Evaluation of ultrasonographic fatty liver and severity of coronary atherosclerosis, and obesity in patients undergoing coronary angiography

Koroner anjiyografi yapılan hastalarda koroner aterosklerozun şiddeti ile ultrasonografik karaciğer yağlanması ve obezite arasındaki ilişkinin değerlendirilmesi

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ABSTRACT

Objective: Aims were to examine associations (1) between non-alcoholic fatty liver disease (NAFLD) and the presence and severity of coronary artery disease (CAD) and obesity, (2) between CAD and NAFLD with aspartate aminotransferase (AST), alanine aminotransferase (ALT) and gamma glutamiltransferase (GGT) levels.

Methods: In this cross-sectional study, the study group consisted of 355 patients (mean age: 57.5±11.4 years), that comply with inclusion criteria and selected of 414 consecutive patients who underwent coronary angiographies. Coronary artery disease was defined as a stenosis at least 50% in at least one major coronary artery. Modified Gensini scoring was used to determine the severity of coronary atherosclerosis. Fatty liver was diagnosed by abdominal ultrasonography (4 stages: Grades 0, 1, 2 and 3). Obesity was defined as body mass index (BMI)≥30 kg/m^2. Statistical evaluations were performed using Student's t test, ANOVA, Chi- square, kappa tests and logistic regression analysis.

Results: There were significant differences among Grades 0, 1 and 2-3 according to presence of CAD and Gensini score. In univariate analysis, age (OR=1.03, p=0.004), gender (OR=3.05, p<0.0001), dyslipidemia (OR=4.40, p<0.0001), diabetes mellitus (OR=2.15, p=0.048), smoking (OR=3.19, p<0.0001), AST (OR=1.01, p=0.042), GGT (OR=1.04, p<0.0001), NAFLD (OR=1.87, p=0.036) and obesity+NAFLD (OR: 2.1, p=0.018) have effects on presence of CAD. In multivariate model, age (OR=1.04, p<0.001), AST (OR=1.01, p<0.05), GGT (OR=1.04, p<0.001), NAFLD (OR=2.58, p<0.01) have independent effects on CAD; however BMI and obesity were ineffective. Non-alcoholic fatty liver disease has an independent effect on Gensini score (OR=2.02, p<0.05).

Conclusions: Ultrasonographic fatty liver have independent effects on both the presence of CAD and severity of coronary atherosclerosis. In addition, increased serum AST and GGT levels may be independently associated with CAD. *(Anadolu Kardiyol Derg 2009; 9: 273-9)*

Key words: Coronary artery atherosclerosis, non-alcoholic fatty liver disease, obesity, predictive models

ÖZET

Amaç: Koroner anjiyografi yapılan hastalarda alkolik olmayan yağlı karaciğer hastalığı (AOYKH) ve obezite ile (1) koroner arter hastalığının (KAH) varlığı ve şiddeti arasında, (2) serum aspartat aminotransferaz (AST), alanin aminotransferaz (ALT) ve gama glutamiltransferaz (GGT) düzeyleri arasındaki ilişkileri incelemek idi.

Yöntemler: Bu enine-kesitli çalışmaya, koroner anjiyografisi yapılan ardışık 414 hasta arasından kriterlerine uygun 355 hasta (ortalama yaş: 57.5±11.4 yıl) alındı. Koroner arter hastalığı en az bir majör koroner arterde en az %50 darlık saptanması olarak tanımlandı. Koroner aterosklerozun şiddetinin belirlenmesinde modifiye Gensini skorlaması kullanıldı. Yağlı karaciğer tanısı ultrasonografik olarak kondu (4 evre: Evre 0, 1, 2 ve 3). Obezite, vücut kitle indeksinin (VKİ) ≥30 kg/m^2 olarak alındı. İstatistiksel değerlendirme, Student's t testi, ANOVA, Ki-kare, kappa testleri ve lojistik regresyon analizi kullanılarak yapıldı.

Bulgular: Evre 0, 1 ve 2-3 arasında, KAH ve Gensini skoruna göre önemli farklar vardı. Tek değişkenli analizde; KAH üzerine yaşın (OR=1.03, p=0.004), cinsiyetin (OR=3.05, p<0.0001), dislipidemi (OR=4.40, p<0.0001), sigaranın (OR=3.19, p<0.0001), diyabet (OR=2.15, p=0.048), AST (OR=1.01,

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p=0.042), GGT (OR=1.04, p<0.0001), AOYKH (OR=1.87, p=0.036) ve obezite+AOYKH (OR=2.1, p=0.018) etkileri vardı. Çok değişkenli bir analiz modelinde KAH'ın varlığı üzerine, yaş (OR=1.04, p<0.001), AST (OR=1.01, p<0.05), GGT (OR=1.04, p<0.001) ve AOYKH'nın (OR=2.58, p<0.01) bağımsız olarak etkili; VKİ ve obezitenin ise etkisiz oldukları bulundu. Gensini skoru üzerine yağlı karaciğer bağımsız bir etkiye sahipti (OR=2.02, p<0.05).
Sonuç: Ultrasonografik yağlı karaciğerin hem KAH'ın varlığı ve hem de koroner aterosklerozun şiddeti üzerine bağımsız etkisi vardır. Ayrıca, artmış serum AST ve GGT seviyeleri de bağımsız olarak KAH ile ilişkili olabilir. *(Anadolu Kardiyol Derg 2009; 9: 273-9)*
Anahtar kelimeler: Koroner arter aterosklerozu, alkolik olmayan yağlı karaciğer hastalığı, obezite, öngördürücü modeller

