Smyrna Tıp Dergisi *Araştırma Makalesi*

Effect of Diet, Exercise and Treatment of Accompanying Disorders on the Rate and Degree of Hepatosteatosis in Patients with Hypertension and Non-alcholic Fatty Liver Disease

Hipertansiyon ve Non-alkolik Karaciğer Yağlanması Olan Hastalarda Diyet Düzenlemesi, Egzersiz ve Eşlik Eden Hastalıkların Tedavisinin Hepatosteatoz Oranı ve Derecesi Üzerine Etkisi

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Abstract

Objective: Non-Alcoholic Fatty Liver disease (NAFLD) is seen in the population with an estimated prevalence of 10-24%. In the management of this disorder; exercise, correction of metabolic status and glucose and lipid regulation is recommended. In this study, the effectiveness of antihypertensive, antidiabetic and antihyperlipidemic therapy with dietary regulations and exercise on hepatosteatosis was investigated.

Material and Method: 141 cases with hypertension that were ultrasonographically diagnosed as hepatosteatosis, were included in this study. After diet, exercise and therapy directed to hypertension and accompanying disorders; all cases were reevaluated by point of weight, body mass index (BMI), blood pressure, lipid profile, fasting glucose level, micro albuminuria and other parameters associated with accompanying disorders. All cases were ultrasonographically reevaluated to detect whether there are any changes in the rate and degree of hepatosteatosis.

Results: 66% of the cases were female and 34% were male. Diabetes mellitus and cardiovascular diseases were accompanying in 24.8% and 7% of the cases respectively. The rates of metabolic syndrome (MS) according to 2 different guidelines were 80.1% and 82.2% respectively. The rate of NAFLD was significantly high in cases with MS. Mean values on admission and after therapy were respectively as follows; BMI: 32.4±5.3 - 32.1±5.1 kg/m², systolic blood pressure: 155.3±26.6 - 132.0±15.3 mmHg, diastolic blood pressure: 94.9±15.0 - 82.6±9.9 mmHg, fasting glucose: 106.9±20.7 - 99.5±13.4 mg/dl, total cholesterol: 215.7±43.9 - 197,5±43,6 mg/dl, triglyceride: 162.0±90.2 - 139.5±67.8 mg/dl, HDL cholesterol: 46.8±10.7 - 49.88±13.0 mg/dl, LDL cholesterol: 136.6±38.3 - 120.9±35.8 mg/dl, 24-hours urine microalbumin: 53.5±106.7 - 47.7±165,7, AST: 26.0±17.2 - 23.9±13.0 IU/L and ALT: 30.5±30.9 - 27.2±25.3 IU/L. Although almost all parameters significantly improved, no significant improvement was seen in rate and degree of hepatosteatosis.

Conclusion: Our study suggested that dietary regulations and exercise along with therapy directed to accompanying disorders did not result in significant improvement in neither rate nor degree of hepatosteatosis. Additionally, blood glucose regulation, lipid regulation and blood pressure normalization seems no effective on reducing degree and frequency of NAFLD.

Keywords: Antihypertensive, antidiabetic, diet, exercise, non-alcoholic fatty liver disease

Özet

Amaç: Non-Alkolik Yağlı Karaciğer Hastalığı'nın (NAYKH) toplumda %10-24 sıklıkta görüldüğü öngörülür. Bu hastalığın tedavisinde egzersiz, metabolic durumun düzeltilmesi ve glukoz ve lipid düzenlenmesi önerilir. Bu çalışmada antihipertansif, antidiyabetik ve antihiperlipidemik tedavi ile birlikte diyet düzenlemeleri ve egzersizin hepatosteatoz üzerine etkisi araştırılmıştır

Gereç ve Yöntem: Ultrasonografik olarak hepatosteatoz tanısı konmuş 141 olgu çalışmaya alındı. Hipertansiyon ve eşlik eden hastalıklara yönelik tedavi ile diyet ve egzersiz sonrası tüm olgular ağırlık, vücut kitle indeksi (VKİ), kan basıncı, lipid profili, açlık kan şekeri, mikroalbüminüri ve eşlik eden hastalıklar ile ilişkili diğer parametreler yönüyle yeniden değerlendirildi. Tüm olgular hepatosteatoz oranı ve derecesinde değişiklik olup olmadığının tespiti için ultrasonografik olarak yeniden değerlendirildi.

