The relationship between nonalcoholic fatty liver disease and the severity of coronary artery disease in patients with metabolic syndrome

Metabolik sendromlu hastalarda alkole bağlı olmayan karaciğer yağlanması ile koroner arter hastalığının ciddiyeti arasındaki ilişki

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Objectives: Nonalcoholic fatty liver disease (NAFLD) is an important complication of metabolic syndrome (MS). We investigated the possible relationship between NAFLD and angiographical severity of coronary artery disease (CAD) in patients with MS.

Study design: This prospective study included 80 patients (35 men, 45 women; mean age 63±10 years; range 42 to 80 years) with a diagnosis of MS according to the ATP III criteria. All patients underwent abdominal ultrasonography to detect NAFLD. Coronary angiography was performed for stable angina pectoris (n=48), unstable angina pectoris (n=21), and prognostic reasons (n=11). The severity of CAD was assessed by the number of vessels involved (vessel score) and the severity score (Gensini score). Significant stenosis was defined as 70% or greater reduction in lumenal diameter.

Results: Ultrasonography revealed NAFLD in 43 patients (53.8%). Patients with NAFLD had significantly higher body mass index, waist circumference, and serum triglyceride level, and significantly lower HDL-cholesterol level (p<0.001). Coronary angiography showed significantly higher vessel (2.5±0.9 *vs* 1.0±1.0) and CAD severity scores (90.2±40.0 *vs* 36.4±28.9) in patients with NAFLD (p<0.001). Univariate analysis showed that the presence of NAFLD (r=0.61, p<0.001), grade of NAFLD (r=0.42, p<0.001), and patient age (r=0.36, p=0.002) were significantly correlated with the CAD severity score. In multivariate linear regression analysis, the presence of NAFLD was the only independent factor affecting the CAD severity score (β: 1.35, p<0.001).

Conclusion: The presence of NAFLD is associated with more severe CAD, requiring that patients with MS be investigated for the presence of NAFLD and those with NAFLD be attentively followed-up for the presence and severity of CAD.

Key words: Arteriosclerosis; coronary artery disease/diagnosis; fatty liver/diagnosis/complications; metabolic syndrome X; ultrasonography.

Amaç: Alkole bağlı olmayan karaciğer yağlanması metabolik sendromun (MS) önemli bir komplikasyonudur. Bu çalışmada MS'li hastalarda alkole bağlı olmayan karaciğer yağlanması ile koroner arter hastalığının (KAH) ciddiyeti arasındaki ilişki araştırıldı.

Çalışma planı: Bu prospektif çalışmaya, ATP III ölçütlerine göre MS tanısı konan 80 hasta (35 erkek, 45 kadın; ort. yaş 63±10; dağılım 42-80) alındı. Tüm hastalarda abdominal ultrasonografi ile alkole bağlı olmayan karaciğer yağlanması araştırıldı ve kararlı angina pektoris (n=48), kararsız angina pektoris (n=21) için ve prognostik amaçlı (n=11) koroner anjiyografi yapıldı. Koroner arter hastalığının ciddiyeti etkilenen damar sayısı (damar skoru) ve ciddiyet skoru (Gensini skoru) ile değerlendirildi. Lümen çapında %70 veya daha fazla azalma ciddi darlık olarak kabul edildi.

Bulgular: Ultrasonografide 43 hastada (%53.8) alkole bağlı olmayan karaciğer yağlanması saptandı. Bu hasta grubunda beden kütle indeksi, bel çevresi ve serum trigliserid düzeyi anlamlı derecede yüksek, HDL-kolesterol düzeyi anlamlı derecede düşük bulundu (p<0.001). Koroner anjiyografide damar skoru (2.5±0.9 ve 1.0±1.0) ve ciddiyet skoru (90.2±40.0 ve 36.4±28.9) da bu grupta anlamlı derecede yüksek idi (p<0.001). Tekdeğişkenli korelasyon analizinde, karaciğer yağlanmasının varlığı (r=0.61, p<0.001), derecesi (r=0.42, p<0.001) ve hasta yaşı (r=0.36, p=0.002) KAH ciddiyeti ile anlamlı ilişki gösterdi. Çokdeğişkenli regresyon analizinde karaciğer yağlanmasının varlığı KAH ciddiyetini etkileyen tek bağımsız faktör idi (β: 1.35, p<0.001).

Sonuç: Akole bağlı olmayan karaciğer yağlanması KAH ciddiyetini artırmaktadır. Bu durum, MS'li hastaların karaciğer yağlanması açısından araştırılmasını ve yağlanma görülenlerin KAH varlığı ve ciddiyetiyle ilgili dikkatli takip edilmesini gerektirmektedir.

