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Association between Nonalcoholic Fatty Liver Disease and Carotid Atherosclerosis

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Abstract

Aim/Background: Nonalcoholic fatty liver disease (NAFLD) frequently accompanies to the criteria of Metabolic Syndrome (MetS) like obesity, diabetes, and dyslipidemia. It is recently approved as a liver attaint of MetS. While MetS is a highly atherogenic condition we examined whether NAFLD was associated with atherosclerosis, as measured by ultrasound in the carotid arteries.

Methods: Carotid intima-media thickness and cardiovascular risk factors were evaluated in 64 patients with an ultrasound diagnosis of primary NAFLD and 64 matched population controls. Metabolic syndrome was established according to WHO and ATP-III criteria. IMT values were evaluated according to protocols of standard measurements of carotid artery.

Results: The metabolic syndrome and all its individual features were significantly (P<0.001) more frequent in NAFLD patients than in control subjects. Patients with NAFLD and controls had similar mean intima-media thickness (IMT) of 1,06±0,71 mm and 0,96±0,66 mm respectively, but plaque prevalence was significantly higher in patients with NAFLD than in controls (18,7% and 9,37%, respectively). Conversely, C-reactive protein levels were elevated in control group comparing to patient group.

Conclusion: In the present study NAFLD did not have increased IMT but had high prevalance of carotid plaque. The presence of MetS did not affect the prevalance of increased IMT and carotid plaque formation. The clinical implication of this study is that patients with NAFLD and control group are at similar risk of CVD. Studies in large NAFLD patient population comparing to control goups should be performed. How be it, patients with NAFLD should undergo periodic cardiovascular risk assessment.

Keywords: NAFLD; Carotid atherosclerosis

Introduction

Nonalcoholic fatty liver disease is described with fat accumulation in the liver without significant amount of alcohol consumption and has a spectrum ranging from simple steatosis to steatohepatitis, cirrhosis and liver failure [1-2]. NAFLD frequently has a relation to the components of metabolic syndrome like diabetes, dyslipidemia, obesity and hypertension [3-4].

Because of associated metabolic disturbances, NAFLDis regarded to have much atherogenic condition and so carries potential high cardiovascular risk [5-6]. Early detection of atherogenesis and the cardiovascular risk related to NAFLD has not been widely researched [7-8]. In this case-control study, we investigated the relation of NAFLD with atherosclerosis by measuring carotid intima-media thickness (IMT) and plaque to detect increased cardiovascular risk.

Materials and Methods

Subjects

We examined all subjects addressed for diagnostic abdominal ultrasound to the Radiology Division of Bursa High-

Speciality, Education and Research Hospital for fatty liver. 64 patients and 64 sex-and age matched control subjects who fulfilled the inclusion criteria were participated in the study after signed informed consent. Complete medical history was taken and physical examination, anthropometric and laboratory assessments were performed. Exclusion criteria included: alcohol consumption of >20 g/day, pregnancy, positive tests indicating the presence of hepatitis B or C virus, autoimmune liver disease, hemochromatosis, Wilson's disease, α-1 antitrypsin deficiency, primary biliary cirrhosis, primary sclerosing cholangitis and toxic liver disease.

Clinical and laboratory studies

The diagnosis of NAFLD was established by the exclusion of common etiologic factors of liver disease and on ultrasound scanning [9]. Antropometric, complete blood count and biochemical evaluations were performed. Biochemical assessments included alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-glutamyltransferase (GGT), alkaline phosphatase (ALP), bilirubin, albumin, total cholesterol, high density lipoprotein-cholesterol (HDL-cholesterol), triglycerides, ferritin, C-reactive protein (CRP), fasting glucose, insulin and c-peptide levels, an oral glucose tolerance test (OGTT). Carotid ultrasound scanning for determination of IMT and plaque was performed.Low-density lipoprotein (LDL) cholesterol was calculated according to the Friedewald formula. Increase in CRP values accepted when above 3,5 mg/dL. Normal ferritin levels were between 28-365 mg/mL in men and 5-148 ng/ml in women. Anthropometric parameters were height, weight, body mass index (BMI), waist and hip circumferences and waist/hip ratio values. Appraisement of obesity was dependent on WHO and NCEP ATP III criteria [10-11]. Definitions of type 2 diabetes, impaired glucose intolerance were depended on American Diabetes Association (ADA) criteria. Patients under oral antidiabetics or insulin therapy were accepted as diabetics. Hypertension was assumed to be present when resting blood pressure was ≥140/90 mm Hg or patients were receiving antihypertensive drug therapy.The homeostasis model assessment of IR (HOMA-IR) method was utilized to establish insülin resistance (IR) [12]. Patients were accepted as 'insulin resistant' when HOMA-IR value was >2.70.

