Insulin resistance and metabolic syndrome in non-alcoholic fatty liver disease with normal alanine aminotransferase levels

Normal alanin aminotransferaz düzeyli nonalkolik yağlı karaciğer hastalığında insülin direnci ve metabolik sendrom

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Background and Aims: *The aim of the study is to investigate insulin resistance and metabolic syndrome criterion in non-alcoholic fatty liver disease patients who have normal alanine aminotransferase levels, which is prevalent in the community.* ***Materials and Methods:*** *The study looked at 100 subjects, randomized into two groups of 50. The study group consisted of subjects with normal alanine aminotransferase levels and hepatosteatosis detected by ultrasonography; the control group, again randomized, were subjects with normal alanine aminotransferase levels but no hepatosteatosis as detected by ultrasonography. Subjects with hepatosteatosis were grouped by grade I, II, or III. Each group was evaluated with respect to metabolic syndrome diagnosis criteria in accordance with The World Health Organization and the National Cholesterol Education Programme-Adult Treatment Panel III.* ***Results:*** *The homeostatic model assessment of insulin resistance values were found to be significantly higher in the group with non-alcoholic fatty liver disease and normal alanine aminotransferase levels (p=0.042); and although alanine aminotransferase level were within the normal range, they were significantly higher in the study group compared to control group (P=0.016). Estimated metabolic syndrome frequency according to The World Health Organization was 36% and 64% in control and study groups respectively, which was statistically significant (p=0.005). The study group's aspartate aminotransferase and alanine aminotransferase levels significantly increased (p<0.001, p=0.004) as hepatosteatose grades, detected by ultrasonography, increased.* ***Conclusion:*** *Individuals with non-alcoholic fatty liver disease should be screened for insulin resistance and metabolic syndrome, independent of alanine aminotransferase levels.*

Key words: *Alanine aminotransferase, insulin resistance, non-alcoholic fatty liver disease*

Giriş ve Amaç: *Çalışmamızın amacı; toplum prevalansı yüksek olan normal alanin aminotransferaz düzeyli nonalkolik yağlı karaciğer hastalığındaki insülin direncini ve metabolik sendrom kriterini araştırmaktır.* ***Gereç ve Yöntem:*** *Çalışmaya ultrasonografi ile hepatosteatozu saptanan ve alanin aminotransferaz düzeyleri normal olan gelişigüzel seçilen 50 kişilik çalışma grubu ile yine normal alanin aminotransferaz düzeyli ultrasonografi ile hepatosteatozu saptanmayan yine gelişigüzel seçilen 50 kişilik kontrol grubu alındı. Hepatosteatozu olanlar evre I, II ve III olarak kendi arasında gruplandı. Her bir grup Dünya Sağlık Örgütü ve Ulusal Kolestrol Eğitim Programı-Erişkin Tedavi Paneli III'e göre metabolik sendrom tanı kriterleri açısından değerlendirildi.* ***Bulgular:*** *Gruplar arasındaki karşılaştırmada insülin rezistansının değerlendirilmesinde homeostatik model değeri normal alanin aminotransferaz düzeyli nonalkolik yağlı karaciğer hastalığı grubunda, kontrol grubuna göre anlamlı olarak yüksek saptandı (p=0.042). Yine normal aralıkta olmakla birlikte alanin aminotransferaz değeri de steatozlularda anlamlı olarak yüksek idi (p=0.016). Dünya Sağlık Örgütü'ne göre hesaplanan metabolik sendrom sıklığı steatozu olmayanlarda %36 iken, normal alanin aminotransferaz düzeyli nonalkolik yağlı karaciğer hastalığı olanlarda %64 ile anlamlı olarak yüksek idi (p=0.005). Hepatosteatozu olan grup ultrasonografide saptanan hepatosteatoz derecelerine göre grupladırıldığında; gruplar arasında evre arttıkça aspartat aminotransferaz ve alanin aminotransferaz değerlerinin de anlamlı olarak arttığı görülmektedir (p<0.001 ve p=0.004).* ***Sonuç:*** *Nonalkolik yağlı karaciğer hastalığı olan bireyler alanin aminotransferaz düzeylerinden bağımsız olarak, insülin direnci ve metabolik sendrom açısından taranmalıdır.*

Anahtar kelimeler: *Alanin aminotransferaz, insülin direnci, nonalkolik yağlı karaciğer hastalığı*

