, triglyceride, HDL, LDL, and random blood sugar were measured according to the manufacturer's instructions. The reagents were purchased from Spectrum Company, Cairo, Egypt.

2.1.2. Quantitation of CD163 by (ELISA)

Serum sCD163 was measured in all enrolled subjects using ELISA kit (NOVA, Beijing, China). The assay is based on a double-antibody sandwich ELISA technique for the quantitative determination of human sCD163 in samples. The assay was performed according to the manufacturer's instructions and results were reported as ng/ml.

2.1.3. Statistical analysis

Data were analyzed using SPSS version 23 for Windows (SPSS Inc., Chicago IL, United States). Quantitative variables were expressed as mean ± SD. The *t*-test was applied for group comparison. For categorical data, the Chi-square test or Fischer exact test was applied. Spearman's correlation coefficient was used to determine the correlations between serum sCD163 levels and the other biomarkers. The diagnostic performance of serum sCD163 levels was assessed by analyzing the receiver operating characteristic (ROC) curves. The ROC curve is a plot of sensitivity versus 1−specificity for the possible cutoff classification. The most commonly used index of accuracy is the area under the ROC curve (AUROC), with values close to 1.0 indicating high diagnostic accuracy. The accuracy of serum sCD163 levels for discriminating cases with NAFLD and severity of NAFLD was determined by calculating the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). A P value less than 0.05 was considered significant.

3. Results

The detailed characteristics of the studied cases were summarized in Tables 1 and 2.

BMI, NAFLD fibrosis score (NFS), uric acid, cholesterol, and triglyceride (TG) levels were significantly elevated in the NAFLD cases compared with healthy controls ($p < 0.05$) (Table 1).

There was a significant increase in AST levels in obese non-diabetic patients compared to obese diabetic patients. A significant decrease in serum total protein was observed in obese non-diabetic patients compared to obese diabetic patients. In addition, diabetic patients showed increased levels of cholesterol and triglyceride compared to healthy controls (Table 2).

The mean serum sCD163 levels in NAFLD patients and healthy controls were shown in table [1]. The mean serum sCD163 levels were significantly higher ($P = 0.001$) in NAFLD patients (9.97 ± 9.97 ng/ml) compared to healthy controls (1.87 ± 0.83 ng/ml).

Also, the circulating level of sCD163 was significantly higher in the obese-diabetic and diabetic non-obese patients as compared with the lean healthy subjects (11.15 ± 7.69 ng/ml and 11.46 ± 13.83 ng/ml vs. 1.87 ± 0.83 ng/ml, $P < 0.05$; respectively) (Table 3). These results indicated that sCD163 may be used as a marker for diabetes.

The present study demonstrated that soluble CD163 is positively correlated with total protein, potassium, cholesterol and triglyceride ($r = 0.326$, $P < 0.019$, $r = 0.309$, $P < 0.026$, $r = 0.68$, $P < 0.001$ & $r = 0.752$, $P < 0.001$; respectively). Furthermore, there was a negative correlation between CD163 and age ($r = -0.417$, $P = 0.002$), as well as LDL levels ($r = -0.445$, $P < 0.002$) (Table 4).

Fig. 1 illustrates the ROC plot to assess the diagnostic accuracy of serum sCD163 in NAFLD patients and healthy control.

ROC curve analysis showed that serum CD163 had a good diagnostic accuracy in the diagnosis of NAFLD ($p < 0.001$).

The optimum cutoff for CD163 was 2.94 (ng/ml) for distinguishing patients with NAFLD from healthy control with sensitivity 85.4% and specificity 92.9%, and the AUROC was 0.932(95% CI: 0.864–1.000).

Fig. 2 illustrates the ROC plot to assess the diagnostic accuracy of serum sCD163 for differentiating patients with ***NAFLD fibrosis Score*** < ***-1.455*** from those with ***NAFLD fibrosis Score*** ≥ ***-1.455***. ROC curve analysis showed that there is poor diagnostic accuracy of serum sCD163 in the detection of patients with NFS < ***-1.455*** from those who had NFS ≥ ***-1.455*** ($P = 0.841$).