Introduction

Coronary artery atherosclerosis begins at young ages and that typically becomes symptomatic after middle-aged with various clinical signs including acute coronary syndrome (ACS) (1, 2). Previous studies have revealed a close relationship between obesity and coronary artery disease (CAD) risk factors (2-5). Non-alcoholic fatty liver disease (NAFLD) is a clinical and pathological condition associated with abdominal obesity, Type 2 diabetes mellitus (DM), hypertension and dyslipidemia. Also, NAFLD affects as high as 14–23% of the general population, and its prevalence reaches 70–90% in obese and type 2 DM patients (6-8). However, the associations shown until now include associations among NAFLD and CAD risk factors and subclinical atherosclerosis markers such as endothelial dysfunction and increased carotid intima-media thickness (7, 9), and NAFLD and CAD (10). Whereas, direct associations among the presence- and degree of fatty liver and both the presence of angiographically proven CAD and the severity of coronary atherosclerosis, and obesity has not been shown yet.

Thus, the first aim of this study was to examine association between NAFLD and both the presence of CAD and severity of coronary atherosclerosis, and obesity. The second aim of the study was to evaluate associations among CAD and NAFLD and serum aspartate aminotransferase (AST), alanine aminotransferase (ALT) and gamma glutamiltransferase (GGT) levels.

Methods

Patients: The study group consisted of 355 patients [253 (71.3%) male, 102 (28.7%) female; mean age: 57.5±11.4 years] that comply with inclusion criteria and selected of 414 consecutive patients who underwent coronary angiography from November 1, 2005 to July 31, 2006. Our study group consisted of patients underwent coronary angiography in our hospital for various reasons such as ACS, chest pain and/or positive effort test or abnormal nuclear imaging. Inclusion criteria included patients who underwent coronary angiography and had no alcohol intake and no history of known liver disease, congestive heart failure, cor pulmonale, malignant disease, acute or chronic infection diseases. Hepatic ultrasound examinations were performed shortly before the patients were discharged. We excluded patients without coronary angiography, with an alcohol intake and those who reported a history of known liver disease, pregnancy, congestive heart failure, severe pulmonary disease, cor pulmonale, chronic renal failure, malignant disease, active infections, and drug-induced fatty liver such as steroids. Also patients who were enrolled in the study but did not have a hepatic ultrasound or did not have an adequate ultrasound imaging of the liver, and those who had a positive HAS test (hepatitis B and C, HIV and syphilis tests) and had deficiencies in the identified biochemical tests were excluded. Clinical and demographic characteristics of enrolled patients were identified, as well as anti-lipid medication (statins or fibrates) and other drugs (such as nitrates, beta blockers, calcium channel blockers, angiotensin converting enzyme inhibitors or angiotensin II receptor blockers, antiaggregants and antidiabetic medications). The Ethics Committee of Hospital approved the study and all patients gave informed consent.

Definitions and laboratory measurements: For obesity body mass index (BMI) was used. The ones who had BMI ≥30 kg/m^2 were stated as obese. For smoking, the ones who smoke 1 or more cigarettes per day were as evaluated as smokers. Diabetes mellitus was defined as fasting blood glucose of 126 mg/dL or greater and patients treated with antidiabetes drugs. Dyslipidemia and metabolic syndrome were diagnosed based on NCEP/ATP III guidelines (2). Hypertension was diagnosed based on JNC VII guidelines (11). According to blood collection procedures, blood samples were collected from all patients within the first 24 hours after being admitted to the hospital for routine biochemistry and total, low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterols, triglycerides, AST, ALT and gamma GGT levels.

Coronary angiography: All patients enrolled in the study had selective left and right coronary angiography with the Judkins technique, using a "Philips Integris 5000" device. Coronary angiographies were evaluated and reported by at least 2 experienced cardiologists who did not have information about the study. Coronary artery disease was diagnosed via an angiogram and detection of at least 50% narrowing in epicardial coronary arteries or their major branches was considered as CAD (12). Modified Gensini scoring was used to determine the severity of coronary atherosclerosis (13, 14). According to this scoring system, coronary arterial system was divided into 8 segments and the most severe luminal narrowing in each coronary segment was graded with 1 to 4 points (between 1 and 49%, 1 point; 50 and 74%, 2 points; 75 and 99% 3 points; 100%, 4 point). Each patient was evaluated with a total score between 0 and 32 points. Each point was multiplied with separate coefficients based on vessel segments: these coefficients were 5 for left major coronary artery, 2.5 for proximal LAD, 1.5 for medial LAD, 1.5 for distal LAD, 1 for diagonal LAD, 2.5 for proximal circumflex artery, 1 for marginal obtus and posterolateral branch, 1.5 for right proximal coronary, 1 for posterodescending artery, and 0.5 for others. The points were added and total Gensini points were calculated for each patient.