Bulgular: Hastaların %66'sı kadın, %34'ü erkekti. Diabetes mellitus ve kardiyovasküler hastalık olgularının sırasıyla %24,8 ve %7'sinde eşlik etmekteydi. İki farklı kılavuza göre metabolic sendrom (MS) oranları sırasıyla %80,1 ve %82,2 idi. MS tanılı olgularda NAYKH oranı anlamlı derecede daha yüksekti. Olguların ilk başvuruda ve tedavi sonrasındaki ortalama değerleri sırasıyla; VKİ: 32.4±5.3 - 32.1±5.1 kg/m², sistolik kan basıncı: 155.3±26.6 - 132.0±15.3 mmHg, diyastolik kan basıncı: 94.9±15.0 - 82.6±9.9 mmHg, açlık glukozu: 106.9±20.7 - 99.5±13.4 mg/dl, total kolesterol: 215.7±43.9 - 197,5±43,6 mg/dl, trigliserid: 162.0±90.2 - 139.5±67.8 mg/dl, HDL kolesterol: 46.8±10.7 - 49.88±13.0 mg/dl, LDL kolesterol: 136.6±38.3 - 120.9±35.8 mg/dl, 24-saatlik idrarda mikroalbumin: 53.5±106.7 - 47.7±165,7, AST: 26.0±17.2 - 23.9±13.0 IU/L and ALT: 30.5±30.9 - 27.2±25.3 IU/L. Hemen tüm parametrelerde anlamlı derecede düzelme görülürken, hepatosteatoz sıklık ve derecesinde azalma görülmedi.

Sonuç: Çalışmada; eşlik eden hastalık tedavisiyle birlikte diyet ve egzersizin hepatosteatozis sıklığında ve derecesinde anlamlı bir iyileşme oluşturmadığını düşündürmektedir. Buna ek olarak kan glukoz regülasyonunun, lipid regülasyonunun ve kan basıncı normalizasyonunun NAYKH'nın sıklık ve derecesini azaltmada etkili olmadığı gözükmektedir.
Anahtar kelimeler: Antihipertansif, antidiyabetik, diyet, egzersiz, non-alkolik yağlı karaciğer hastalığı

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Introduction

Hepatosteatosisis described as fat deposition that exceeds 5% of the dry weight of liver, or with more than 5% of hepatocytes filled by fat vacuoles determined by histopathologic examination. It is usually diagnosed incidentally when performing laboratory analysis and abdominal ultrasonography due to other disorders (1). Currently, fatty liver diseases are divided into three main categories; non alcoholic fatty liver diseases (NAFLD), alcoholic fatty liver diseases (AFLD) and fatty cirrhosis (FC). Non-alcoholic fatty liver diseases are further divided into 2 categories; simple fatty liver and non-alcoholic steatohepatitis (NASH) (2,3,4,5,6).

In 25% of the patients with NASH, cirrhosis develops and 10% of these patients die due to liver disorders (3,6). Laboratory and ultrasonographic examinations without histopathologicalevaluation may be misleading when establishing distinctive diagnosis between fatty liver, hepatosteatosis, liver cirrhosis and other disorders of liver. Distinctive morphological features of NASH are steatosis, lobular inflammation with polymorph nuclear leukocytes and perisinusoidal fibrosis (7,8).

Obesity, type 2 diabetes mellitus, alcohol and dyslipidemia are frequently seen etiological factors of fatty liver. Although, it has been shown that exercise and correction of metabolic status may be beneficial. To date, there is no drug which is proved effective and widely accepted in management of this disease (5,6).

In this study; frequency of fatty liver in hypertensive patients, its relation to accompanying disorders such as obesity, diabetes mellitus, dyslipidemia, and metabolic syndrome and improvement in fatty liver disease after treatment of accompanying disorders was investigated.