Liver biopsy was not performed for ethical reasons. Ultrasound examination is most extensively aplicable method to diagnose NAFLD. The diagnosis of metabolic syndrome was set up according to National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP-III) and WHO criteria [10-11]. Patients should have at least three of the criteria to be diagnosed with metabolic syndrome. The study was approved by the hospital ethics committee.

Carotid ultrasound

A Philips HD 11 XE- L12-3 and L12-5 equipment with a 9-MHz multi frequency transducer was used for B-mode and Doppler carotid ultrasound. Aradio diagnostics and sonography specialist who was unaware of the patients' and control subjects' circumstances scanned the right and left carotid arteries and recorded images on videotape. In the present study İMT measurements were carried out from the far wall of the distal 10 mm of left and right common carotid arteries. IMT values were evaluated according to protocols of standard measurements of carotid artery [13-14]. Increased IMT was defined as a focal thickening of 1.0 mm in any of 12 carotid segments. A plaque was defined as a focal thickening above of 1.2 mm in any of carotid artery segments.

Statistical analyses

Comparisons of patients and control subjects were made with unpaired t tests or the Mann–Whitney U test, when appropriate, for continuous variables and by 2 analyses for categorical variables. Pearson's correlation coefficients were constructed to test the relationship between continuous variables. ANOVA statistic was used to compare sex- and age-adjusted IMT values between different groups of NAFLD and MetS. P values <0.05 were considered as statitically significant. Analyses were performed with SPSS 10.0 software.

Results

Anthropometric, clinical features and laboratory results

Table 1: Clinical and Laboratory Data of Patients with NAFLLD and controlled subject.

Varaiables	Patients (n=64)	Controls(n=64)	P value
Clinical			
Men/women	31/33	31/33	
Age, Years	48.62±11.6	45.92±13.1	
High Blood pressure	27(%42.1)	14(%21.8)	<0.001
Diabetes	13(%20.3)	6(9.37)	0.136
History of CHD	10(%15.6)	8(%12.5)	0.120
Dislipidemia	30	31	0.069
Current Smoker	17(%26.5)	13(%20.3)	0.142
BMI, kg/m3	30.6±5.24	27.4±5.31	<0.001
Waist Circumference, cm	102.2±13.0	91.48±12.5	<0.001
Waist in IP ratio	0.92±0.07	0.88±0.08	0.010
Systolic blood pressure, mm Hg	129.7±14.5	129.2±13.2	0.782
Diastolic blood pressure, mm Hg	79.8±7.21	78.8±8.43	0.195
Obesity n who	51(%79.6)	41(%64)	0.119
Obesity n nce p	52(%81.2)	27(%42.1)	<0.001

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Mts who	39(%60.9)	23(%35.9)	<0.001
Mts nce P	24(%37.5)	9(%14)	<0.001
Laboratory			
Fasting glucose, mg/dL	104.7±29.7	94.89±16.3	0.011
120-minute glucose, mg/dL	136.9±59.6	114.5±34.8	0.009
Fasting insulin, µU/mL	14.6±8.7	8.51±5.1	<0.001
Fasting c-peptide , ng/mL	2.96±1.23	1.87±0.99	<0.001
Insulin resistance (HOMA)	3.79±2.32	2.00±1.28	<0.001
Insulin resistance	42(%65.6)	16(%25)	<0.001
Total Cholestrol, mg/dL	200.9±38.4	190.2±31.1	0.142
LDL Cholestrol, mg/dL	121.7±30.3	116.1±27.2	0.345
HDL Cholestrol, mg/dL	47.83±13.3	49.13±11.5	0.257
Triglycerides, mg/dL	162.5±79.4	122.9±72.9	<0.001
ALT, mU/ mL	44.41±28.5	19.25±13.8	<0.001
AST, mU/ mL	34.94±20.3	21.70±9.62	<0.001
GGT, mU/ mL	42.7±39.7	23.59±13.1	<0.001
CRP, mg/L	2.17±4.18	4.31±7.59	<0.001
Ferritin, ng/mL	69.7±54.9	51.4±49.9	0.028