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a fatty liver disease that develops without the consumption of considerable amounts of alcohol. It may progress from simple steatosis to non-alcoholic steatohepatitis (NASH), and finally to liver cirrhosis (1,2). It is thought that a portion of patients diagnosed with cryptogenic liver cirrhosis in the past might have developed the disease due to fatty liver (3,4). Presently, there is general agreement that insulin resistance is associated with NAFLD (5). Evidence from studies of subgroups of patients with NASH accompanied by inflammation show that NAFLD is part of metabolic syndrome (MS) (6-9). In fact, it is recommended that patients diagnosed with NASH should be evaluated by oral glucose tolerance test (OGTT) to determine whether they have MS and glucose intolerance (10). Although recent studies have shown an association between simple steatosis (prevalence is estimated at 15%-39%) and MS, cases of steatossis with normal alanine aminotransferase

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(ALT) levels are thought to have a benign clinical course (11,12).

In this study, we aimed to compare the incidence of insulin resistance in patients diagnosed with hepatosteatosis by ultrasonography (USG) who had normal ALT levels with patients without steatosis.

MATERIALS and METHODS

This study was performed in the Department of Internal Diseases at Afyon Kocatepe University, between March 2005 and February 2006. Ethical approval was obtained from the ethical committee of Afyon Kocatepe University. The guidelines issued in the Helsinki Declaration by the World Medical Association were followed and the study was conducted under Good Clinical Practices and Good Laboratory Practices by the World Psychiatry Association.

Patients were selected through random sampling; the first and fourth patients presenting to the Department of Radiology, who had conditions that were non-emergency in nature, were asked to participate. The candidates were informed about the study and those who were interested were offered details of the study based on an informed consent form. Written consent was obtained from all participants. The patients with hepatosteatosis were assigned to the steatosis group and participants without hepatosteatosis assigned to the control group.

Alkaline phosphatase (ALP), aspartate aminotransferase (AST), ALT and gamma-glutamyl transpeptidase (GGT) levels were determined in all the participants. The cut-off value of ALT was considered at >30 U/L in female participants and >40 U/L in male participants. HBsAg, Anti-HBc, immunoglobuline G (IgG) and Anti hepatitis C Virus (HCV), indicators of chronic viral hepatitis, had to be ruled out for the diagnosis of NAFLD. Those who did not to have HBsAg, Anti-HBc IgG and Anti-HCV were included in the study. Since none of the participants had HBc IgG, HBV-DNA was not investigated to diagnose occult hepatitis B infection. Since patients with hepatosteatosis with no viral indicators did not show a suspicious familial history or a clinical picture for metabolic or autoimmune hepatitis, ferritin, ceruloplasmin, alpha 1 antitrypsin, anti-nuclear antibody (ANA), smooth muscle antibody (anti-SM) and liver-kidney microsome antibody (anti-LKM) levels were not investigated. Exclusion criteria were ALP, AST, ALT and GGT levels higher than the cut-off values, alcohol intake higher than 20 gr/day for two years, diagnoses of viral, metabolic and autoimmune hepatitis, regular uses of glucocorticoid, oestrogen, amiodarone, tamoxifen, aspirin, methotrexate, diltiazem and nifedipin; patients who had jejuno-ilial bypass, aggressive resection of the small bowel and gastropexy, intentional or unintentional extreme weight loss in the past 6 months (more than 5 kg a month) and inflammatory bowel disease, or a similar serious systemic diseases, or a malignant disease, were also excluded from the study.

Three participants in the steatosis group and one in the control group were excluded from the study since they had AST and ALT levels 1-2 times higher than the cut-off values. There were no other conditions that required participants in either group to be excluded.

Body mass index (BMI) and ratio of waist to hip circumference (WHR) were recorded, and every six hours arterial blood pressure was measured under appropriate conditions in the remaining participants. OGTT was performed on all participants who were not known to have diabetes in order to measure their glucose tolerance levels. A blood specimen was taken to determine fasting glucose levels and three blood specimens were taken at intervals of five minutes to determine fasting insulin levels. The mean fasting insulin level was estimated for all the participants. Homeostatic model assessment of insulin resistance (HOMA-IR) was based on the mean values. Lipid profiles [triglyceride and high density lippoprotein (HDL)] were also determined by using the fasting glucose level specimens. Microalbuminuria was investigated in 24-hour urine specimens. The patients with hepatosteatosis were classified into subgroups depending on the stage of the condition; i.e. hepatostetosis grade I, II or III (Table 1). The degree of liver steatosis on USG was based on hepatic echogenicity and clarity of intrahepatic vessel contours, the posterior segment of the liver and the diaphragm (13,14). Each group was evaluated in terms of the criteria for MS issued by the World Health Organization (WHO) and the National Cholesterol Education Program's Adult Treatment Panel III (NCEP ATP III) (15,16). The incidence of MS was compared between the steatosis and control groups.