Material and Method

Three thousand and nine hundred cases referred to hypertension policlinic between 2002 and 2006, were retrospectively analyzed for the presence of hepatosteatosis with or without accompanying disorders such as dyslipidemia, obesity, metabolic syndrome and type 2 diabetes mellitus. Of these cases, 208 patients who had been diagnosed as hepatosteatosis by ultrasonography were selected for the study. Afterward, 70 patients were removed from the study by several reasons. Ultimately, study was completed on 141 cases.

All cases were anthropometrically and ultrasonographically evaluated both before and after treatment to determine alteration in the degree of hepatosteatosis.

Inclusion criterias were age>18 and presence of essential hypertension whereas exclusion criteria included acute and chronic liver diseases (e.g. hepatitis), more than 40 g/d alcohol intake, severe kidney disease or renal function abnormalities (creatinine>1.5 mg/dl), severe cardiac failure (NYHA III-IV), a history of cardiovascular and/or cerebrovascular event in last six months, childbearing, diagnosis of secondary hypertension, severe chronic obstructive lung disease, cancer, hypo/hyper thyroidism, immunosuppressive therapy and hormone replacement therapy in last 1 month.

Detailed past medical history was obtained for every patient from medical records. Additionally, age, gender, length, weight, waist circumference, body mass index (BMI), education level, smoking and drinking habit, age of diagnosis and duration of hypertension, blood pressure, pulse rate, insulin level, lipid profile, fasting glucose level, renal and hepatic function tests, fundoscopic findings, whether the existence of micro albuminuria, left ventricle hypertrophy, hepatomegaly and/or hepatosteatosis (by ultrasonography) were all searched for every patient on admission. Patients were also examined for using antihyperlipidemic, antihypertensiveand antidiabetic medications.

After therapy directed to hypertension and accompanying disorders (obesity, dyslipidemia, diabetes mellitus) all cases were evaluated again. Dose and number of antihypertensive drugs used by each patient in order to control hypertension,were also noted.

Blood pressure was measured by indirect method three times for each patient using standard mercury sphyngomanometer after 5 minutes rest in the sitting position from both arms. Mean value of last two measurement was accepted as blood pressure. Waist circumference and body mass index were calculated by standard method. Diagnosis of diabetes mellitus and impaired glucose tolerance was made according to American Diabetes Association (ADA) guidelines (9), (table 1).

Table 1. *ADA criteria for the diagnosis of diabetes mellitus and prediabetes*

	Diagnostic Criteria for diabetes mellitus
1.	Hemoglobin A1C ≥6.5 percent. The test should be performed in a standardized method
OR	
2.	Fasting Plasma Glucose ≥126 mg/dL(7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h.
OR	
3.	Two-hour plasma glucose ≥200 mg/dL(11.1 mmol/L) during an OGTT.
OR	
4.	In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L).
	Diagnostic Criteria for prediabetes
1.	Fasting plasma glucose 100-125 mg/dL (5.6-6.9 mmol/L)
2.	Two hours plasma glucose on the 75-g OGTT 140-199 mg/dL (7.8-11.0 mmol/L) [IGT]
3.	Hemoglobin A1C 5.7-6.4 percent

Blood samples were drawn following 12 hours of fasting. Analyses were performed by using Abbott Aeroset Autoanalyser. Measuring methods were; hexokinase for fasting glucose level, cholesterol esterase for cholesterol level, enzymatic colorimetric method for triglyceride, HDL cholesterol, gamma glutamiltranspeptidase and uric acid levels. Transaminases were measured by photometric method, insulin levels were measured by chemiluminescence method using Diagnostic Products Corporation (DPC) kit. The existence and degree of hypertensive retinopathy was determined according to Keith-Wagener-Barker staging system. Left ventricular hypertrophy was assigned based on echocardiographic and electrocardiographic evidences.

Insulin resistance was calculated by using HOMA-IR (Homeostasis Model Assessment-Insulin Resistance) formulation.

$$\text{HOMA-IR} = \frac{\text{fasting serum insulin level (} \mu\text{U/ml) x fasting blood glucose (mmol/L)}}{22,5}$$

The cut-off level for microalbuminuri was accepted as the excretion of more than 30 mg/24-hour urine microalbumin.

Dyslipidemia was classified as follows; lipoprotein lipase deficiency (type 1), familial hypercholesterolemia (type 2a), familial combined hyperlipidemia (type 2b), familial type 3 hyperlipoproteinemia (type 3), familial combined hyperlipidemia (type 4) and familial hypertriglyceridemia (type 5).