Anahtar sözcükler: Arterioskleroz; koroner arter hastalığı/tanı; yağlı karaciğer hastalığı/tanı/komplikasyon; metabolik sendrom X; ultrasonografi.

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Metabolic syndrome (MS) is a combination of impaired glucose metabolism, abdominal obesity, dyslipidemia, and hypertension and is an important predictor of type 2 diabetes and cardiovascular disease.[1] Nonalcoholic fatty liver disease (NAFLD), which is an important complication of MS, is one of the most frequently encountered liver disease in the United States and Europe, affecting approximately 20% of the general population.[2] A few studies have evaluated the association between NAFLD and coronary artery disease (CAD).[3,4] In all these studies, CAD was diagnosed from symptoms and clinical records rather than by coronary angiography. To date, no studies have focused on the relationship between NAFLD and the severity of CAD. The aim of the present study was to evaluate the relationship between NAFLD and the indices of the severity of CAD detected by coronary angiography in a group of MS patients.

PATIENTS AND METHODS

Study population. We studied a consecutive series of 80 patients with a clinical diagnosis of MS according to the National Cholesterol Education Program Adult Treatment Panel III (ATP III) criteria.[5] Metabolic syndrome was diagnosed based on the presence of at least three or more of the following criteria: fasting hyperglycemia (≥110 mg/dl), hypertriglyceridemia (≥150 mg/dl), low level of high-density lipoprotein cholesterol (<40 mg/dl for men, <50 mg/dl for women), high blood pressure (≥130/85 mmHg), and abdominal obesity (≥110 cm for men, ≥88 cm for women).[5] There were 35 men and 45 women in the study (mean age 63±10 years; range 42 to 80 years). Thirty-three patients (41.3%) never smoked, 12 patients (15%) were current smokers, and 35 patients (43.8%) were former smokers. There were 73 patients (91.3%) with hypertension and 36 patients (45%) had a family history of CAD.

Patients with hepatitis B infection (hepatitis B surface antigen, antibody to hepatitis B surface antigen, antibody to hepatitis B core antigen), hepatitis C infection (antibody to hepatitis C virus), alcohol consumption (ethanol ingestion more than 20 g/day), and those having diabetes mellitus, acute coronary syndrome, and heart failure were excluded from the study.

The study was approved by our institutional ethics committee and all patients gave their informed consent.

Baseline variables. Clinical variables included age, sex, smoking status, family history of CAD, body mass index, waist circumference, and systolic and diastolic blood pressure. Waist circumference was measured at the midpoint between the bottom of the rib cage and the top of the iliac crest during breath holding after full expiration. Systolic and diastolic Blood pressure was obtained by averaging three consecutive measurements taken after 10-min seated rest, with cuff-size suitable for arm circumference and within a precision of 5 mmHg.

For biochemical variables, venous blood samples were drawn after 10 hours of overnight fasting and total cholesterol, triglycerides, HDL-cholesterol, and glucose were measured with a Beckman LX-20 autoanalyzer (Beckman Coulter, La Brea, CA, USA).

Ultrasound imaging. Abdominal ultrasonography was performed using a real-time electronic convex-type scanner (Toshiba Nemio 20 with 3.75 MHz convex-type transducer) by an experienced radiologist who was blind to medical history and coronary angiography results. Ultrasonographic criteria for the diagnosis of steatosis included a hyperechoic appearance of the liver parenchyma with fine, tightly packed echoes and posterior beam attenuation. The severity of steatosis was graded as mild, moderate, or severe.[6,7] If there was normal hepatic echotexture and normal beam attenuation, the liver was considered to be normal. Mild hepatic steatosis was defined as the presence of a minimal increase in echogenicity of the liver parenchyma, with a slight decrease in definition of the portal vein walls and minimal or no posterior beam attenuation. Severe steatosis was identified by grossly increased hepatic parenchymal echotexture that only permitted visualization of the main portal vein walls and a strikingly increased posterior beam attenuation. Moderate steatosis was said to be present when the characteristics of these parameters (hepatic echogenicity, portal venous definition, and beam attenuation) fell between mild and severe. In case of confounding coexistence, the grade was assigned according to the most predominant abnormal finding.

