Original Article

The association of serum level of CTRP1 with Common Bile Duct Diameter and Other Manifestations in Patients with Non-alcoholic Fatty Liver

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Abstract

Background: Nonalcoholic fatty liver diseases (NAFLD) is one of the main chronic liver diseases and raises the risk of morbidity and mortality due to its inevitable outcomes. Understanding the clinical manifestations of the liver is critical to identify NAFLD patients with the greatest risk of developing nonalcoholic steatohepatitis and cirrhosis. In the liver, C1q/TNF-related protein 1 (CTRP1) modulates both glucose and lipid metabolism and improves insulin sensitivity which may affect the pathologies of the liver. **Materials and Methods:** This study was conducted on 22 patients with NAFLD confirmed by ultrasonography and 21 healthy subjects. Clinical and histological variables were analyzed. The ultrasonography procedure was used to quantity Common bile duct (CBD). Liver stiffness (LS) was measured by transient elastography. **Results**: There was a significant difference in CTRP1 levels between NAFLD patients and controls (p=0.032). Moreover, there was a significant positive correlation between CTRP1 level and liver enzymes including AST (r=0.667; p=0.001), ALT (r=0.433; p=0.044), and γ-GT (r=0.428; p=0.047) in NAFLD patients. There was also a significant positive correlation between CTRP1 level and CBD (r= 0.469; p=0.028) in NAFLD patients. Moreover, the largest CBD was measured as 5.99 mm. **Conclusion:** It seems that CTRP1 is a novel adipokine related to the pathogenesis of NAFLD and is associated with the clinical manifestations of the liver such as liver enzymes, and CBD.

Keywords*:* Nonalcoholic fatty liver diseases (NAFLD), C1q/TNF-related protein 1 (CTRP1), Common bile duct (CBD), Liver stiffness (LS).

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Introduction

Nonalcoholic fatty liver disease (NAFLD) is recognized as one of the most prevalent liver diseases involving a great proportion of the general population. NAFLD is strongly related with the entire spectrum of metabolic-related diseases such as obesity, type two diabetes, and cardiovascular diseases [1]. Regarding many similar mechanism underlying metabolic disorders, the existence of common molecular regulators contributing to the incidence of these diseases is predictable. Rising evidence indicated the critical role of adipokines in the pathomechanism of NAFLD. Adipokines secreted by various tissues, particularly adipose, regulate several processes such as glucose and lipid metabolism [2]. Previous studies

indicated that Adipokines can regulate many biological processes involved in hepatic function, such as inflammation, angiogenesis, vasodilation, and deposition of fat. Therefore, these molecules are supposed to regulate disease severity in NAFLD patients. Subsequently, their serum levels may be correlated with parameters of hepatic function which are linked to the complications of such patients [3].

Among these adipokines, C1q/TNF-related proteins (CTRPs) as recently recognized adipokines have an important role in energy homeostasis and diseases related to the liver [4]. CTRP1 as a novel metabolic hormone is a member of CTRPs family which is shown to have imperative roles in glucose and lipid metabolism. CTRP1 improves glucose and lipid oxidation, insulin sensitivity, and overall energy homeostasis [5]. Previous studies reported that an abnormal secretion of CTRP1 results in defects in energy homeostasis and following insulin resistance (IR) in different tissues, particularly in the liver. Moreover, it is indicated that CTRP1 declines the formation of plaques and induces the generation of aldosterone. Consequently, CTRP1 may be linked to the pathogenesis of NAFLD in various ways [6-8].

Clinical manifestations of the liver i.e. fibrosis, steatosis, and focal lesions along with the bile ducts measurement such as common bile duct (CBD) provide critical information about the greatest risk of developing nonalcoholic steatohepatitis and cirrhosis in patients with NAFLD [9]. Although there are several studies on the association of CTRP1 with metabolic characteristics in patients suffering from metabolic abnormalities, no study has been conducted on the association of this CTRP with CBD in NAFLD.

Regarding the important role of CTRP1 as a novel adipokine related to the pathogenesis of NAFLD and its possible correlation with the clinical manifestations of the liver such as liver enzymes, liver stiffness (LS), and CBD, here, we aimed to examine such associations in NAFLD patients compared to healthy subjects in order to provide new information underlying the possible development of nonalcoholic steatohepatitis and cirrhosis in relation with the secretion of CTRP1 along with the changes in clinical manifestations of the liver.