At cutoff value of 3.42 (ng/mL), the sensitivity and specificity of sCD163 were 33.3% and 88.9% respectively for distinguishing patients with NFS < ***-1.455*** from those who had NFS ≥ ***-1.455*** with an AUROC of 0.522(95% CI: 0.346–0.699).

Fig. 3 illustrates the ROC plot to assess the diagnostic accuracy of serum CD163 for differentiating patients with ***NAFLD fibrosis Score*** <***0.675*** from those with ***NAFLD fibrosis Score*** ≥***0.675***.

ROC curve analysis showed that serum CD163 had a poor diagnostic accuracy in the diagnosis of patients with NFS ≥ ***0.675*** ($p =$ **0.405).**

ROC curve showed the optimum cutoff for CD163 was 10.258 (ng/ml) for distinguishing patients with NFS ***Score*** <***0.675*** from those with NFS ≥***0.675*** with sensitivity 66.7% and specificity 70%; an AUROC of 0.593(95% CI: 0.352–0.834).

Fig. 4 illustrates the ROC plot to assess the diagnostic accuracy of serum CD163 for differentiating patients with ***Fib-4 score*** <***1.30*** from those with ***Fib-4 score*** ≥ ***1.30***.

ROC curve analysis showed that there is a poor diagnostic accuracy of serum CD163 in the detection of patients with ***Fib-4 score*** ≥***1.30*** ($P = 0.079$).

ROC curve showed the optimum cutoff for CD163 was 4.528 (ng/ml) for distinguishing patients with ***Fib-4 score*** < ***1.30*** from those with ***Fib-4 score*** ≥ ***1.30*** with sensitivity 64.3% and specificity 64%; an AUROC of 0.671(95% CI: 0.494–0.849).

Fig. 5 illustrates the ROC plot to assess the diagnostic accuracy of serum CD163 for differentiating patients with ***Fib-4 score*** ≤***2.67***

Table 1
Demographic, clinical and biochemical parameters of the control and NAFLD patients.

Parameters	Healthy control group (N = 14)	NAFLD patients (N = 41)	P-value
Age (Years)	48.9 ± 10.1	47.7 ± 11.6	0.731
Sex (male/female)	5/9	2/39	0.009**
Female %	64.3%	95.1%	
BMI (kg/m^2)	23.8 ± 1.5	31.9 ± 7.7	<0.001***
HbA1C (%)	5.8 ± 1.2	6.4 ± 1.1	0.085
ALT (U/L)	23.1 ± 5.3	23.7 ± 8.9	0.747
AST(U/L)	21.4 ± 4.3	22.5 ± 6.4	0.542
GGT(U/L)	41.6 ± 12.3	47.1 ± 40.8	0.639
ALP(U/L)	100.4 ± 29.9	106 ± 46.1	0.685
ALB(g/dl)	3.9 ± 0.3	3.7 ± 0.5	0.122
Total bilirubin(mg/dl)	0.6 ± 0.2	0.6 ± 0.4	0.717
Urea (mg/dl)	22 ± 3.9	36.1 ± 49.1	0.308
Creatinine (mg/dl)	0.7 ± 0.1	1.3 ± 1.8	0.091
Na^+ (mmol/l)	135 ± 3.2	137.2 ± 4.2	0.093
K^+ (mmol/l)	4.2 ± 0.4	4.4 ± 0.6	0.344
Uric acid (mg/dl)	4.4 ± 0.9	5.51 ± 2.69	0.038*
Cholesterol(mg/dl)	150.9 ± 17.8	194.15 ± 51.48	0.004**
Triglycerides (mg/dl)	99.43 ± 21.62	225.47 ± 313.2	0.026*
LDL	93.5 ± 13.63	101.1 ± 35.57	0.298
HDL	49.2 ± 7.49	49.76 ± 14.76	0.868
Hb(g/dl)	12.1 ± 0.99	11.9 ± 1.76	0.639
PLT ($\chi 10^3/\mu L$)s	264.7143 ± 50.185	261.5744 ± 210.62	0.956
WBCs ($\chi 10^3/\mu L$)	10.1 ± 2.4	7.7 ± 4.05	0.038*
NAFLD fibrosis score (NFS)	−2.733 ± 0.887	−1.04 ± 2.87	0.036*
FIB-4 score	0.55 ± 0.39	1.896 ± 3.58	0.169
CD-163 (ng/ml)	1.87 ± 0.83	9.97 ± 9.97	<0.001**