Sixty four patients (31 male, 33 female) and sixty four control subjects (31 male and 34 female) who were diagnosed with fatty liver by ultrasonographic examination participated in the study. Antropometrical, clinical features and laboratory data in both group were compared and shown at (Table 1). Patients with NAFLD had a higher frequency of high blood pressure than control group as statistically. Only ten patients with NAFLD had a history of CHD and there was no significant difference when compared to those in control group. BMI and central obesity measures were higher significantly in NAFLD group than in control subjects.

Fasting and 120-minute glucose values were higher in patients with NAFLD than those in control indivudials and were not significant (Table 1). Fournew cases of diabetes among NALFD patients and threecases in control subjects were detected by OGGT. Fasting insulin, fasting c-peptid and HOMA-IR values were significantly higher in NAFLD patients. Herewith, NAFLD patients had high frequences of insulin resistancy significantly. Total cholesterol, LDL cholesterol and HDL cholesterol levels were similar in two groups, but in NAFLD group triglycerides were higher than those in controls. The levels of serum alanine aminotransferase (ALT), aspartate aminotransferase (AST) and γ-glutamyl transpeptidase (GGT) were higher in NAFLD patients significantly.Interestingly a high ferritin level was present only in one female NAFLD patient and was not detected in control group. This patient had metablic syndrome and was insulin resistant, but IMT values werein normal ranges.

Unexpectedly, in the present study, CRP levels were higher in control group than those in NAFLD patients. Elevated serum CRP was present in 6 (6,25%) of NAFLD patients and 19 (23,4%) of control subjects (P<0.001). For all that, interestingly, control group with high CRP values had increased IMT and plaque formation significantly.

Findings due to metabolic syndrome

Three metabolic risk factors related to MetS (obesity-increased BMI, central obesity, hypertension, insulin resistance) were significantly(P<0,001) more frequent in NAFLD patients than those in control subjects. But the frequency of diabetes and dislipidemia were similar in both NAFLD and control groups. As to both WHO and ATP-III criteria,the frequency of MetS in NAFLD patients was higher than normal subjects.(60,9% and 37,5% versus 35,9%and 14% respectively). According to the presence of metabolic syndrome, in NAFLD group plaque formation was higher than control group (Table 2).

Table 2: Relationship of individual metabolic risk factors and defined MetS with abnormal IMT and plaques in NAFLD patients and control groups.

	NAFLD		Controls	
Carotid A the- Sclerosis	**Abnormal 1MT (n:7) (10.9%)**	**Plague (n: 12) (18. 7%)**	**Abnormal 1MT (n: 12) (18. 7%)**	**Plague (n:6) (9.37%)**
CRP	0-0%	2(33.3%)	3(15.7%)	3(15.7%)
Ferittin	1(100%)	0(0%)	0(0%)	0(0%)
Hypertension	3(11.1%)	7(25.9%)	4(28.5%)	2(14.2%)
Dysilpidmia Obesity	2(6.66%)	6(22.2%)	4(21.0%)	3(15.7%)
WHO	4(7.84%)	9(17.6%)	7(17.0%)	7(17.0%)
NCEP	4(7.69%)	11(21.1%)	5(18.5%)	1(3.70%)
Diabetes Metabolic Syndrome				
WHO	2(5.12%)	8(20.5%)	4(17.3%)	1(11.1%)
NCEP	2(8.33%)	7(29.1%)	1(11.1%)	1(11.1%)

Outcomes of carotid ultrasound examinations

Aimed to present the predictors inducing the occurance of carotid atherosclerosis in NAFLD patients comparing to control group (Table 2). At the same time, the abnormal IMT rates and plaque formation according to the presence of metabolic risk factors in NAFLD patients and control group were shown at (Table 2) and no risk factor seemed to be as the predictor of carotid atherosclerosis.

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Table 3: Carotid IMT and Plaque in Patients with NAFLD and Control subjects.