Ultrasonographic examination: Abdominal ultrasonography (Toshiba-SSA-250A) was performed shortly before the patient was discharged and after a fasting period of 12 hours, by a radiologist who did not have information about the patient. Right kidney echogenity was used for determination of liver parenchyma echogenity. With the same kidney cortex and liver parenchyma echogenity it is evaluated as normal, *no fatty liver (Grade 0)*. Fat infiltration in liver is described in 3 ultrasonographic stages (Fig. 1) (15, 16). *Mild (Grade1):* Minimal diffuse increase in hepatic echogenity, diaphragm, and intrahepatic vessel contours seem normal. *Medium (Grade 2):* Medium grade diffuse increase in hepatic echogenity, mild deterioration in the image of diaphragm and intrahepatic vessels. *Severe (Grade 3):* Apparent increase in echogenity. Posterior segment of the right hepatic lobe is difficult to display. Intrahepatic vessel structure and diaphragm contours are vague or not seen.

Study Groups: Patients were divided into 2 main groups of those with (250 patients) and without CAD (105 patients) (present or absent) and were grouped according to the number of diseased vessel [one-, two-, or three-vessel disease (1VD, 2VD or 3VD)]. Furthermore, all patients were classified according to presence or absence of obesity and fatty liver and its severity. Based on this classification, all patients were divided into 3 subgroups as Grade 0 (no fatty liver), Grade 1 (mild fatty liver), and Grades 2-3 (medium to severe fatty liver). After Gensini scores were determined, 36 points (median value) was chosen as an appropriate cut-off value and patients were divided into two groups of those with Gensini score ≤36 points (absent or mild coronary atherosclerosis, mean: 9.7±11.8) and Gensini score >36 points (medium-severe coronary atherosclerosis, mean: 88.0±38.5). In addition, 20% of all patients (71 patients) had an additional hepatic ultrasonography performed to identify the "intraobserver" variation in the ultrasonographic evaluation.

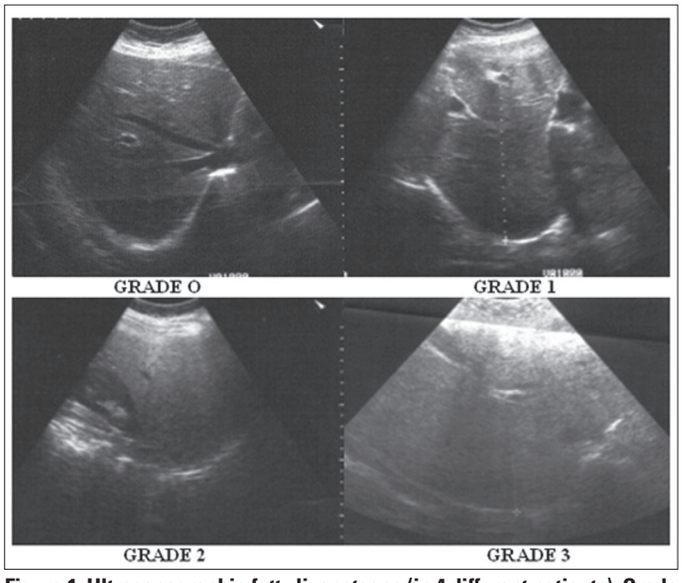

Figure 1. Ultrasonographic fatty liver stages (in 4 different patients). Grade 0- no fatty liver, Grade 1- mild fatty liver, Grade 2- moderate fatty liver, Grade 3- severe fatty liver

Statistical evaluation: Statistical evaluation was performed with SPSS 11.5 software package for Windows (Chicago, IL, USA). Quantitative variables are given as mean±standard deviation, and qualitative variables are expressed as frequency and percentage. Two groups with different parameters were compared with Student's unpaired t test. When more than two groups were compared for parameters, analysis of variance (ANOVA) was used; post hoc analysis was performed using Tukey-HSD test. Qualitative variables were compared using Chi-square or Fisher's exact test. Kappa statistic was performed to determine the intraobserver variation. The presence of CAD and the severity of coronary atherosclerosis (Gensini score) were evaluated as the dependent variables. Age, gender, diabetes mellitus (DM), hypertension, smoking, blood lipids, BMI, obesity, fatty liver, liver enzymes such as AST, ALT and GGT, anti-lipid and the other drugs were included in the analysis as independent variables. Logistic regression analyses were performed to determine the independent variables influencing both the presence of CAD and the severity of coronary atherosclerosis. Significance was defined with $p<0.05$.

Results

Clinical characteristics: Of 355 patients in the study group, 265 (74.6%) had ACS, 50 (14.1%) had stable angina, 40 (11.3%) had atypical angina or atypical chest pain. Of 265 patients with ACS, 132 (49.8%) had unstable angina, 78 (29.4%) had non-Q wave myocardial infarction (MI), 55 (20.8%) had ST-elevation MI. A total of 169 (47.6%) patients were obese and 109 (30.7%) had metabolic syndrome.