a: significant difference from healthy controls.
*: P ≤ 0.05, **: P ≤ 0.01, ***: P ≤ 0.001.

Table 2
Demographic, clinical and biochemical parameters of the control and patient population.

Parameters	Control group (N = 14)	Obese diabetic group (N = 15)	Diabetic Non-obese group (N = 14)	Obese Non-diabetic group (N = 12)
Age (Years)	48.8 ± 10.1	47.4 ± 13.7	47.3 ± 13.8	48.43 ± 4.69
Sex (male/female)	5/9	0/15[a]**	1/13	1/11
Female %	64.3%	100%	92.9%	91.7%
BMI (kg/m^2)	23.8 ± 1.5	34.13 ± 4.1[a]***	24.1 ± 1.08[b]***	38.9 ± 7.86[ac]***
HbA1C (%)	5.8 ± 1.2	6.7 ± 0.76	7.2 ± 1.26[a]**	5.7 ± 0.6[c]**
ALT (U/L)	23.1 ± 5.4	23.5 ± 10.75	21.9 ± 6.4	25.8 ± 9.1
AST(U/L)	21.4 ± 4.2	19.7 ± 6.69	22.8 ± 6.03	25.5 ± 5.5*
GGT(U/L)	41.6 ± 12.3	57.6 ± 63.34	37.3 ± 11.1	42.9 ± 11.05
ALP(U/L)	100.4 ± 29.97	99.5 ± 52.2	103.5 ± 36.1	115.5 ± 50.2
ALB(g/dl)	3.9 ± 0.33	3.7 ± 0.62	3.8 ± 0.5	3.7 ± 0.3
Total bilirubin(mg/dl)	0.6 ± 0.2	0.7 ± 0.59	0.5 ± 0.2	0.59 ± 0.19
Urea (mg/dl)	22 ± 3.98	60.38 ± 77.3[a]*	20.36 ± 3.96 b*	24.3 ± 5.5[b]*
Creatinine (mg/dl)	0.75 ± 0.1	1.85 ± 2.55	1.12 ± 1.57	0.7 ± 0.17
Na^+ (mmol/l)	135 ± 3.2	136.1 ± 4.98	137.8 ± 2.88	137.9 ± 4.39
K^+ (mmol/l)	4.19 ± 0.4	4.59 ± 0.83	4.28 ± 0.38	4.2 ± 0.25
Uric acid (mg/dl)	4.4 ± 0.87	5.84 ± 3.69	4.97 ± 1.98	5.45 ± 1.49
Cholesterol(mg/dl)	150.9 ± 17.8	175.4 ± 17.46	209.33 ± 76.7[a]**	194.58 ± 35.22[a]*
Triglycerides (mg/dl)	99.4 ± 21.6	192.2 ± 138.3	323.1 ± 504.4[a]*	155.58 ± 86.3
LDL (mg/dl)	93.5 ± 13.6	103 ± 24.1	84.5 ± 43.17	114.6 ± 32.21
HDL (mg/dl)	49.2 ± 7.49	44.3 ± 19.8	57 ± 9.44	47.7 ± 12.1
WBCs ($\chi 10^3/\mu L$)	10.1 ± 2.4	10.2 ± 5.08	5.89 ± 2.4 [ab]**	6.56 ± 2.46 [ab]**
Hb(g/dl)	12.1 ± 0.99	11.56 ± 1.65	12.34 ± 2	11.9 ± 1.6
PLT ($\chi 10^3/\mu L$)s	264.714 ± 59.185	341.333 ± 317.116	177.254 ± 77.44[b]*	260.250 ± 92.283
NAFLD fibrosis score (NFS)	−2.73 ± 0.89	−1.38 ± 4.1	−0.35 ± 1.54[a]*	−1.32 ± 1.98
FIB-4 score	0.55 ± 0.047	1.55 ± 1.69	3.11 ± 6.15[a]*	1.1 ± 0.58