Varaiables	Patients(n=64)	Controls(n=64)	P value
Mean IMT, mm	1.06±0.71	0.96±0.66	0.125
Maximum IMT, mm	2.70±0.71	3.90±0.66	<0.001
Carotid plaque	12(18.7%)	6(9.37%)	<0.001

Patients with NAFLD showed increased mean IMT and a 2-fold higher frequency of plaque comparing to normal subjects, but conversely maximum IMT value was higher in normal group than those in patients with NAFLD (Table 3). The differences for mean IMT between NAFLD and controls were 0.10 mm in favour of NAFLD group and 1.1 mm for maximum IMT in favour of healthy controls. Figure 1 shows patient-control differences in IMT and plaque frequency according to the gender. In NAFLD group IMT values were higher in women than those in men. Conversely, in control group IMT values were higher in men than those in women.

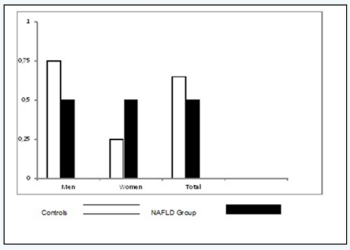

Figure 1a: Mean carotid IMT size in patient with NAFLD and controls according to gender.

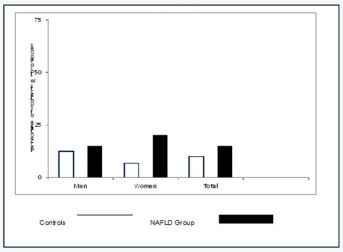

Figure 1b: Plaque frequency (percentage of subjects with plaque) in patients with NAFLD and controls according to gender.

When we compared all participants subdividing into 4 subgroups as with andwithout NAFLD and with and without MetS, IMT values did not show significant differences and were almost similar in four subgroups (Figure 2).

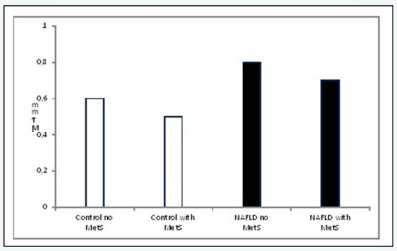

Figure 2: IMT values according to the presence of MetS by WHO definition.

Discussion

This study aimed to evaluate the coexistance and size of cardiovascular risk factors and carotid atherosclerosis in patients with primary NAFLD diagnosed by ultrasound examination. As to recent studies, patients with NAFLD frequently presents various combinations of parameters related to MetS [3-4]. While MetS has high risk of atherosclerosis and is associated with NAFLD, studies to determinate early atherosclerosis and detection of novel atherosclerotic risk factors in NAFLD patients were widely studied recently as stated by Targher G et al. [5]& Lim S et al. [6].

In this study, the prevalance presence of carotid atherosclerosis was investigated in patients with NAFLD being coexistence with or without metabolic syndrome. Carotid atherosclerosis has a significant value to predict the oncoming atherosclerotic process. Stated that values of carotid intima-media thickness were reliable and accurate method to detect early athrerosclerosis [7-8]. Various methods are available for measurements of carotid aretry intima-media thickness as showed by Casella IB and Baldassarre D [13-14]. NAFLD and the progress of an atherosclerosis now a rising issue in the field of cardiovscular risk factors as stated by Brea A et al. [14],Volzke H et al. [15] Nestel PJ et al. [16].

In the present study, abnormal IMT and carotid plaque incidence, as the signs of developing atherosclerosis, were not associated with MetS and its individual parameters in patients with NAFLD and in controls (Table 2). According to the literature, in subjects with MetS, incidence and progression of augmented carotid IMT and carotid plaque occurance were increased Kim HC et al, Targher G et al & Bonora et al. [18-20] said that presence of Mets in NAFLD cases enhances occurance of carotid atherosclerosis [18-20]. In this study in NAFLD group with WHO-MetS had an increase in plaque formation than those in controls but this result was not significant. Regardless of MetS, in NAFLD and control groups have similar ratio according to the presence of increased IMT and carotid plaque formation and these findings suggest that, solely NAFLD did not increase the occurance of atherosclerosis (Table 3). Kim HJ et al and Younossi Zobair M et al. [21-22] said that NAFLD could occur in adolescents and in leans even in the absence of MetS [21-22], likewise, carotid atherogenesis might progress even so in healty and young persons [23-27]. These findings give hints that NAFLD is not always and un questionable an atherogenic state. Large numbers of individuals with and without NAFLD as well as with and without MetS should be studied for carotid atherosclerosis.