Clinical, ultrasonographic and angiographic findings: In CAD group, prevalence of risk factors such as age, men gender, DM, dyslipidemia, smoking were significantly higher ($p<0.05$) than groups without CAD (Table 1). Fatty liver rate, AST and GGT levels and the use of anti-lipids and other drugs were significantly higher ($p<0.05$) in CAD group than in non-CAD group (Table 1). According to the number of diseased vessel (1VD, 2VD, 3VD), there were significant differences between groups in terms of age, gender, dyslipidemia and smoking ($p<0.0001$, respectively), GGT ($p=0.010$) and fatty liver ($p=0.022$) but there was no significant difference between groups in terms of DM ($p=0.052$), hypertension, BMI, obesity, metabolic syndrome, AST and ALT levels ($p>0.05$, respectively). In group of Gensini score>36 (n=177), age (59.9±10.4 vs 55.1±11.9, $p<0.0001$), male gender (79.7% vs 62.9%, $p<0.0001$) and smoking (65.5% vs 52.2%, $p=0.011$), fatty liver (37.9% vs 27.0%, $p=0.028$), AST (46.3±79.7 vs 32.5±41.6 vs $p=0.042$), GGT (36.5±24.3 vs 31.0±23.5, $p=0.032$), use of anti-lipid (52.5% vs 25.3%, $p<0.0001$) and other medications (65.0% vs 44.4%, $p<0.0001$) were significantly higher than that of Gensini score ≤36 group (n=178), but there were no significant differences between groups in terms of DM, hypertension, BMI, obesity, metabolic syndrome, blood lipids and ALT ($p>0.05$, respectively). In obese patients, DM ($p=0.003$), hypertension ($p=0.005$), metabolic syndrome ($p<0.0001$) and Grades 2-3 fatty liver ($p<0.0001$) rates and triglycerides levels ($p<0.0001$) were significantly higher than that of non-obese patients. Obese individuals insignificantly have lower mean age ($p>0.05$). There

Table 1. Clinical, laboratory and angiographic findings in patients undergoing coronary angiography

Parameters	Coronary Artery Disease		
	Present (n=250)	Absent (n=105)	*p
Age, years	58.7±10.9	54.8±12.1	0.004
Men gender, n(%)	196 (78.4)	57(54.3)	0.0001
Diabetes mellitus, n(%)	42 (16.8)	9 (8.6)	0.044
Dyslipidemia, n(%)	200 (80.0)	50 (47.6)	0.0001
Hypertension, n(%)	56 (22.4)	18 (17.1)	0.26
Smoking, n(%)	168 (67.2)	41 (39.0)	0.0001
Prior MI, n(%)	97 (38.8)	0 (0)	0.0001
Body mass index, kg/m^2	29.1±4.6	28.7±4.6	0.51
Obesity, n(%)	122 (48.8)	47 (44.8)	0.48
Metabolic syndrome, n(%)	77 (30.8)	32 (30.5)	0.95
Total cholesterol, mg/dL	195.2±52.1	194.1±46.7	0.85
LDL cholesterol, mg/dL	132.0±40.9	133.0±36.4	0.82
HDL cholesterol, mg/dL	42.1±8.2	44.8±9.5	0.007
Triglycerides, mg/dL	191±130	188±144	0.83
AST, U/L	44.0±74.1	28.2±22.7	0.033
ALT, U/L	28.7±16.9	25.2±12.9	0.059
GGT, U/L	36.5±27.2	27.2±11.5	0.001
Fatty liver, n(%)	93 (37.2)	22 (21.0)	0.003
Gensini score	68.7±44.5	1.3±2.9	0.0001
Anti-lipid drugs, n(%)	117 (46.8)	21 (20)	0.0001
Other drugs, n(%)	156 (62.4)	38 (36.2)	0.0001

Values are presented mean±SD or proportions/percentages, where appropriate.
*p values for unpaired t-test and Chi-square test
ALT- alanine aminotransferase, AST- aspartate aminotransferase, GGT- gamma glutamiltransferase, HDL- high- density lipoprotein, LDL- lowdensity lipoprotein, MI-myocardial infarction, obesity- body mass index >30 kg/m2. Other drugs are given in the text

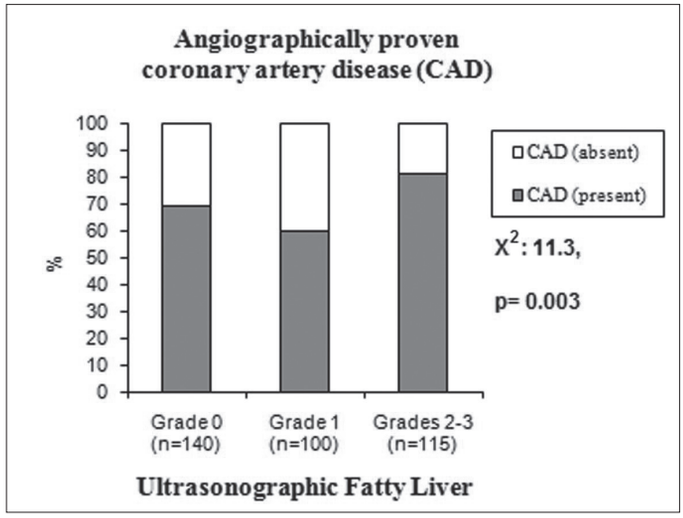

Figure 2. Relation between ultrasonographic fatty liver and both the presence of coronary artery disease (CAD). Grade 0- no fatty liver, Grade 1-mild fatty liver, Grade 2- moderate fatty liver, Grade 3- severe fatty liver