Methods

Study Population. A total of 43 subjects including 22 with NAFLD and 21 healthy individuals aged 43–72 years participated in this study. The participants were recruited from who referred to Shariati Hospital from March 2012 until November 2013. Ultrasonography was applied to diagnose NAFLD patients. This study was approved by the Ethics Committee of Tehran University of Medical Sciences (TUMS). Written informed consents were collected from all participants prior to the study. Participants were excluded if they had excessive alcohol consumption (> 30 g/d), or were diagnosed by severe related diseases such as viral hepatitis, hemochromatosis, autoimmune liver disease, and renal disease. Moreover, they were not eligible if had medication that caused steatosis including steroids, tamoxifen, estrogens, diltiazem, valproic acid, or methotrexate [5]. Liver ultrasound examination revealed the diameter of CBD and intrahepatic bile ducts due to the presence of a CBD stone.

Anthropometric and laboratory measurements. Anthropometric indices of all participants including age, weight, height, and waist circumference (WC) were measured. Body mass index (BMI) was evaluated as body weight (kg) divided by the square of height (m2). Waist–hip ratio (WHR) was calculated according to the ratio of WC in cm divided by hip circumference in cm. For measuring the systolic and diastolic blood pressures, a manual sphygmomanometer was used.

Biochemical and Laboratory Measurements. Serum was separated from blood samples collected from participants after overnight fasting. Blood samples were collected from all participants in EDTA-containing tubes after overnight fasting. Next, blood samples were centrifuged for collection of plasma and stored at -80°C for the next analysis. Aspartateamino transferase (AST), alanine aminotransferase (ALT), and gamma-glutamyl transferase (γ-GT) were measured by auto analyzer using commercial kits (Pars Azmoon, Tehran, Iran). Any other biochemical parameters were analyzed by enzymatic process using assay kit adapted in hospitals. Homeostasis model assessment of IR (HOMA-IR) was calculated to recognize the insulin resistance (IR), using the

equation of fasting blood glucose (mg/dL) × fasting blood insulin (μU/mL) / 405. Adiponectin level was measured using the ELISA Kit (Elabscience, Wuhan, China) based on the manufacturer's protocol.

CTRP1 Measurement. CTRP1 levels were measured using an ELISA kit (Biovendor research and diagnostic products) with a minimum detectable concentration of 0.016 ng/ml, Intra assay Coefficients of Variability (CV) was 2.7% and Inter-assay CV was 8.5%.

LS measurement. LS was calculated using transient elastography by the FibroScan 502 machine (EchoSense, Paris, France, 5MHz). The M probe was applied for individuals with thoracic perimeter less than 110 cm and the XL probe for 110 cm and above, based on the manufacture's protocol. The probe was placed on the subject's skin, overlying the right lobe of the liver, through the intercostal spaces. Each subject had at least ten measurements and the median value was documented. With an inter-quartile range of less than 30 % of the median reading, values were regarded as valid.

Statistical Analysis. Values were presented as mean ± standard error of mean (SEM). Normality was tested for all quantitative variables by means of the Shapiro-Wilk test. Independent student t-test was applied for the comparison of data between NAFLD and healthy participants. Pearson correlation analysis was done to assess the possible correlation between CTRP-1 and biochemical features. P-value of <0.05 was considered statistically significant. SPSS 20 (SPSS, Chicago, IL, USA) was applied to analyze the results.

Results

The clinical and laboratory characteristics of study participants are provided in Table 1. Based on the results, BMI (p=0.000), WHR (p= 0.000), creatinine (p=0,000), TG (p=0.019), ALT (p=0.001) γ-GT (p=0.001), insulin (p=0.001), HOMA-IR (p=0.001), and LS (p=0.004) were significantly different among two groups. Mean value of CTRP1 and adiponectin between two groups are depicted in fig 1 and 2, respectively. The circulating levels of CTRP1 and adiponectin were significantly different in the two groups (p<0.05). Indeed, the NAFLD group had a higher level of CTRP1 (p=0.032) and lower level of adiponectin (p=0.002) compared to the control group.

Table1. Anthropometric and laboratory characteristics of study population.

	Healthy subjects	NAFLD subjects	Total difference p value
Age, years	52.96±8.34	51.84±6.32	0.448
SBP, mmHg	120.33±21.22	132.57±19.40	0.003
DBP, mmHg	75.31±13.89	84.20±13.82	0.002
BMI, kg/m2	23.90±4.7	28.58±3.68	0.000
WHR, -	0.93±0.07	0.99±0.03	0.000
FBG, mg/dL	91.79±7.53	93.93±8.97	0.198
Urea nitrogen, mg/dL	29.7±6.54	29.79±8.61	0.956
Creatinine, mg/dL	1.10±0.24	1.3±0.17	0.000
TG, mg/dL	124.31±38.15	150.44±67.95	0.019
LDL-C, mg/dL	106.84±26.36	118.90±34.16	0.050
HDL-C, mg/dL	54.38±11.98	52.26±12.53	0.389
AST, U/L	21.41±5.58	23.68±9.41	0.147
ALT, U/L	19.39±7.82	28.76±17.33	0.001
γ-GT, U/L	21.94±14.09	34.57±22.86	0.001
Insulin, μU/mL	4.95±5.57	9.25±5.48	0.001
HOMA-IR, -	1.13±1.30	2.15±1.27	0.001
LS, kPa	4.08±1.21	5.18±1.78	0.004
CBD, mm	4.61±1.38	4.52±1.44	0.812