Prevalence of MetS in our NAFLD and control groups were 60,9% and 35,9% respectively and results were statistically significant. But in the present study NAFLD did not have close relation with increased IMT and carotid plaque. The presence of MetS did not change the outcomes. Presence of MetS did not alter the generation of abnormal IMT and carotid plaque and these findings were not concordant with the view of NAFLD

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as a hepatic component of MetS [28]. Additionally, hepatic fat accumulation was not significantly related to patients' lipid profile, atherogenic condition.

Howbeit, conversely to certain previous study findings, in the present study we determined that patients with NAFLD might not have advanced carotid atherosclerosis and NAFLD could not be a predictor of an increased IMT [23-25]. Targher G et al, Petit JM et al and Oren A et al revealed that carotid arteriosclerosis could be present in young and healty adults.

Process of atherogenesis in NAFLD can be revealed by measuring CRP levels [29]. In the pathogenesis of NAFLD oxydative stress has an importanat role. Pro-atherogenic effect in NAFLD is considered to become from exessive oxydative stress. Alongside being the source of oxydative stress, ROS (reactive oxydative species) eventuate from fatty acid beta-oxydation and cause hepatocyt injury, cytokin release and yield an inflammatory milieu which can initiate also steatosis and steatohepatitis and then additionally an atherognic effect together with the increased level of serum CRP. In our study CRP levels were higher in control group than those in NAFLD subjects, despite the presence of MetS. In the present study CRP levels were not increased in insülin resistant individuals. Moreover, CRP levels were not related to the serum ALT levels and IMT values. So CRP and ALT both did not show any association with the inflammatory state.

Additionally, abnormal lipoprotein metabolism (due to the insulin resistance and MetS) in NAFLD can enhance the cardiovascular risk and effect the formation of atherosclerosis [30]. A considerable and common mechanism of hepatosteatosis is as belows: increased fatty acid flow from adipose tissue and small intestine because of the removed inhibition of lipoprotein lipase enzyme effect on lipolyse secondary to insulin resistance, reduced beta-oxydation and increaed synthesis of free fatty acids in hepatocytes and reduced triglyceride excretion from liver cells. The latest depends on the deteriorated synthesis of Apo-B100 and diminished formation of VLDL. Because of the reducing hepatic Apo B synthesis in NAFLD, triglyceride rich VLDL is not excreted and accumulates in liver. Increased intracellular free fatty acids cause an enhancement of cytochrome P450 4A and cytochrome P 2E1. These products then induce the occurance of ROS. Excessive ROS initiate lipid peroxydation of hepatocyte membrane lipids and then destruction of liver cells emerges [31]. In the present study, in NAFLD patients and controls with dyslipidemia, percentages of those with abnormal IMT and carotid plaque were similar and results were not significant. Whereas, serum triglyceride levels were increased in NAFLD patients than those in control subjects significantly.

Free radicals are occured also during the enzymatic and non-enzymatic oxydoreduction reactions concerned with iron and copper [32]. Free radicals break up double bonds between carbon atoms in unsaturated fatty acids with the catalytic effect of iron and ascorbic acid. The result is the onset of lipid peroxydation. Ferritin is the form of iron storage, and iron is released to provide the necessaty of the body. The role of excessive iron storage is not exactly clear in pathogenesis of NAFLD. In NAFLD, because of being an acute phase reactant ferritin may be increased secondary to the inflammation and liver cell damage. In this study, only one patient had high ferritin level. This female NAFLD patient was obese and insulin resistant and had hypertension with normal ALT levels. In both groups ferritin levels were also not correlated with increased IMT values and presence of plaque.

In conclusion, in our study NAFLD was not associated with carotid atherosclerosis or atherogenetic state even with and without MetS. While NAFLD is considered as a component of MetS, the findings and results of our study maydirect attentions to other causes which lead to the formation of atherosclerosis. The frequency of CAD, components of MetS or defined MetS may show disparity in NAFLD according to the recent studies. Howbeit, in NAFLD patients with or without MetS, should be evaluated for an unknown and ocult and potential cardiovasculsar risk as well as a serious liver disease.

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