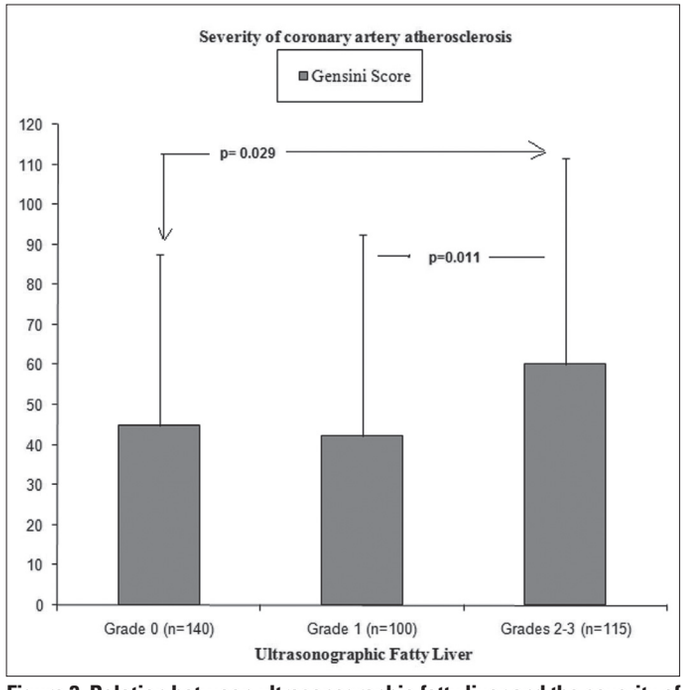

Figure 3. Relation between ultrasonographic fatty liver and the severity of coronary atherosclerosis (Gensini score). Grade 0- no fatty liver, Grade 1-mild fatty liver, Grade 2- moderate fatty liver, Grade 3- severe fatty liver

were no significant differences in terms of CAD rate and Gensini score between obese and non-obese patients, (p>0.05, respectively). In other hand, according to fatty liver there were significant differences (p<0.05) between groups in terms of coronary risk factors (Table 2). Again, CAD rate (Fig. 2) and Gensini score (Fig. 3) were significantly higher (p<0.05) in Grades 2-3 group than in both Grades 0 and 1 groups (Table 2).

Logistic regression analysis for the presence of CAD: In the univariate analysis age [OR:1.03 (95% CI 1.01-1.05), p=0.004], gender [OR:3.05 (95% CI 1.87-4.97), p<0.0001], dyslipidemia [OR:4.40 (95% CI 2.68-7.1), p<0.0001], DM [OR:2.15 (95% CI 1.01-4.60), p=0.048], smoking [OR:3.19 (95% CI 1.99-5.13), p<0.0001], AST [OR:1.01 (95% CI 1.00-1.02), p=0.042], ALT [OR:1.01 (95% CI 0.99-1.03), p=0.062], GGT [OR:1.04 (95% CI 1.02-1.06), p<0.0001], fatty liver [OR:1.87 (95% CI 1.04-3.37), p=0.036] and obesity plus fatty liver [OR:2.10 (95% CI 1.13-3.91), p=0.018] were determinants of CAD presence. All independent variables, which correlate with the presence of CAD were presented in the multiple logistic regression model (Table 3). Age, total and LDL cholesterols, AST, GGT, anti-lipid drugs and fatty liver have independent effects on the presence of CAD (Table 3). Also in the other multiple regression model generated by including age, BMI, obesity, fatty liver and liver enzymes we found that BMI, obesity and ALT did not have influence on the presence of CAD (p>0.05, respectively), whereas age [OR:1.04 (95% CI 1.02-1.06), p<0.001], AST [OR:1.01 (95% CI 1.00-1.02), p<0.05], GGT [OR:1.04 (95% CI 1.01-1.06), p<0.001] and fatty liver [OR:2.58 (95% CI 1.36-4.88), p<0.01] have independent effects.

Table 2. Clinical, laboratory and angiographic findings according to fatty liver grades

Parameters	Ultrasonographic Fatty Liver			F or X^2	*p
	Grade 0 (n=140)	Grade 1 (n=100)	Grades 2–3 (n=115)		
Age, years	59.4±12.5	57.2±10.2	55.6±10.7[a]	3.7	0.025
Men gender, n(%)	93 (66.4)	64 (64)	96 (83.5)	12.5	0.002
Diabetes mellitus, n(%)	14 (10.0)	13 (13.0)	24 (20.9)	6.3	0.043
Dyslipidemia, n(%)	98 (70)	58 (58)	94 (81.7)	14.5	0.001
Hypertension, n(%)	27 (19.3)	20 (20)	27 (23.5)	0.7	0.69
Smoking, n(%)	80 (57.1)	56 (56)	73 (63.5)	1.5	0.46
Body mass index, kg/m^2	26.5±4.5	29.3±4.0	31.7±3.3[b]	52.8	0.0001
Obesity, n(%)	31 (22.1)	46 (46)	92 (80)	84.8	0.0001
Metabolic syndrome, n(%)	25 (17.9)	34 (34)	50 (43.5)	20.2	0.0001
Total cholesterol, mg/dL	191±43	189±55	203±54	2.4	0.093
LDL cholesterol, mg/dL	130±35	128±41	138±42	2.2	0.11
HDL cholesterol, mg/dL	43.6±8.8	43.5±9.4	41.4±7.7	2.5	0.081
Triglycerides, mg/dL	145±79	180±115	253±175[b]	23.1	0.0001
AST, U/L	48.6±90.9	31.9±35.8	34.5±35.6	2.5	0.082
ALT, U/L	26.8±17.7	25.09±14.3	30.9±14.6[c]	3.9	0.021
GGT, U/L	34.5±28.9	30.0±13.3	36.1±24.6	1.8	0.165
CAD, n(%)	97 (69.3)	60 (60)	93 (80.9)	11.3	0.003
Gensini score	44.8±42.8	41.2±50.3	60.2±51.5[a, c]	5.0	0.007
Gensini score>36, n(%)	69 (49.3)	41 (41)	67 (58.3)	6.4	0.041
Anti-lipid drugs, n(%)	53 (37.9)	33 (33)	52 (45.2)	3.5	0.177
Other drugs, n(%)	67 (47.9)	56 (56)	71 (61.7)	5.0	0.082

