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Original Article

Serum soluble TWEAK levels in non-alcoholic fatty liver disease

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Abstract

Aim: Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease. The exact pathogenesis of NAFLD has not been fully elucidated. Tumor necrosis factor-like weak inducer of apoptosis (TWEAK) is a member of TNF superfamily and it has been implicated in the pathogenesis of several diseases including liver inflammation and fibrosis. Current study was conducted to evaluate serum sTWEAK levels in patients with NAFLD.

Material and Methods: Seventeen patients with biopsy proven non-alcoholic steatohepatitis (NASH), 22 patients with simple hepatosteatosis and 30 healthy controls were included in the study and serum sTWEAK concentrations were measured using commercial ELISA kits.

Results: Mean serum sTWEAK concentration was significantly lower in the NASH group when compared to the simple hepatosteatosis group and healthy controls (199.6±101.2 pg/mL, 246.1±65.7 pg/mL and 277.6±117.6 pg/mL respectively, p=0.029). ROC analyses for sTWEAK to differentiate NASH patients from healthy controls and from simple hepatosteatosis revealed that AUC for sTWEAK was 0.712 (%95 CI, 0.543-0.880). For the specified cut off value, 171.1 pg/mL positive and negative predictive values calculated were 64.3% and 85.5% respectively.

Conclusion: Serum sTWEAK concentration is decreasedin patients with NASH when compared to patients with simple hepatosteatosis and healthy controls.

Keywords: Nonalcoholic steatohepatitis; tumor necrosis factor-like weak inducer of apoptosis; sTWEAK; fibroblast growth factor-inducible 14; Fn 14

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease in the world. Clinic spectrum rangesfrom simple hepatosteatosis to end stage liver disease.Demographical distribution of NAFLD varies worldwide but the prevalence is increasingand it has become one of the most important etiologies for endstage liver disease globally(1). Nonalcoholic steatohepatitis (NASH) is the key point in NAFLD because it is characterized by inflammation and progressive fibrosis. Pathophysiologic mechanisms underlying NASH are poorly defined but several cytokines as well as other factors such as insulin resistance, oxidative stress, gut derived metabolic products, microbiota and immune mechanisms have been shown to take roles (2-5).

Tumor necrosis factor-like weak inducer of apoptosis (TWEAK) is a member of the tumor necrosis factor (TNF) superfamily. It is a cell surface-associated transmembrane protein. Membrane bound TWEAK is cleaved by proteases freeing the extracellular domain. This biologically active, solublepart (sTWEAK)can be detected in plasma and it functions as a cytokine (6). sTWEAK exerts its effects through binding to its receptor known as fibroblast growth factor-inducible 14 (Fn14) (7). TWEAK has been shown to be associated with various diseases such as myocardial remodeling, atherosclerosis, heart failure, renal diseases

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and a number of inflammatory diseases (8-11). There are also studies in the literature implicating possible role of TWEAK in the development of liver inflammation and fibrosis (12-14).In this context, current studywas conducted to evaluate serum sTWEAK levels in patients with NAFLD.