*: P ≤ 0.05, **: P ≤ 0.01, ***: P ≤ 0.001.
[a] Significant difference from healthy controls.
[b] Significant difference from obese diabetic group.
[c] Significant difference from diabetic non-obese group.

from those with ***Fib-4 score* >*2.67***. ROC curve analysis showed that there is poor diagnostic efficacy of serum CD163 in the detection of patients with ***Fib-4 score* ≤*2.67*** (P = 0.231).

ROC curve showed the optimum cutoff for CD163 was 2.726 (ng/ml) for distinguishing patients with ***Fib-4 score* ≤*2.67*** from those with ***Fib-4 score* > *2.67*** with sensitivity 60% and specificity 91.2%; an AUROC of 0.668(95% CI: 0.325–1.000).

4. Discussion

The current study reports high levels of sCD163 in the serum of NAFLD cases especially obese-diabetic and diabetic non-obese

Table 3
Serum CD 163 in different studied groups.

Parameters	Control (lean) group (N = 14)	Obese& diabetic group (N = 15)	Diabetic & non-obese group (N = 14)	Obese & non-diabetic group (N = 12)	P-value
CD163 (ng/ml)	**1.87 ± 0.8**	**11.15 ± 7.69**	**11.46 ± 13.8**	**6.75 ± 6.6**	**P1 = 0.006**** **P2 = 0.005**** **P3 = 0.157** **P4 = 0.924** **P5 = 0.195** **P6 = 0.172**

P1 between control and obese diabetic patients.
P2 between control and diabetic non-obese patients.
P3 between control and obese non-diabetic patients.
P4 between obese diabetic and diabetic non-obese patients.
P5 between obese diabetic and obese non-diabetic patients.
P6 between diabetic non-obese and obese non-diabetic patients.

Table 4
Correlation between CD163 and other biomarkers.

Parameters	Concentration of CD163 (ng/ml)	
	R	P-value
Age(Yrs.)	−0.417	0.002**
BMI (kg/m^2)	0.053	0.703
FIB-4 score	0.203	0.145
NFS	0.189	0.175
HbA1c (per gm %)	0.066	0.682
ALT(U/L)	−0.105	0.454
AST(U/L)	−0.092	0.51
GGT(U/L)	0.173	0.225
ALP(U/L)	−0.096	0.508
ALB(g/dl)	−0.205	0.14
TP(g/dl)	0.326	0.019*
Total bilirubin(mg/dl)	−0.075	0.597
Urea (mg/dl)	−0.039	0.79
Creatinine (mg/dl)	0.19	0.177
Na^+ (mmol/l)	0.014	0.923
K^+ (mmol/l)	0.309	0.026*
Uric acid (mg/dl)	0.134	0.365
Cholesterol(mg/dl)	0.68	<0.001***
Triglycerides (mg/dl)	0.752	<0.001***
LDL	−0.445	0.002**
HDL	0.07	0.638
WBCs(10^3/μL)	−0.017	0.902
Hemoglobin(g/dl)	−0.117	0.196
platelet count(10^3/μL)	−0.117	0.394

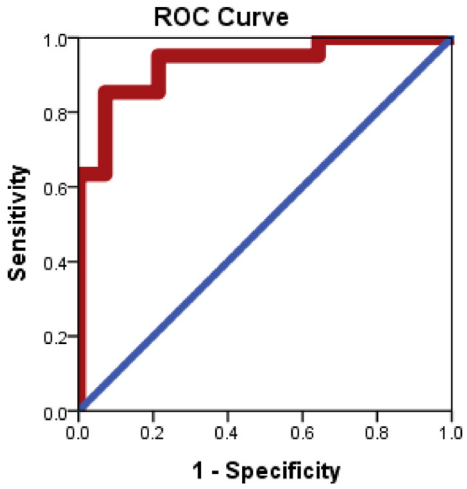

Fig. 1. ROC curve of CD163 (ng/ml) to differentiate between NAFLD from healthy control.