Values are presented mean ± SD or proportions/percentages, where appropriate.
* p values for Chi- square test or one-way ANOVA analysis for comparison of variables across groups
PostHoc Tukey-HSD test for pair wise comparisons between groups: a- p<0.05 for Grade 2-3 vs Grade 0, b- p<0.0001 for Grade 2-3 vs both Grade 0 and Grade1, c- p<0.05 for Grade 2-3 vs Grade 1.
Grade 0- no fatty liver, Grade 1- mild fatty liver, Grade 2-3 - moderate to severe fatty liver.
ALT- alanine aminotransferase, AST- aspartate aminotransferase, CAD- coronary artery disease, GGT- gamma glutamiltransferase, HDL- high- density lipoprotein, LDL- low- density lipoprotein, obesity- body mass index>30 kg/m2, Other drugs are given in the text

Logistic regression analysis for the severity of CAD: According to Gensini score age, gender, total and LDL cholesterol, AST, fatty liver and anti-lipid drugs use have independent effects (p<0.05) on the severity of coronary atherosclerosis (Table 4). Whereas we found that DM, hypertension, smoking, HDL cholesterol, triglycerides, BMI, obesity and ALT did not have influence on the Gensini score (p>0.05, for all) (Table 4).

In this study there was significant agreement between 2 separate evaluations to determine the intraobserver variation (kappa= 0.88, p<0.0001).

Discussion

In this study, we showed direct relations among both the presence and severity of CAD and NAFLD in consecutive patients underwent coronary angiography. Non-alcoholic fatty liver disease is a clinical and pathological condition associated with abdominal obesity, DM, hypertension, dyslipidemia and insulin resistance. It is also considered the hepatic manifestation of metabolic syndrome and present in up to one-third of the general population and in the majority of patients with metabolic risk factors (7, 17).

Diagnosis of non-alcoholic fatty liver disease: The diagnosis of NAFLD requires evidence of fatty infiltration of the liver in the absence of excessive alcohol consumption and of other secondary causes of chronic liver disease. In this study we also excluded the patients with an alcohol intake and the secondary causes. Although liver biopsy is currently gold standard for diagnosis, in this study we used a noninvasive and fast method, abdominal ultrasonography which is the most widely used imaging test for detecting fatty liver. It is reported to have a good sensitivity (91.3%) and specificity (83.8%) and an accuracy of 86.7% for the diagnosis of fatty liver (15, 18).

Associations among coronary risk factors, obesity and NAFLD: In our study group NAFLD rate was 32.4%. In spite of the close similarity between the reported rates (6-8) and our rate, obesity and metabolic syndrome rates between patients with and without CAD in our study group was, contrary to expected, not significant. Whereas, NAFLD rate is significantly higher both in the CAD group and in patients with medium-severe

Table 3. Multiple logistic regression analysis for the presence of coronary artery disease

	Odds Ratio	95% CI		
	(OR)	Lower	Upper	p
Age, years	1.04	1.02	1.07	0.001
Men gender	1.46	0.59	3.66	0.41
Diabetes mellitus	1.33	0.55	3.23	0.52
Hypertension	1.44	0.70	2.97	0.31
Smoking	3.14	1.37	7.17	0.007
Total cholesterol, mg/dL	1.02	1.00	1.03	0.028
LDL cholesterol, mg/dL	0.98	0.96	1.00	0.036
HDL cholesterol, mg/dL	0.97	0.93	1.00	0.071
Triglycerides, mg/dL	0.99	0.99	1.00	0.12
AST, U/L	1.01	1.00	1.02	0.025
ALT, U/L	0.98	0.96	1.00	0.11
GGT, IU/L	1.03	1.01	1.06	0.007
Obesity	1.17	0.62	2.22	0.63
Fatty liver, Grade 2-3	2.13	1.01	4.48	0.046
Anti-lipid drugs	0.29	0.13	0.66	0.003
Other drugs	0.66	0.31	1.40	0.27

ALT- alanine aminotransferase, AST- aspartate aminotransferase, CI - confidence interval, GGT- gamma glutamiltransferase, HDL- high-density lipoprotein, LDL- low -density lipoprotein, obesity- body mass index >30 kg/m^2, other drugs are given in the text

Table 4. Multiple logistic regression analysis for the severity of coronary atherosclerosis (Gensini score)