*Correlation is significant at .05. Continuous variables with normal distribution were described as mean ± SEM. NAFLD, non-alcoholic fatty liver disease; SBP ,systolic blood pressure; DBP, diastolic blood pressure; BMI ,body mass index; WHR ,waist-to-hip ratio; FBG ,fasting blood glucose; TG, triglycerides; HDL- C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; ALT ,alanine amino transferase; AST, aspartate amino transferase; ɤ-GT , gamma glutamyl transferase; LS ,liver stiffness; HOMA-IR, homeostasis model assessment of insulin resistance; CBD, common bile duct;

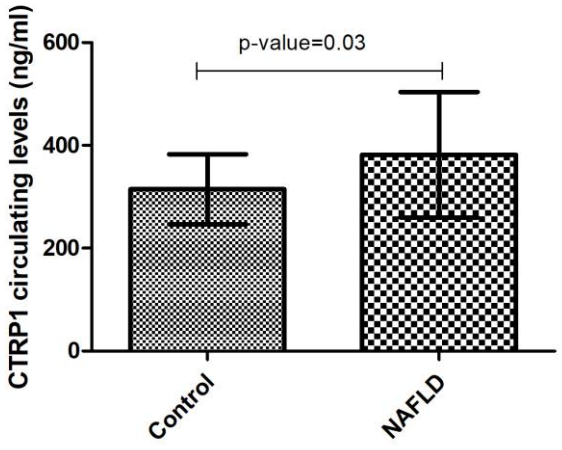

Figure 1. Graphic representation of the circulating level of CTRP1 in NAFLD group compared to control group. Data was shown as mean ± standard error of mean (SEM).

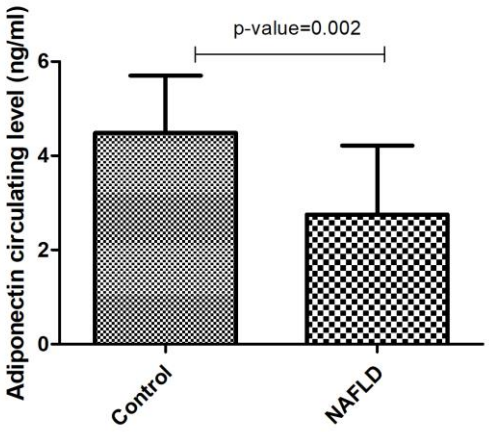

Figure 2. Graphic representation of the circulating level of adiponectin in NAFLD group compared to control group. Data was shown as mean ± standard error of mean (SEM).

We also analyzed the correlation between CTRP1 levels and liver enzymes including AST, ALT, γ-GT, insulin, HOMA-IR, LS, and CBD in the whole study population as provided in Table 2. We observed a significant positive correlation between CTRP1 level and liver enzymes including AST (r=0.667; p=0.001), ALT (r=0.433; p=0.044), and γ-GT (r=0.428; p=0.047) in NAFLD patients. There was also a significant positive correlation between CTRP1 level and CBD (r= 0.469; p=0.028) in NAFLD patients.

Table 2. The correlation of CTRP1 circulating levels with clinical manifestations of the liver in healthy and NAFLD subjects.

	Healthy subjects		NAFLD subjects	
CTRP1	**p**	**r**	**p**	**r**
AST, U/L	0.973	-0.008	0.001	0.667
ALT, U/L	0.360	-0.216	0.044	0.433
γ-GT, U/L	0.302	0.237	0.047	0.428
Insulin, µU/mL	0.868	0.039	0.160	0.310
HOMA-IR, -	0.751	0.076	0.100	0.360
LS, kPa	0.444	0.175	0.204	0.296
CBD, mm	0.753	0.073	0.028	0.469

*Correlation is significant at .05. NAFLD, non-alcoholic fatty liver disease; AST, aspartate amino transferase; ALT ,alanine amino transferase; ɤ-GT , gamma glutamyl transferase; LS ,liver stiffness; HOMA-IR, homeostasis model assessment of insulin resistance; CBD, common bile duct; CTRP1, C1q/TNF-related protein 1.

Discussion

The main finding of this study was a higher significant level of plasma CTRP1 in NAFLD patient compared to healthy subjects. Moreover, we measured the clinical manifestations of the liver of all participants including liver enzymes, LS, and CBD and their significant positive correlation with the circulating level of CTRP1.