MATERIAL and METHODS

This was a cross-sectional study. The local Comity of Ethics of Necmettin Erbakan University, Meram Faculty of Medicine, approved the study protocol. Seventeen patients with biopsy proven NASH, 22 patients with simple hepatosteatosisand 30 healthy controls were included in the study. Written informed consentswere taken from all participants. Simple hepatosteatosis group consisted of patients with normal transaminases and various degree of liver steatosis diagnosed withabdominal ultrasound. According to abdominal ultrasound findings, liver steatosis was graded as; grade 0: no steatosis, grade I: increased liver echogenicity with visible periportal and diaphragmatic echogenicity, grade II: increased hepatic echogenicity with imperceptible periportal echogenicity, without obscuration of diaphragm and grade III: increased hepatic echogenicity with imperceptible periportaland hepatic venous echogenicity and obscuration of diaphragm. NASH group on the other hand consisted of patients with elevated liver enzymes and the presence of steatohepatitis confirmed with liver biopsy. Hepatitis B core antigen, hepatitis B surface antigen, anti-HCV antibody, autoimmune hepatitis markers (anti-nuclear antibody, anti-smooth muscle antibody, anti-liver-kidney microsomal antibody),serum copper and ceruloplasmin levels and serum transferring saturation were obtained for all patients in the NASH group to exclude any other etiological risk factor for chronic liver disease.Control group consisted of 30 healthy people with normal liver enzymes and negative serological tests for hepatitis B and C (Hepatitis B surface antigen, Hepatitis B core antigen, anti-HCV antibody) and absence of liver steatosis confirmed with abdominal ultrasound examination. Patients with known chronic liver diseases of any other etiology, patients with considerable alcohol consumption (>20 g/day for males and >10g/day for females), patients with known malignancies, autoimmune diseases, or any active infections were excluded. Blood pressure measurements and anthropometric measurementswere obtained in all patients in addition to routine physical examination. The weight and height of the participants were measuredin light clothing using calibrated scales. Body-mass index (BMI) was computed using formula: BMI=body weight/(height)^2.

Blood samples for biochemical analysis were obtained early in the morning. Serum glucose and bilirubin levels, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma-glutamyltransferase (GGT) activities were measured by using standard auto analyzer methods on Abbott Architect 16000 system (Abbott Laboratories, Abbott Park, IL, USA) with the original reagents according to the manifacturer's instructions. Serum samples for sTWEAKwere separated by centrifugation at 4000 rpm/min for 5 minutes at 4 °C and samples were immediately transferred to freezer to be stored at -80 °C until they were analyzed. sTWEAK levels were measured with a commercially available kit based on enzyme-linked immunosorbent assay (eBioscience, Human TWEAK Instant Elisa, Cat no: BMS2006INST). The results were givenas pg/mL. Intra- and interassay coefficients of variation were 5.1% and 7.9% respectively. Fibrosis-4 (FIB-4) score, AST to Platelet Ratio Index (APRI) and AST to ALT ratio (AAR) were calculated for the patient and the control groups using formulas: FIB-4 = [AST (U/L)× age (years)]/[(ALT (U/L)1/2× Plt (109/L)], APRI = 100 × [AST/AST upper limit of normal)/Plt (109/L)] and AAR=AST/ALT

Statistical analyses were done using computer software "IBM SPSS Statistics for Windows, Version 19.0" (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean±standard deviation. One sample Kolmogorov-Smirnov test was used to test continuous variables for normal distribution. Comparisonsof tested parameters were done using Kruskall–Wallis test when more than two group exists. Mann–Whitney U test was used to search for the significance of difference between two groups. Spearman's rho test was used to test for the significance of the linear correlation between continuous variables. Receiver operating characteristic (ROC)analyses were done to test the ability of serum sTWEAKconcentration to differentiate patients with steatohepatitis from patients with simple hepatosteatosis. Statistical significance was defined as $p<0.05$ for all analyses.

RESULTS

Age and gender distribution were found to be similar in all three groups ($p>0.05$). Mean fasting serum glucose, directand indirect bilirubin levels, AST, ALT, GGT and ALPactivities were significantly higher and mean serum hemoglobin concentration was significantly lower in the NASH group than the simple hepatosteatosis group and healthy controls (Table 1).Considering anthropometric measurements, waist to hip ratio and BMI were significantly higher in the NASH groupwhen compared to both simple hepatosteatosis group and healthy controls. Mean diastolic and systolicblood pressures were also found to be significantly higher in the NASH group. As previously defined, FIB-4 score, APRI and AARwere calculated as non-invasive fibrosis scores for all patients in all the three groups. Mean AAR, APRI and FIB-4 scores were significantly higher in the NASH group then thesimple hepatosteatosis group and healthy controls.Laboratory data and demographical characteristics of the groups were summarized in Table 1.