	Odds Ratio	95% CI		
	(OR)	Lower	Upper	p
Age, years	1.05	1.03	1.08	0.0001
Men gender,	2.85	1.19	6.81	0.018
Diabetes mellitus	1.53	0.74	3.14	0.25
Hypertension	1.08	0.57	2.03	0.81
Smoking	1.11	0.53	2.32	0.78
Total cholesterol, mg/dL	1.04	1.02	1.05	0.0001
LDL cholesterol, mg/dL	0.96	0.94	0.98	0.0001
HDL cholesterol, mg/dL	0.99	0.95	1.02	0.43
Triglycerides, mg/dL	0.99	0.99	1.00	0.096
AST, U/L	1.01	1.00	1.02	0.011
ALT, IU/L	0.98	0.96	1.00	0.042
GGT, U/L	1.01	1.00	1.02	0.064
Obesity	1.03	0.58	1.84	0.90
Fatty liver, Grade 2-3	2.02	1.06	3.85	0.033
Anti-lipid drugs	0.29	0.15	0.59	0.001
Other drugs	0.69	0.34	1.40	0.30

ALT- alanine aminotransferase, AST- aspartate aminotransferase, CI - confidence interval, GGT- gamma glutamiltransferase, HDL- high-density lipoprotein, LDL- low -density lipoprotein, obesity- body mass index >30 kg/m^2, other drugs are given in the text

atherosclerosis. Our study group consists of patients undergoing coronary angiography in our hospital for various reasons (including ACS and patients referred to our hospital for coronary angiography from other centers with a preliminary diagnosis of CAD). Among these, the high number of obesity, considered a high risk for CAD and liver fattening being present in almost half of the obese patients suggests NAFLD may contribute further to the presence of CAD. Again, classic risk factors were higher in CAD patients were an expected result. Metabolic syndrome and NAFLD were significantly higher in obese patients. These findings are consistent with literature (3, 4, 7, 8). Whereas there was no significant difference between obese and non-obese patients for the presence of CAD and Gensini score, used to assess the severity of coronary atherosclerosis. The reason for this may be the clinical characteristics of our study group. Obese individuals seem to have a lower mean age. This may indicate that they have coronary angiography performed at an earlier stage in the course of their disease, when there is not yet an adequate increase in the severity of coronary atherosclerosis. In addition, there is a study that indicates BMI is a risk factor in angiographically proven CAD patients for unstable angina and MI (19), and study that reports obesity paradox (i.e. inverse relationship between the severity of CAD and obesity) in patients underwent coronary angiography (5). In the subgroups formed based on the degree of fatty liver, this becomes more evident, i.e. patients with medium–severe liver fattening were significantly younger than patients who did not have fattening, and the severity of coronary atherosclerosis in this patient group was significantly higher. It is reported that NAFLD may be a risk factor (indirect) for CAD, due to its association with subclinical markers for atherosclerosis (9, 11). Arslan et al. (10) reported that NAFLD is independently associated with presence of CAD.

Associations among NAFLD, CAD and liver enzymes: In our study, although ALT level was significantly higher in patients with medium-severe fatty liver, it was not associated with the presence of CAD. Again, AST was higher in CAD patients and had an independent effect. It may be at least in part due to inclusion of MI patients. Another important point is that significant increase observed in serum GGT levels in CAD patients. Moreover, all multivariate analysis showed that high GGT might have an independent on CAD. High GGT level, in an appropriate cut-off value, may be useful to predict presence and severity of CAD. Additional studies are required. It has been reported that GGT level may increase in CAD and this increase is an important indicator to assess prognosis (20).

Factors independently influencing presence and severity of CAD: Fatty liver, for the presence of CAD, was an independent risk factor when coronary risk factors such as gender, hypertension, smoking, DM, blood lipids and drugs were excluded from the multiple analysis Fatty liver was still an independent risk factor even after adjusting all risk factors (Table 3). It was interesting that obesity per se have not an

independent effect. Serum ALT level independently has no effect on the presence of CAD, whereas AST and GGT have independent effects. On the other hand, according to Gensini score (Table 4), age, gender, total and LDL cholesterol, AST, ALT, fatty liver and anti-lipid drugs have independent effects on severity of coronary atherosclerosis. In this study the use of anti-lipid, and other drugs such as antiischemic and antiaggregants were higher in the CAD group, which was an expected result. Naturally, the majority of CAD patients were already using these drugs due to prior indications. The important point was that was no significant difference between groups for the drugs in terms of degree of fatty liver (Table 2).

Study limitations: The first limitation was the lack of a histological confirmation of diagnosis of fatty liver. This study could not define the association between the histological significance and the metabolic abnormalities. It is known that abdominal ultrasonography has a good sensitivity/specificity in detecting moderate and severe fatty liver, but its sensitivity is reduced when hepatic fat infiltration on biopsy is <33% (21). Thus, our results can probably be considered conservative estimates of the relationship between NAFLD and CAD. The second limitation was connected with clinical characteristics. Our study group consisted of patients underwent coronary angiography in our hospital for various reasons including ACS. Therefore this study could not define associations between patients with and without ACS. For example, AST may not be independently associated with CAD in only patients without MI. AST and the other variables may be investigated in only patients with or without ACS.