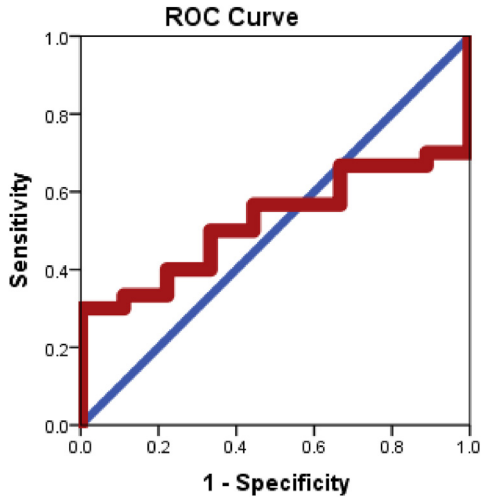

Fig. 2. ROC curve of CD163 (ng/ml) to differentiate between patients with NAFLD fibrosis Score < −1.455 from those with NAFLD fibrosis Score ≥ −1.455.

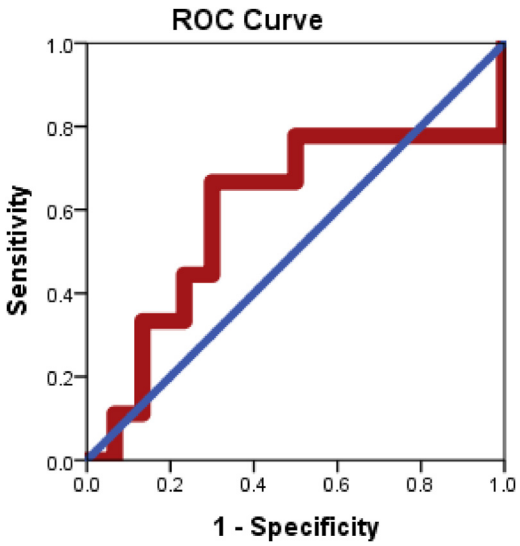

Fig. 3. ROC curve of CD163 (ng/ml) to differentiate between patients with NAFLD fibrosis Score < 0.675 from those with NAFLD fibrosis Score ≥0.675.

subjects, thus simultaneously extending the pathophysiological importance of this marker in diabetes-related metabolic disease. These results may reflect a higher degree of macrophage activation

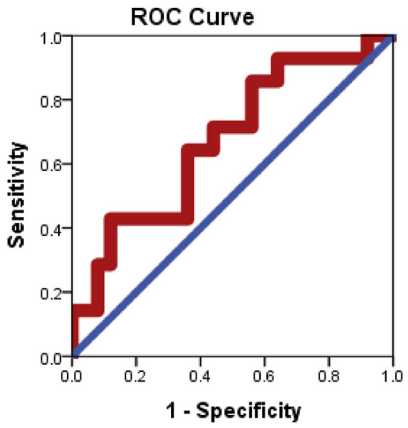

Fig. 4. ROC curve of CD163 (ng/ml) to differentiate between patients with FIB-4< 1.30 from those with Fib-4 score ≥ 1.30.

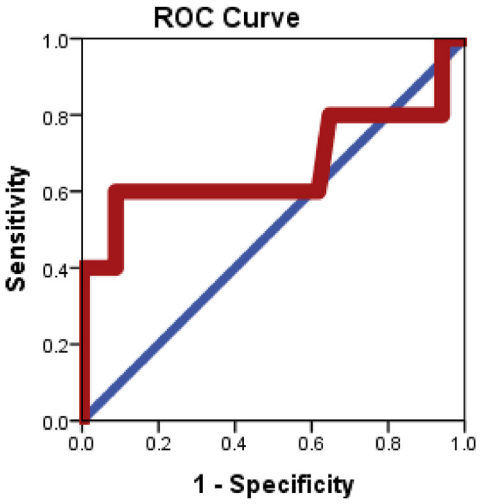

Fig. 5. ROC curve of CD163 (ng/ml) to differentiate between patients with FIB-4≤ 2.67 from those with Fib-4 score >2.67.

in patients with NAFLD whereas both Kupffer cells and adipose tissue macrophages probably contribute to sCD163 levels. These results are consistent with Mueller and coworkers study which indicated a significant association between sCD163, NASH, and fibrosis [8].