Mean serum sTWEAK concentration was 199.6±101.2pg/mL in the NASH group. Measured mean serum sTWEAK concentrations were 246.1±65.7pg/mL and 277.6±117.6pg/mLin the simple hepatosteatosis group and healthy controls respectively and the difference

between all three groups was statistically significant (p=0.029). Statistical analyses revealed that NASH patients had significantly lower serum sTWEAK concentrations then patients with simple hepatosteatosis and healthy controls (p=0.034 and p=0.013 respectively) but the difference between simple hepatosteatosis group and healthy controls was not statistically significant (p>0.05). Mean serum sTWEAK levels for the groups are summarized in Figure1.

Statistical analyses revealed significant negative correlations between sTWEAK levels and BMI, AST, ALT, serum albumin concentration and APRI scores (table 2).

Table 1. Clinical and laboratory data and demographical characteristics of the groups

	Control group (n = 30)	Simple Hepatosteatosis (n = 22)	NASH (n = 17)	p
Age (years)	42.9±6.7	44.7±11.1	49.7±9.3	0.54
Male (n,%)	17(56.7)	11(50)	6(35.3)	0.37
BMI (kg/m2)	24.1±2.2a	28.5±3.2b	29.2±7.8b	<0.001
Waist to hip ratio	85.4±9.1 a	92.3±8.2 a,b	101.3±13.3 b	0.033
SBP (mmHg)	104.5±10.6 a	125.9±10.5 b	121.47±13.2 b	<0.001
DBP (mmHg)	68.2±7.5 a	75±8.0 b	77.1±8.5 b	0.001
sTWEAK(pg/mL)	277.6±117.6a	246.1±65.7 a	199.6±101.2 b	0.029
Glucose (mg/dL)	94.9±14.5 a	100.4±14.2 a	150.5±69.0 b	0.003
BUN (mg/dL)	27.5±6.2	27.7±6.8	29.4±10.1	0.68
Creatinine (mg/dL)	0.76±0.12	0.74±0.16	0.74±0.22	0.43
ALT (U/L)	19.9±11.4 a	24.7±12.7 a	123.0±143.8 b	<0.001
AST (U/L)	20.3±4.8 a	21.2±7.1 a	66.5±41.3 b	<0.001
GGT (U/L)	22.±12.1 a	30.3±12.5 b	94.9±121.8 c	<0.001
ALP (U/L)	67.0±12.6 a	73.6±12.9 b	110.4±104.1 b	0.006
T.Bil (mg/dL)	0.65±0.29	0.66±0.36	0.96±0.68	0.10
D.Bil (mg/dL)	0.20±0.11 a	0.20±0.08 a	0.33±0.18 b	0.004
TP (g/dL)	7.2±0.3	7.15±0.6	6.9±0.9	0.42
Alb (g/dL)	4.3±0.3	4.3±0.4	4.0±0.5	0.22
TG (mg/dL)	115.9±58.9	177.8±106.6	160.1±66.8	0.055
Total cholesterol (mg/dL)	187.4±29.4	213.8±61.3	210.8±58.9	0.12
LDL-C (mg/dL)	115.8±36.1	136.1±43.2	136.5±58.8	0.27
HDL (mg/dL)	45.1±12.9	46.2±7.9	41.0±8.4	0.25
Hemoglobin (g/dL)	14.7±1.5 a	14.8±1.2 a	13.4±2.2 b	0.029
Hct (%)	42.5±3.7	44.0±73.2	40.2±5.4	0.052
Leukocyte (mm3)	7.0±1.2	7.7±1.6	7.6±1.8	0.25
Thrombocyte (mm3)	248.2±54.5	268.0±51.6	268.1±72.8	0.32
APRI	0.26±0.09 a	0.25±0.21 a	0.76±0.48 b	<0.001
FIB-4	0.85±.25 a	0.78±.35 a	1.27±0.45 b	0.001
AAR	1.21±.47 a	0.93±.25 b	0.80±0.39 b	0.005