Clinical implications: The current study shows that fatty liver is directly associated with both the presence and the severity of CAD and not just one aspect of obesity or metabolic syndrome. Again, previously known associations between CAD and coronary risk factors and obesity and fatty liver also were confirmed. We showed that NAFLD was associated with higher prevalence of CAD and this association was independent. Non-alcoholic fatty liver disease also has an independent effect on severity of coronary atherosclerosis. Thus hepatic ultrasound examination routinely may perform for patients with suspected CAD. Again, high GGT level may be associated with both the presence and severity of CAD, which are needed additional studies.

Conclusions

The presence of ultrasonographic fatty liver and its severity may have an independent effect on both the presence of CAD and the severity of coronary atherosclerosis. However, obesity may not have a direct association with the presence and severity of CAD. In addition, increased serum AST and GGT levels may be independently associated with CAD.

References

1. Tuzcu EM, Kapadia SR, Tutar E, Ziada KM, Hobbs RE, McCarthy PM, et al. High prevalence of coronary atherosclerosis in asymptomatic teenagers and young adults: Evidence from intravascular ultrasound. Circulation 2001; 103: 2705-10.
2. Third report of the national cholesterol education program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (ATP III) final report. Circulation 2002; 106: 3143-421.
3. Hubert HB, Feinleib M, McNamara PM, Castelli WP. Obesity as an independent risk factor for cardiovascular disease: a 26- year follow-up of participants in the Framingham Heart Study. Circulation 1983; 67: 968-7.
4. Brown CD, Higgins M, Donato KA, Rohde FC, Garrison R, Obarzanek E, et al. Body mass index and the prevalence of hypertension and dyslipidemia. Obes Res 2000; 8: 605-19.
5. Rubinshtein R, David A, Jaffe R, Shahla J, Lewis BS. Relation between obesity and severity of coronary artery disease in patients undergoing coronary angiography. Am J Cardiol 2006; 97: 1277-80.
6. Nomura H, Kashiwagi S, Hayashi J, Kajiyama W, Tani S, Goto M. Prevalence of fatty liver in a general population of Okinawa, Japan. Jpn J Med 1988; 27: 142-9.
7. Targher G. Non-alcoholic fatty liver disease, the metabolic syndrome and the risk of cardiovascular disease: The plot thickens. Diabet Med 2007; 24: 1-6.
8. Kim HJ, Kim HJ, Lee KE, Kim DJ, Kim SK, Ahn CW, et al. Metabolic significance of nonalcoholic fatty liver disease in nonobese, nondiabetic adults. Arch Intern Med 2004 25; 164: 2169-75.
9. Brea A, Mosquera D, Martin E, Arizti A, Cordero JL, Ros E. Nonalcoholic fatty liver disease is associated with carotid atherosclerosis. A case-control study. Arterioscler Thromb Vasc Biol 2005; 25: 1045-50.
10. Arslan U, Türkoğlu S, Balcıoğlu S, Tavıl Y, Karakan T, Çengel A. Association between nonalcoholic fatty liver disease and coronary artery disease. Coron Artery Dis 2007; 18: 433-6.
11. The sixth report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. Arch Intern Med 1997; 157: 2413-46.
12. Leaman DM, Brower RW, Meester GT, Serruys P, van den Brand M. Coronary artery atherosclerosis: severity of the disease, severity of angina pectoris and compromised left ventricular function. Circulation 1981; 63: 285-9.
13. Hayashi M, Fujimoto K, Urushibata K, Uchikawa S, Imamura H, Kubo K. Nocturnal oxygen desaturation correlates with the severity of coronary atherosclerosis in coronary artery disease. Chest 2003; 124; 936-41.
14. Bozkurt E. Keleş S, Açıkel M, Islek M, Atesal S. Plasma homocysteine level and the angiographic extent of coronary artery disease. Angiology 2004; 55: 265-70.
15. Osawa H, Morry Y. Sonographic diagnosis of fatty liver using a histogram technique that compares liver and renal cortical echo amplitudes. J Clic Ultrasound 1996; 24: 25-9.
16. el-Hassan AY, Ibrahim EM, al-Mulhim FA, Nabhan AA, Chammas MY. Fatty infiltration of the liver: analysis of prevalence, radiological and clinical features and influence on patient management. Br J Radiol 1992; 65: 774-8.
17. Adams LA and Angulo P. Recent concepts in non-alcoholic fatty liver disease. Diabetic Medicine 2005; 22: 1129-33.
18. Joy D, Thava VR, Scott BB. Diagnosis of fatty liver disease: is biopsy necessary? Eur J Gastroenterol Hepatol 2003; 15: 539-43.
19. Wolk R, Berger P, Lennon RJ, Brilakis ES, Somers VK. Body mass index: a risk factor for unstable angina and myocardial infarction in patients with angiographically confirmed coronary artery disease. Circulation 2003; 108: 2206-11.
20. Ruttmann E, Brant LJ, Concin H, Diem G, Rapp K, Ulmer H. Vorarlberg Health Monitoring and Promotion Program Study Group. Gamma-glutamyltransferase as a risk factor for cardiovascular disease mortality: an epidemiological investigation in a cohort of 163,944 Austrian adults. Circulation 2005; 112: 2130-7.
21. Saadeh S, Younossi ZM, Remer EM, Gramlich T, Ong JP, Hurley M, et al. The utility of radiological imaging in nonalcoholic fatty liver disease. Gastroenterology 2002; 123: 745-50.