Increased sCD163 serum concentrations have been reported in patients with liver diseases [9–11]. sCD163 which measured in circulation has been found to be associated with metabolic disorders and it is considered as a strong predictor of the development of type 2 diabetes [12].

In agreement with our results, a previous study showed sCD163 as a strong and independent predictor of insulin resistance in sex- and BMI-matched individuals with type 2 diabetes, impaired glucose tolerance, and non-impaired glucose tolerance [13].

Also, patients in the obese non-diabetic group showed a slight increase in sCD163 than control subjects, but this increase did not reach the significant level. This is in contrast with the study of Zanni et al. who reported high levels of sCD163 in non-diabetic obese compared with lean subjects [14].

The present study indicated that sCD163 is positively correlated with total protein, potassium, cholesterol, and triglyceride. Furthermore, the present study showed that sCD163 has a negative correlation with LDL levels. Previous studies reported associations between sCD163 levels, triglyceride, and HDL-C levels [27]. Furthermore, lipid droplets inside the CD163-positive cells in patients with NASH, possibly reflecting cholesterol and its metabolites, which may contribute to macrophage activation [2,15].

In addition, the current study showed that there was slight elevation in renal functions in NAFLD patients. It is not surprising that these diseases may be linked as there is growing evidence that links NAFLD with impairment of renal function. Mounting evidence on liver-kidney interactions including; altered renin-angiotensin system (RAS) activation, impaired antioxidant defense and damaged lipogenesis is currently emerging as a major area of research.

The liver is the main regulator of glucose and lipid metabolism as well as the main source of inflammatory elements supposed to be involved in the development of kidney and cardiovascular disease. It is known that obesity is an independent risk factor for chronic kidney disease (CKD) and it is associated with the development of proteinuria and pathologic findings of podocyte hypertrophy and focal segmental glomerular sclerosis even in the absence of hypertension and diabetes.Moreover, studies have shown that obesity as well as metabolic syndrome is a strong predictor of the development of NAFLD. While the complex "crosstalk" among the liver, adipose tissue, and kidneys make it difficult to define the specific processes underlying NAFLD as a cause of CKD [16].

Furthermore, awareness of kidney disease among those with NAFLD-renal impairment and liver disease among those with NAFLD is suboptimal. It was estimated that there are more than 90% of individuals with kidney disease unaware that they have weak or failing kidneys and more than 95% of persons with NAFLD unaware that they are affected by a liver disease. Also, there are several studies on patients with NAFLD showing the prevalence of CKD between 4% and 40%. In addition, correlation between the severity of NAFLD and the progression of CKD was appeared [17].

5. Conclusions

Taken together, the results of this study suggest that serum levels of sCD163 could be used as a diagnostic marker for NAFLD disease. However, it didn't correlate with NAFLD fibrosis score of those patients and thus it couldn't predict the severity of the disease.

Declaration of competing interest

There are no conflicts of interest.