Table 1. Findings from USG in liver steatosis

Grade	Ultrasonography Findings
Grade 1	A slight increase in hepatic echogenicity Clear image of intrahepatic vessel contours and diaphragm
Grade 2	A moderate increase in hepatic echogenicity Inability to see intrahepatic vessel contours and diaphragm clearly
Grade 3	A considerable increase in hepatic echogenicity Failure to see the posterior segment of the liver, intrahepatic vessels and diaphragm

Table 2. Socio-demographic, clinical and laboratory features of the study groups

Variables	Steatosis Group (n=50)		Control Group (n=50)		P
	Mean±SD	Range	Mean±SD	Range	
Age (years)	49.2±8.9	24-65	47.6±11.6	17-73	0.307
Gender (n, M/F)	29/21		36/14		0.142
FBG (mg/dl)	121.6±43.4	76-260	116.5±51.9	80-321	0.065
2 h OGTT (mg/dl)	159.8±89.6	58-491	143.8±84	71-420	0.156
HOMA-IR	3.72±3.39	0.51-22.1	2.5±1.7	0.1-11.4	0.042
Systolic BP (mmHg)	133±19	100-190	130±20.5	100-190	0.254
Diastolic BP (mmHg)	83.8±8.78	70-100	81.3±10.5	60-110	0.107
Triglycerides (mg/dl)	189.6±89.9	50-568	169.1±94.7	11-436	0.184
HDL-cholesterol (mg/dl)	46.09±10.8	28-81	49.3±10.5	26-84	0.052
BMI (kg/m^2)	29.1±3.6	23-39	27.9±4.63	19-41	0.130
Waist circumference (cm)	97±9.2	74-119	92.6±11.5	60-116	0.067
WHR	0.87±0.2	0.73-1.14	0.84±0.2	0.71-1.07	0.062
Microalb. (mg/day)	125.6±153.8	0.45-956	113.3±157.6	13.2-973.2	0.506
AST (U/L)	20.6±4.65	9-31	18.4±4.9	11-32	**0.016**
ALT (U/L)	25.2±8.3	7-40	19.3±7.84	3-39	**<0.001**

FBG; fasting blood glucose, OGTT; oral glucose tolerance test, HOMA-IR; calculated by homeostasis model of insulin resistance, BP; blood pressure, BMI; body mass index, WHR; ratio of waist circumference to hip circumference, Microalb; microalbuminuria, AST; aspartate aminotransferasa, ALT; alanine aminotransferase.

Table 3. The incidence of MS compared between the groups

	Steatosis Group (n=50)	Control Group (n=50)	P
According to WHO, the incidence of MS (n, %)	32 (64)	18 (36)	**0.005**
According to NCEP ATP III, the incidence of MS (n,%)	30 (60)	22 (44)	0.080

WHO; World Health Organization, NCEP ATP III; National Cholesterol Education Program's Adult Treatment Panel III, MS; metabolic syndrome

Statistical Analyses

Mean values were expressed in mean±SD. Chi-square test and Mann-Whitney U test were used to compare the steatosis and control groups.

RESULTS

The steatosis group included 50 patients, 29 (58%) were female and 21 (42%) male; mean patient age was 49.2±8.9 years. The control group included 50 participants, 36 (72%) were female and 14 (28%) male; mean age of the group was 47.6±11.6 years. HOMA-IR, AST and ALT were significantly higher in the steatosis group (p=0.042, p=0.016 and p<0.001 respectively), but there was not a significant difference in age, gender, systolic and diastolic arterial blood pressures, BMI, WHR, waist circumference, triglyceride, HDL-cholesterol, fasting plasma glucose, plasma glucose at two hours of OGTT and microalbuminuria between the groups (Table 2). Estimated MS frequency according to WHO was 36% and 64% in the control and study groups respectively and this was statistically significant (p=0.005). However, based on the criteria issued by NCEP ATP III only, the incidence of MS did not significantly differ between the groups (Table 3).

There was a significant relationship between severity of hepatosteatosis and AST and ALT (p<0.001 and p=0.004). As the grade of hepatosteatosis increased so did AST and ALT levels. However, the relation between severity of hepatosteatosis and HOMA-IR was not significant, although as severity of hepatosteatosis increased so did HOMA-IR (Table 4).

DISCUSSION

Non-alcoholic fatty liver disease (NAFLD) typically appears in the fourth and fifth decades of life, although it may develop in childhood. Some studies have revealed that the disease is more frequent in males while others have reported that it is more common in females (2,17). In the present study, we found no significant difference in gender between the patients with steatosis and the control group. In addition, age did not differ significantly and the mean age of 50 patients with steatosis was 49.2 years.