BMI: Body mass index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, sTWEAK: soluble tumor necrosis factor-like weak inducer of apoptosis, BUN: Blood urea nitrogen, ALT: alanine aminotransferase, AST: aspartate aminotransferase, GGT: gamma-glutamyltransferase, ALP: alkaline phosphatase, T.Bil: total bilirubin, D.Bil: direct bilirubin, TP: total protein, Alb: Albumin, TG: triglyceride, LDL-C: Low density lipoprotein, HDL: high density lipoprotein, Hct: hematocrit, APRI: AST to Platelet Ratio Index, FIB-4: Fibrosis-4 score, AAR: AST to ALT ratio

Table 2. Correlation analyses

	sTWEAK	
	Spearman's rho	P
BMI (kg/m²)	-0.301	0.012
Waist to hip ratio	-0.97	0.43
Glucose (mg/dL)	-0.18	0.886
AST (U/L)	-0.258	0.032
ALT (U/L)	-0.346	0.004
GGT (U/L)	-0.218	0.088
ALP (U/L)	-0.101	0.438
Alb (g/dL)	0.301	0.016
Total cholesterol (mg/dL)	-0.19	0.902
TG (mg/dL)	-0.219	0.147
Thrombocyte (mm³)	0.219	0.071
FIB-4	-0.174	0.153
APRI	-0.367	0.002
AAR	0.237	0.050

sTWEAK: soluble tumor necrosis factor-like weak inducer of apoptosis, BMI: Body mass index, AST: aspartate aminotransferase, ALT: alanine aminotransferase, GGT: gamma-glutamyltransferase, ALP: alkaline phosphatase, Alb: Albumin, TG: triglyceride,FIB-4: Fibrosis-4 score, APRI: AST to Platelet Ratio Index, AAR: AST to ALT ratio.

Table 3. Liver biopsy findings

Histology		n (%)
Degree of steatosis		
	5%-33%	10 (58.8)
	33%-66%	5 (29.4)
	>66%	2 (11.8)
Inflammation		
	Grade 1	7 (41.2)
	Grade 2	6 (35.3)
	Grade 3	4 (23.5)
Ballooning		
	none	5 (29.4)
	mild	5 (29.4)
	severe	7 (41.2)
Fibrosis		
	None	4 (23.5)
	Mild	4 (23.5)
	Moderate	4 (23.5)
	Severe	5 (29.5)

As previously stated, all patients in the NASH group had liver biopsies performed. Liver biopsy findings of the NASH patients are givenin Table 3. None of the biopsy findings (ballooning, degree of steatosis, inflammation and fibrosis) were found to be associated with serum sTWEAK levels (p>0.05).

All patients in the NASH group and simple hepatosteatosis group had various degrees of liver steatosis diagnosed with abdominal ultrasound. Serum sTWEAK levels were not found to be associated with degree of steatosis in abdominal ultrasound (p>0.5).

ROC curves were obtained to test the ability ofsTWEAKto differentiate NASH patients from patients with simple hepatosteatosis and healthy controls. CalculatedAUC for sTWEAK was 0.712 (%95 CI, 0.543-0.880) and the specified cut off value of 171.1 pg/mL yielded a negativepredictive value of 85.5% and a positive predictive value of 64.3%.Healthy controls were excluded from the analysis and AUC was recalculated to test the ability of sTWEAK to differentiate NASH patients among all patients with hepatosteatosis in abdominal ultrasound. AUC for sTWEAK was 0.701 (%95 CI, 0.510-0.891) and a cut off value 176.6 pg/mL yielded a positive predictive value of 83.3% and a negative predictive value of 74.1% (Figure 2).