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References

[1] Kazankov K, Tordjman J, Møller HJ, Vilstrup H, Poitou C, Bedossa P, et al. Macrophage activation marker soluble CD163 and non-alcoholic fatty liver disease in morbidly obese patients undergoing bariatric surgery. J Gastroenterol Hepatol 2015b;30:1293–300.
[2] Kazankov K, Møller HJ, Lange A, Birkebæk NH, Holland-Fischer P, Solvig J, et al. The macrophage activation marker sCD163 is associated with changes in NAFLD and metabolic profile during lifestyle intervention in obese children. Pediatric Obesity 2015a;10:226–33.
[3] Wang J, Guo W, Du H, Yu H, Jiang W, Zhu T, et al. Elevated soluble CD163 plasma levels are associated with disease severity in patients with hemorrhagic fever with renal syndrome. PloS One 2014;9:e112127.
[4] Andersen ES, Rodgaard-Hansen S Fau - Moessner B, Moessner B Fau - Christensen PB, Christensen Pb Fau - Moller HJ, Moller Hj Fau - Weis N, Weis N. Macrophage-related serum biomarkers soluble CD163 (sCD163) and

soluble mannose receptor (sMR) to differentiate mild liver fibrosis from cirrhosis in patients with chronic hepatitis C: a pilot study. Eur J Clin Microbiol Infect Dis 2014;33:117–22.
[5] Kazankov K, Barrera F, Moller HJ, Bibby BM, Vilstrup H, George J, et al. Soluble CD163, a macrophage activation marker, is independently associated with fibrosis in patients with chronic viral hepatitis B and C. Hepatology 2014;60:521–30.
[6] Angulo P, Hui JM, Marchesini G, Bugianesi E, George J, Farrell GC, et al. The NAFLD fibrosis score: a noninvasive system that identifies liver fibrosis in patients with NAFLD. Hepatology (Baltimore, Md.) 2007;45:846–54.
[7] Calès P, Lainé F, Boursier J, Deugnier Y, Moal V, Oberti F, et al. Comparison of blood tests for liver fibrosis specific or not to NAFLD. J Hepatol 2009;50:165–73.
[8] Mueller JL, Feeney ER, Zheng H, Misdraji J, Kruger AJ, Alatrakchi N, et al. Circulating soluble CD163 is associated with steatohepatitis and advanced fibrosis in nonalcoholic fatty liver disease. Clin Transl Gastroenterol 2015;6:e114.
[9] Dolganiuc A, Norkina O, Kodys K, Catalano D, Bakis G, Marshall C, et al. Viral and host factors induce macrophage activation and loss of toll-like receptor tolerance in chronic HCV infection. Gastroenterology 2007;133:1627–36.
[10] Hiraoka A, Horiike N, Akbar SMF, Michitaka K, Matsuyama T, Onji M. Expression of CD163 in the liver of patients with viral hepatitis. Pathol Res Pract 2005;201:379–84.
[11] Holland-Fischer P, Grønbæk H, Sandahl TD, Moestrup SK, Riggio O, Ridola L, et al. Kupffer cells are activated in cirrhotic portal hypertension and not normalised by TIPS. Gut 2011;60:1389–93.
[12] Møller HJ, Frikke-Schmidt R, Moestrup SK, Nordestgaard BG, Tybjærg-Hansen A. Serum soluble CD163 predicts risk of type 2 diabetes in the general population. Clin Chem 2011;57:291–7.
[13] Parkner T, Sorensen LP, Nielsen AR, Fischer CP, Bibby BM, Nielsen S, et al. Soluble CD163: a biomarker linking macrophages and insulin resistance. Diabetologia 2012;55:1856–62.
[14] Zanni MV, Burdo TH, Makimura H, Williams KC, Grinspoon SK. Relationship between monocyte/macrophage activation marker soluble CD163 and insulin resistance in obese and normal-weight subjects. Clin Endocrinol 2012;77:385–90.
[15] Walenbergh SM, Koek GH, Bieghs V, Shiri-Sverdlov R. Non-alcoholic steatohepatitis: the role of oxidized low-density lipoproteins. J Hepatol 2013;58:801–10.
[16] Marcuccilli M, Chonchol M. NAFLD and chronic kidney disease. Int J Mol Sci 2016;17:562. https://doi.org/10.3390/ijms17040562.
[17] Le HM, Yeo HY, Henry L, Nguyen HM. Nonalcoholic fatty liver disease and renal function impairment: a cross-sectional population-based study on its relationship from 1999 to 2016. Hepatol Commun 2019;3:1334–46.