Table 4. Relations between grades of steatosis (diagnosed by USG) and socio-demographic features and anthropometric and laboratory findings in steatosis group

Variables	Grade I (n=12)	Grade II (n=28)	Grade III (n=10)	P
Age (years)	53.6±6.0	47.8±9.0	48.1±10.4	0.164
Gender (n, M/F)	8/4	16/12	5/5	0.726
FBG (mg/dl)	107.6±31.6	122.5±47.1	135.8±43.6	0.084
2 h OGTT (mg/dl)	137.9±54.3	156.1±99.9	196.5±89.3	0.175
HOMA-IR	3.6±5.8	3.7±2.2	3.8±2.3	0.072
Systolic BP (mmHg)	133.7±20.5	130.1±12.6	140.0±29.8	0.733
Diastolic BP (mmHg)	85.4±9.8	81.9±6.2	87.0±12.5	0.352
Triglycerides (mg/dl)	179.4±107.8	191.4±90.4	196.6±71.6	0.727
HDL-cholesterol (mg/dl)	48.7±8.4	46.6±12.3	41.2±7.6	0.138
BMI (kg/m^2)	28.8±2.9	28.8±4.1	30.5±3.0	0.115
Waist circumference (cm)	93.0±9.0	97.6±8.9	100.5±9.7	0.260
WHR	0.83±0.20	0.88±0.20	0.90±0.1	0.080
Microalb. (mg/day)	82.3±47.0	115.0±115.0	207.5±275.9	0.502
AST (U/L)	17.0±3.6	20.6±3.6	25.3±4.5	**<0.001**
ALT (U/L)	19.2±6.7	26.1±8.1	29.9±7.3	**0.004**

FBG; fasting blood glucose, OGTT; oral glucose tolerance test, HOMA-IR; calculated by homeostasis model of insulin resistance, BP; blood pressure, BMI; body mass index, WHR; ratio of waist circumference to hip circumference, Microalb; microalbuminuria, AST; aspartate aminotransferase, ALT; alanine aminotransferase.

Elements of MS are more common in patients with NAFLD and NASH than in the general population. In a study by Angulo et al., of 144 patients with NAFLD, 28% had diabetes mellitus (DM), 60% had obesity and 27% had hyperlipidemia (18). In a study by Matteoni, of 132 patients with NAFLD, 33% had DM, 70% had obesity and 92% had hyperlipidemia (19). In another study, of 30 patients with NAFLD who had either NASH or simple steatosis, 80% had obesity, 33% had DM, 80% had hyperlidemia and 50% had hypertension (20). In the present study, and consistent with the literature, the incidence of arterial blood pressure ≥140/90 mmHg was 36%, the incidence of arterial blood pressure ≥130/85 mmHg was 56%, the incidence of diabetes was 46%, and the incidence of obesity was 34%, based on BMI, and 54% based on WHR. These incidences were higher than those in the general population. In fact, in epidemiological studies from Turkey, the incidence of DM was 13.7%, the incidence of hypertension was 30%, the incidence of obesity of 32% (21). In a study by Marchesini in 1999, 46 patients with chronic high transaminase levels and hepatosteatosis diagnosed by USG were compared with 92 controls; insulin resistance based on HOMA was found to be significantly high in the patients with hepatosteatosis (22). The researcher performed another study in 2001 on 30 patients diagnosed with NAFLD by liver biopsy due to chronic high transaminase levels, having normal glucose tolerance, and BMI lower than 30. The results of this study were compared with those obtained from 10 patients who were administered oral antidiabetic agents and from 10 healthy controls. Of 30 patients with NAFLD, 21 were found to have NASH and nine were found to have simple steatosis on biopsy. Insulin resistance was investigated with glycemic clamp technique. The investigator reported that insulin resistance was significantly higher in the patients with NAFLD and those with diabetes than in the healthy controls (23). Compatible with the results of the abovementioned two studies, we found that insulin resistance was significantly higher in the patients with NAFLD than in the control group. This finding confirms the relation between insulin resistance and NAFLD. However, in the study by Marchesini in 2001, the study group included patients with high transaminase levels and NAFLD shown on biopsy, and most of them had NASH. Conversely, in the present study, the study group included patients not exposed to biopsy to diagnose NAFLD since they had normal ALT levels. They were diagnosed with NAFLD due to steatosis that was shown by USG and by excluding other liver diseases. Unlike the abovementioned studies, the present study was directed towards investigation of insulin resistance in patients with NAFLD and normal ALT levels. Although