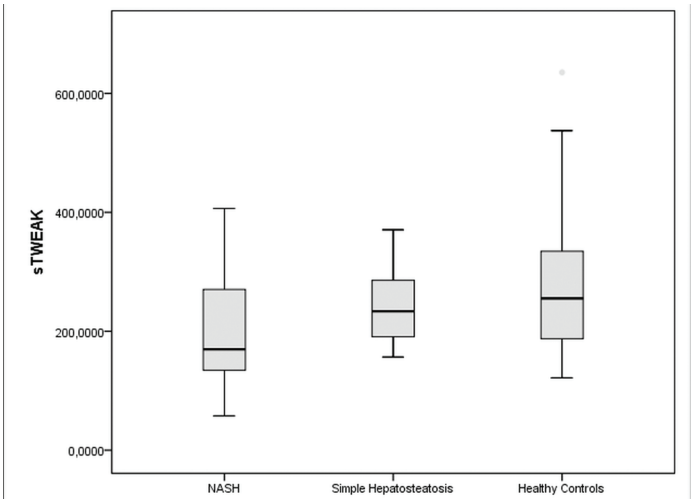

Figure 1. Serum sTWEAK concentrations in NASH, simple hepatosteatosis and healthy control groups

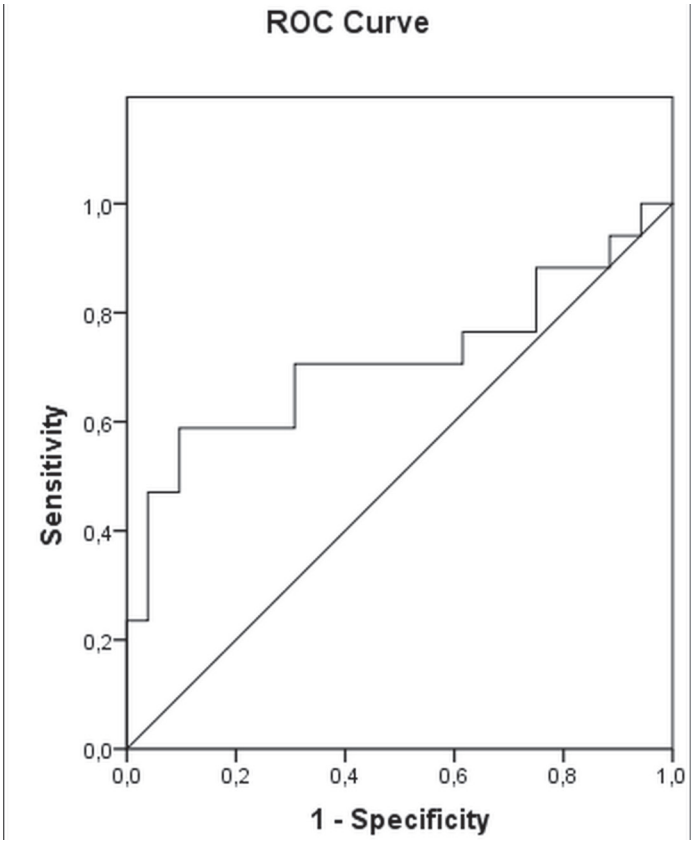

Figure 2. ROC analysis for sTWEAK

DISCUSSION

NAFLD is the most common liver disease in the world. It is also a growing health problem in our country and in our district (15). From clinical point of view, it is of particular importance to differentiate NASH patients from simple hepatosteatosis because a significant proportionof patients with NASH may progress to cirrhosis. Currently, there is no optimal validated non-invasive marker to diagnose patients with NASH,and liver biopsy remains to be the gold standard. The exact pathophysiological mechanisms underlying NAFLD are also poorly understood.

TWEAK has been shown to be associated with various cellular responses such as stimulation of cell growth, promotion of angiogenesis and fibrogenesis and induction of several inflammatory cytokines. Expression of TWEAK and its receptor in normal tissues without an apparent tissue injury have been shown to be very low. On the other hand, TWEAK and particularly Fn 14 expression have been shown to be dramatically upregulated in case of tissue damage. Several studies have also shown that TWEAK/Fn14 pathway is involved in both acute and chronic forms of liver injury in different clinical settings and experimental models (16-17).

The results of the current study have shown that serum sTWEAK levels are decreased in patients with NASH whencompared to patients with simple hepatosteatosis and healthy controls. The number of studies investigating serum sTWEAK levels in patients with NAFLD are limited. In fact, to our knowledge there is only one other study in the field and the results of that study are also in consistency with our results. In the study conducted by Lozano-Bartolomé J et al. (18) sTWEAK levels wereshown to be decreased in patients with NAFLD and low sTWEAK concentration was found to be independently associated with the presence of NAFLD.