Coronary angiography and scoring. The indications for coronary angiography were stable angina pectoris in 48 patients (60%), unstable angina pectoris in 21 patients (26.3%), and prognostic reasons after myocardial infarction in 11 patients (13.8%). Selective coronary cineangiography was performed by the femoral approach using the Judkins technique and Philips Integris H 3000 angiography system (Philips Medical Systems, The Netherlands). Multiple views were obtained in all the patients, with visualization of the left anterior descending and left circumflex coronary in at least four views, and the right coronary

Table 1. Comparison of clinical characteristics and risk factors between patients with and without nonalcoholic fatty liver disease (NAFLD)

	NAFLD present (n=43)			NAFLD absent (n=37)			
	n	%	Mean±SD	n	%	Mean±SD	*p*
Age (years)			62±11			63±9	N S
Current smokers	7	16.3		5	13.5		N S
Gender							N S
Male	21	48.8		14	37.8		
Female	22	51.2		23	62.2		
Family history of coronary artery disease	20	46.5		16	43.2		N S
Hypertension	39	90.7		34	91.9		N S
Waist circumfrence (cm)			112±14			97.6±8.4	<0.001
Body mass index (kg/m^2)			32±2.3			27±1.4	<0.001
Fasting sugar (mg/dl)			92±23			88±21	N S
Total cholesterol (mg/dl)			186±35			182±44	N S
HDL-cholesterol (mg/dl)			36±7			41±9	<0.001
LDL-cholesterol (mg/dl)			125±30			120±45	N S
Triglyceride (mg/dl)			179±67			141±71	<0.001
Alanine aminotransferase (ALT) (mg/dl)			45±11			38±9	N S

NS: Not significant.

artery in at least two views. Coronary angiograms were recorded on compact discs in DICOM format.

Disease severity was assessed in terms of the number of vessels involved (vessel score) and with a severity score. Significant stenosis was determined visually and defined as 70% or greater reduction in lumenal diameter in any view compared with the nearest normal segment. Vessel score ranged from 0 to 3, depending on the vessels involved. Left main artery stenosis was scored as single vessel disease.

Severity of CAD was assessed using the Gensini score.[8] In this scoring system, a severity score is derived for each coronary stenosis based on the degree of luminal narrowing and its topographic importance. Reduction in the lumen diameter, and the roentgenographic appearance of concentric lesions and eccentric plaques are evaluated. Reductions of 1-25%, 26-50%, 51-75%, 76-90%, 91-99%, and total occlusion are scored as 1, 2, 4, 8, 16, and 32, respectively. Each principal vascular segment is assigned a multiplier that represents its functional importance in maintaining myocardial supply, being 5 for the left main coronary artery, 2.5 for the proximal segments of the left anterior descending coronary artery (LAD) and circumflex artery, 1.5 for the mid-segment of the LAD, 1 for the right coronary artery, the distal segment of the LAD, the posterolateral artery, and the obtuse marginal artery, and 0.5 for other segments. Angiographic scoring was performed by two observers who were blinded to ultrasound results and clinical data.

Statistical analysis. The results were expressed as mean ± standard deviation (SD) and frequencies. For univariate analysis of differences between the two groups, continuous variables were assessed with the unpaired Student's t-test, and nominal variables with the chi-square test. Correlations between CAD severity and other parameters were analyzed using Pearson correlation analysis. Multivariate stepwise linear regression analysis was performed to determine independent variables. A *P* value of less then 0.05 was considered significant. All analyses were performed using the SPSS for Windows 10.0.1 statistical software.

RESULTS

Ultrasonographic examination revealed NAFLD in 43 patients (53.8%), being mild in 23 (28.8%) and moderate in 20 (25%) patients. Thirty-seven patients (46.3%) had no NAFLD.

There were no significant differences between patients with and without NAFLD with regard to age, sex, smoking status, blood pressure, family history of CAD, and biochemical parameters of fasting sugar, total cholesterol, LDL-cholesterol, and alanine aminotransferase (Table 1). However, body mass index, waist circumference, and serum triglyceride level were significantly higher, whereas HDL-cholesterol was significantly lower in patients with NAFLD (p<0.001).

Coronary angiographic findings. Coronary angiographic data showed that patients with NAFLD had significantly higher vessel (2.5±0.9 *vs* 1.0±1.0) and CAD severity scores (90.2±40.0 *vs* 36.4±28.9)

than patients without NAFLD (p<0.001). Coronary angiograms were normal with no detectable coronary atheroma in 14 patients (37.8%) without NAFLD, compared to only three patients (7%) with NAFLD. The distribution of vessel scores indicating stenosis greater than 70% is shown in Fig. 1.

Correlations with CAD severity. Univariate analysis showed that the presence of NAFLD (r=0.61, p<0.001), grade of NAFLD (r=0.42, p<0.001), and patient age (r=0.36, p=0.002) were significantly correlated with the CAD severity score. In multivariate linear regression analysis, the presence of NAFLD was the only independent factor affecting the CAD severity score (β: 1.35, p<0.001).

Interobserver and intraobserver variability for repeated evaluations of angiograms of 20 randomly selected subjects was low (for CAD severity score: interobserver variability 4.7±3.9%; intraobserver variability 5.9±4.8%).