Chronic liver diseases such as NAFLD are reliable for developing hepatic fibrosis, cirrhosis, and hepatocellular carcinoma. NAFLD along with cholestatic liver diseases include a large number of conditions in which the damage is mainly focused on the liver and biliary system. These circumstances are linked to a specific pattern of chronic liver diseases focused on the bile ducts injury and are associated with biliary cirrhosis and liver failure [10].

As the liver produces bile containing bile salts, cholesterol, and bilirubin, its disorders such as cirrhosis may contribute to the altered size of bile ducts from the liver to the gallbladder. In turn, bile duct obstructions may worsen chronic liver diseases, such as cirrhosis. Remarkably, people with liver and bile ducts disorders have a greater risk of developing related cancers [11-13]. Ultrasound imaging is a usual technique for the identification of biliary diseases which mostly occur in intrahepatic and extrahepatic biliary dilatation. The diameter of a common bile duct (CBD) is measured and recorded by this technique. Remarkably, some studies use sonography to measure the diameter changes of the CBD after cholecystectomy Based on available literature, the dilatation of the common bile duct seems to be helpful in distinguishing obstructive from non-obstructive causes of jaundice. Accordingly, it seems that increased level of CTRP1 act as a possible part in mediating CBD malstructure in NAFLD patients [14]. According to previous studies, the normal size of CBD is ranged between 4-12 mm with an average of 7.39 ± 1.64 mm [15]. Moreover, the upper limit of normal for the CBD is regarded as 4–10 mm [16-18].

There is growing evidence suggesting the involvement of several factors including IR in the pathogenesis of NAFLD, however, it still needs further

investigations [19-23]. Previous studies indicated that Adipokines can control different biological and molecular mechanisms involved in the hepatic function, such as inflammation, insulin sensitivity, and fat deposition [24-26]. Consequently, their circulating levels may propose correlations with parameters of hepatic clinical manifestations [3]. Among adipokines, CTRPs family, as a newly introduced family of adiponectin paralogs are important factors regulating energy homeostasis and IR [27-31]. However, their exact role in the pathogenesis of NAFLD, the related hepatic manifestations, and the following disposition of nonalcoholic steatohepatitis and cirrhosis have not been elucidated. In our recent study, we indicated the important role of CTRP1 in the pathogenesis of NAFLD with regulating glucose and lipid metabolism. Indeed, CTRP1 improves glucose and fatty acid oxidation and insulin sensitivity in tissues such as liver [5-8]. Nevertheless, the association between CTRP1 and hepatic manifestations such as liver enzymes, LS, and CBD is not examined in previous studies and thus, the present study aimed to explore such associations in NAFLD patients compared to healthy subjects for the first time.

Several studies indicated the higher circulating levels of CTRP1 in patients with type two diabetes, metabolic syndrome and coronary artery disease [32-34]. In contrast, it was reported that CTRP1 level was significantly decreased in diet-induced obese mice which was correlated with improving the insulin sensitivity and decreasing the weight gain. It is stated that CTRP1 may decrease fat accumulation by enhancing fatty acid oxidation and energy expenditure through AMP-activated protein kinase (AMPK) activation, which stimulates mitochondrial fat oxidation. We propose several possibilities about the higher levels of CTRP1 and insulin together in the NAFLD patients compared to controls. First, it seems likely that the higher level of CTRP1 with a positive correlation with liver manifestations such as liver enzymes and CBD may be attributed to its compensatory role for improving insulin sensitivity. Second, it may also show CTRP1 resistance in response to NAFLD development [5]. It should be noted that a higher expression of insulin, as a hallmark of IR, caused to fatty acid synthesis and accumulation in the liver [35]. Putting these together, CTRP1 may improve fat deposition and subsequent liver and bile duct damage through increasing insulin sensitivity.

Furthermore, CTRP1 as a paralog of adiponectin, mediates some of its hepatoprotective functions, through compensating the action of adiponectin [35, 36]. This was supported by previous studies which indicated a higher level of CTRP1 in adiponectin-deficient mice [34, 37-40]. Since the adiponectin level was significantly lower in NAFLD patients compared to healthy subjects, the compensatory role of CTRP1 for loss of adiponectin may be considered here [41, 42].

Conclusion

Collectively, this study suggests the association between CTRP1 level and clinical manifestations of the liver i.e. hepatic enzymes including AST, ALT, and γ-GT and also CBD in NAFLD detection which provides new information underlying the possible development of nonalcoholic steatohepatitis and cirrhosis in patients with NAFLD. However, further investigations are required.

Conflict of Interest

There is no conflict of interest among authors.

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