At first glance, this decrease in serum sTWEAK concentrationin NASH patients seems to be contradictory, becauseNASH is associated with various degrees of hepatocellular inflammation and parenchymal fibrosis and acting as a cytokine and being involved in various inflammatory conditions, sTWEAK would also be expected to rise in NASH patients. Nevertheless, we believe that the condition in vivo settings might be much more complex. A possible explanation of the decrease in serum sTWEAK concentration would bea dramatic increase in the liver expression of Fn14 in NASH patients due to ongoing tissue injury that would result in entrapment of circulating sTWEAK molecules by the increased Fn14 receptors. Indeed, this scenario would both explain an increase of TWEAK/Fn14 activity at tissue level and decreased serum sTWEAK concentrations in NASH patients. Increased TWEAK/Fn14 binding would stimulate TWEAK associated inflammatory and fibrogenetic pathways within the liver contributing to NASH pathogenesis even though measured serumsTWEAK concentration is low. In fact, previous studies of TWEAK/Fn14 pathway have yielded somebreadcrumbs that supports our hypothesis. First of allFn14 was shown to be highly inducible in several studies, meaning that, under normal conditions Fn14 expression is very low in healthy tissues and its expression increases several fold in case of tissue injury. Karaca et al. (19) have demonstrated that baseline Fn 14 expression is very low in liver samples from healthy mice and rapidly undergoes approximately 50 times increase after partial hepatectomy. The same study also revealed that TWEAK/Fn14 axis is important for stimulation of liver progenitor cells and activation of hepatocyte and cholangiocyte proliferation. Also, in a very well-designed study conducted by Wilhelm et al. (20) it has been shown that expression of TWEAK and Fn 14 were very low in histologically normal liver tissues but Fn 14 expression was increased up to 58-fold after carbon tetrachloride induced liver injury. In that study, tissue concentrations of TWEAK, Fn 14 and their associated mRNA were also shown to be increased in liver biopsy samples from patients with NAFLD and immunohistochemical analysis have demonstrated that hepatic stellate cells and myofibroblasts expressed TWEAK and Fn14. Because of these findings the authorsargued that TWEAK/Fn14 axis may take role in the pathogenesis of liver fibrosis upon acute and chronic liver injury and TWEAK may exert its function on hepatic stellate cells in a paracrine/autocrine manner which also supports our hypothesis.

Another interesting point noteworthy to emphasize is that, there arestudies in the literature where low serum sTWEAKconcentrations hasbeen reported in various diseases associated with increased cardiovascular risk such as coronary and peripheral arterial disease, end-stage renal disease and type 2 diabetes mellitus (9,21-23). NASH is also well documented to be associated with increased cardiovascular risk, obesity, metabolic syndrome and diabetes mellitus. A low level of chronic inflammation is well known to accompany this spectrum of metabolic disorders. Therefore,it would be logical to expect that Fn 14 activation in NASH may not be confined to the liver itself only but a much extensive activation throughout the body with resultant entrapment of circulating sTWEAK may also contribute to decreased sTWEAKconcentration in these patients. Indeed, a negative correlation between serum sTWEAK concentration and inflammatory markers have also been described in the literature (24).

The main limitation of the current study is smallness of sample size and its cross-sectional design; therefore, a causality relationship could not be demonstrated. Further studies with larger patient numbers investigating sTWEAK concentrations and simultaneous TWEAK and Fn14 expressions in the liver biopsy samples from the patients with NASH would clarify the possible role of TWEAK/Fn14 pathway in the pathogenesis of NASH.

In conclusion, serum sTWEAK concentration is decreased in patients with NASH. sTWEAK may have a potential role to be used as abiomarker to differentiate NASH patients

from simple hepatosteatosis with moderate specificity and sensitivity.

Competing interests: The authors declare that they have no competing interest.

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Ethical approval: The local Comity of Ethics of Necmettin Erbakan University, Meram Faculty of Medicine, approved the study protocol.

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