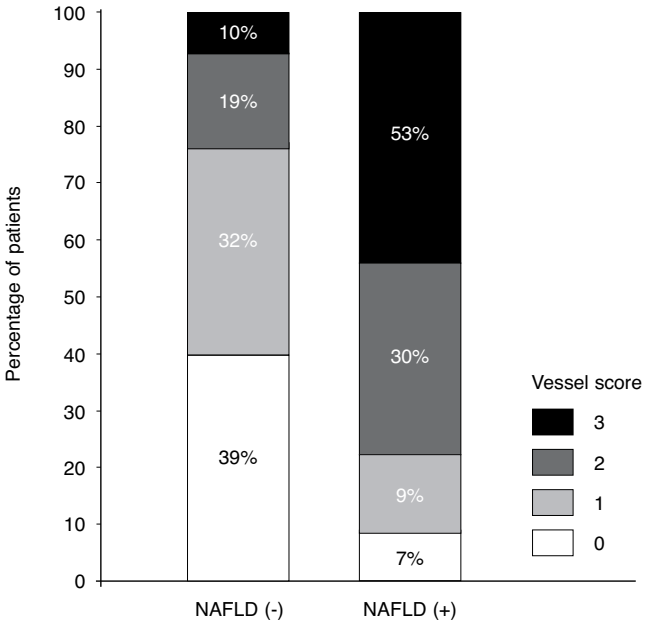

Figure 1. Distribution of the percentage of patients having stenosis of greater than 70% on a 4-point vessel scoring. NAFLD: Nonalcoholic fatty liver disease.

DISCUSSION

The results of the present study demonstrate that there is a relationship between the presence of NAFLD and the severity of CAD detected by coronary angiography. It has been shown that cardiovascular mortality is increased in patients with a diagnosis of NAFLD,[9] and that NAFLD is associated with an increased risk for future cardiovascular events among type 2 diabetic individuals,[4] independent of classical risk factors, and the presence of MS.[10]

Since the probability of having NAFLD increases with the classical risk factors for CAD, it could be argued that the observed relationship between NAFLD and CAD may actually be dependent on these factors. However, this appears to be unlikely because multivariate regression analysis with all possible factors included demonstrated that NAFLD was the only significant independent risk factor for CAD severity score. Consistent with our results, Völzke et al.[11] found a relationship between hepatic steatosis and carotid atherosclerosis, which was free from other atherogenic risk factors.

Lin et al.[3] demonstrated that NAFLD was an independent risk factor for ischemic heart disease and that abdominal sonographic examination was very helpful for the evaluation of risks associated with ischemic heart disease, especially in overweight subjects. In their study, definition of ischemic heart disease was based on evidence from resting electrocardiography. To our knowledge, none of the above-mentioned studies evaluated the severity of CAD by coronary angiography, which is the gold standard for the diagnosis of CAD.

Several mechanistic explanations have been proposed for the relationship between CAD and NAFLD. It has been demonstrated that there is a significant relationship between CAD and inflammation.[12] It is also known that there is an increased systemic inflammatory response in MS patients.[13] Choi and Diehl[14] demonstrated that this inflammatory response was even more prominent in patients with NAFLD.

Increased oxidative stress, on the other hand, may play a role in the progression from hepatic steatosis to steatohepatitis, fibrosis, and cirrhosis.[15-17] This may be another possible mechanism for the marked proatherogenic effect of NAFLD. Reactive oxygen species derived from steatosis-stimulated fatty acid oxidation, existing hepatocyte injury, and cytokine release increase inflammation and worsen liver disease of NAFLD, contributing to high oxidative/inflammatory status associated with MS.[10,18,19]

Limitations of the study. The diagnosis of NAFLD was not confirmed by liver biopsy for ethical reasons. However, it has been shown that ultrasound examination is very sensitive in the detection of significant hepatic steatosis,[6,10,20] with sensitivity and specificity rates of 89% and 93%, respectively.[21] Thus, ultrasonography is a reliable noninvasive method for the diagnosis of fatty liver.

In this study we did not evaluate CRP levels because there are so many studies showing a significant association between CRP levels and the severity of CAD with.[22,23]

Clinical implications. Morbidity and mortality from CAD is higher in patients with MS.[24] Therefore, the diagnosis of CAD in patients with MS is of critical importance. Based on the results of the present study, the presence of NAFLD in patients with MS was associated with more severe CAD. Therefore, NAFLD should be sought in patients with MS by abdominal ultrasonography, which is a simple, noninvasive, and routinely employed technique in the follow-up of MS patients.[25] Patients with NAFLD should then be investigated for the presence and severity of CAD.

In conclusion, among MS patients, those with NAFLD have more severe coronary atherosclerosis compared to patients without NAFLD, which cannot be explained by the classical risk factors for CAD. Further studies focusing on the mechanisms of this NAFLD-dependent effect are needed.

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