ALT levels were normal in the study group, they were significantly higher than those in the control group. In addition, as the degree of hepatosteatosis increased, so did ALT levels. However, these increases in ALT levels were in the normal range ($p<0.001$ and $p=0.004$). Both these higher transaminase levels, though in the normal range, and high insulin resistance, suggested that inflammation began following the first impact, i.e. insulin resistance, and a progression to the next impact occurred in the patients with NAFLD accompanied by normal ALT levels. Like the present study, the study by Marchesini included a subgroup of 51 patients with NAFLD accompanied by normal ALT levels; it revealed that out of these patients, eight had steatosis alone, 21 had steatosis and inflammation, and 22 had steatosis, inflammation and fibrosis. These patients underwent biopsy since they had hepatomegaly that could not be explained, and because they were liver transplant donors, but histopathological findings obtained from these patients did not differ from those obtained from 50 patients with NAFLD accompanied by high ALT levels. It was emphasized that normal ALT levels were not a predictor for histopathology in patients with NAFLD (24). The results of the present study were not based on histopathological examinations. However, the finding that the patients with NAFLD had high insulin resistance and higher ALT levels than the control group, though again these were in the normal range, suggests that some of these patients might have had inflammation. Additionally, the finding that showed that as the degree of hepatosteatosis increased, so did ALT levels (though in normal ranges), suggests the presence of inflammation.

Criteria issued by NCEP ATP III are the most common and easy to use for screening metabolic syndrome. However, they are not directed towards determining insulin resistance and hyperinsulinemia, which are limitations with these criteria. In view of the advantages and disadvantages of all diagnostic criteria, guidelines issued by the WHO, though the oldest, seem to be the most reliable (15). In this study, we used the criteria issued by the WHO and NCEP ATP III criteria for the diagnosis of MS. The incidence of MS based on the criteria by the WHO was significantly higher in the patients with NAFLD than in the control group, while there was not a significant difference in the incidence of MS based on NCEP ATP III criteria between the groups. Thus, we obtained evidence for the incidence of MS based on both criteria. In addition, screenings for MS in NAFLD patients, in which insulin resistance plays an important role, should be performed according to the WHO criteria since it takes this into account.

In recent years, there have been a lot of studies on fatty liver disease with normal ALT levels, and several of these studies have designs similar to the present study (5,25,26). In a study by Angelico, 308 people presenting to the Endocrinology Clinic with suspected metabolic disorder were exposed to OGTT and USG for hepatosteatosis. Out of 236 people found not to have diabetes, 100 (42.3%) had MS (25). However, 236 patients, about 29%, were found to have either mild steatosis or no steatosis. The incidence of MS reported does not exactly reflect the incidence of MS in patients with NAFLD. In another study, out of 3000 presenting to a metabolism unit, 147 patients were found to have NAFLD; and out of 600 patients presenting to a liver unit, 179 were found to have NAFLD. The diagnosis of NAFLD was based on high transaminase levels and presence of steatosis on USG after excluding other conditions, and only 183 patients had a liver biopsy; biopsy showed NASH in 133 patients (72.6%). The incidence of MS was 64% in the metabolism unit and 22% in the liver unit (5). In a similar study, 25 patients with NAFLD and 17 controls were compared. Out of 25 patients with NAFLD, 15 (56%) were found to have NASH and 10 were found to have simple steatosis on liver biopsy. The incidence of MS in 25 NAFLD patients was 56% (26). In all three studies mentioned above, the incidence of MS was 42.3%, 22-64%, and 56% in patients with NAFLD. In the present study the incidence of MS was 64% based on the criteria issued by the WHO, and 60% with NAFLD based on NCEP ATP III criteria. Of three abovementioned studies, two included patients with NAFLD accompanied by high ALT levels (25,26), and in the other study, about 29% of the patients had mild or no hepatosteatosis on USG (25). Although the present study aimed to determine the incidence of MS like the studies reported above, both criteria issued by the WHO and NCEP ATP III criteria were used to determine the incidence of MS; the study included only the NAFLD patients with normal ALT levels. To conclude, the incidence of MS is high in patients with NAFLD (diagnosed by USG) accompanied by normal ALT levels. Although transaminase levels were normal in the patients with steatosis, they were significantly higher than in the patients without steatosis. In addition, insulin resistance was significantly higher in the patients with steatosis. These two findings suggest that a proportion of patients with steatosis might have had inflammation. Appropriate precautions including diets that reduce insulin resistance and losing weight should be taken without waiting for increases in ALT levels.

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