Ultrasonographic evaluation was made by Toshiba-nemio ultrasonography device using 3,5 megahertz convex probe. Hepatomegaly was described as longitudinal axis of the liver exceeding 150 mm. Grading of hepatosteatosis was made as follows; mild increase in echogenity of liver parenchyma and diaphragm and edges of intrahepatic vessel walls appearing normal (grade 1), moderate increase in echogenicity of liver parenchyma and mild difficulty in distinction of diaphragm and edges of intrahepatic vessel walls (grade 2), marked increase in echogenicity of liver parenchyma and diaphragm and edges of intrahepatic vessel walls roughly visible or invisible (grade 3).

All statistical analyses were performed by using SPSS for Windows 13.0 program. Values were expressed as mean±standard deviation. The statistical significance of the results was calculated using student's t-test and chi-square multiple regression analysis.

Results

One hundred and forty one patients with hypertension were included in this study. Ninety three (66%) of the cases were female and 48 (34%) were male. Diabetes mellitus and cardiovascular diseases were accompanying in 24.8% and 7% of the cases respectively. Positive family history of hypertension, diabetes mellitus and early coronary artery diseases were 32,6%, 11,3% and 5,7% respectively. On the other hand 39% of the cases had positive family history for both hypertension and cardiovascular diseases.

On admission, mean weight of the cases was 81.2±13.0 kg (min:51 , max:113), mean BMI was 32.4±5.3 kg/m² (min:22,4 , max:47,6) and mean waist circumference was 100.9±10.6 cm (min:70 , max:130). Mean number of antihypertensive drug which have been taken by the cases was 1.7±1.1, mean systolic blood pressure was measured to be 155.3±26.6 mmHg (min:90 , max:228) and mean diastolic blood pressure was 94.9±15.0 mmHg (min:60 , max:140). Mean measured levels of fasting glucose was 106.9±20.7 mg/dl (min:74 , max:201), insulin level was 11.4±8 µU/ml (min:1 , max:67.6), total

cholesterol was 215.7±43.9 mg/dl (min:127 , max:338), triglyceride level was 162.0±90.2 mg/dl (min:31 , max:628), HDL cholesterol level was 46.8±10.7 mg/dl (min:26 , max:92), LDL cholesterol level was 136.6±38.3 mg/dl (min:50 , max:239), creatinine was 1.0±0.4 mg/dl (min:0,5 , max:5.4), 24-hours urine microalbumin amount was 53.5±106.7 (min:0.7 , max:684), AST was 26.0±17.2 IU/L (min:12 , max:140), ALT was 30.5±30.9 IU/L (min:8 , max:276), GGT was 42.9±51.1 mg/dl (min:7 , max:379) and uric acid was 5.3±3.5 mg/dl (min:2.3 , max:39).

On the last visit; mean weight of the cases was 80.12±12.8 kg (min:51 , max:119), mean BMI was 32.1±5.1 kg/m² (min:22.4 , max:45.9) and mean waist circumference was 98.2±10.6 cm (min:75 , max:127). Mean number of antihypertensive drug which have been taken by the cases was 2.6±1, mean systolic blood pressure was 132.0±15.3 mmHg (min:90 , max:180) and mean diastolic blood pressure was 82.6±9.9 mmHg (min:64 , max:120). Mean measured levels of fasting glucose was 99.5±13.4 mg/dl (min:70 , max:155), insulin level was 11.2±6.8 µU/ml (min:1.7 , max:47.3), total cholesterol was 197.5±43.6 mg/dl (min:129 , max:396), triglyceride level was 139.5±67.8 mg/dl (min:47 , max:343), HDL cholesterol level was 49.88±13.0 mg/dl (min:28 , max:89), LDL cholesterol level was 120.9±35.8 mg/dl (min:41 , max:287), creatinine was 0.9±0.4 mg/dl (min:0.4 , max:5.3), 24-hours urine microalbumin amount was 47.7±165,7 mg (min:1 , max:1569), AST was 23.9±13.0 IU/L (min:11 , max:136), ALT was 27.2±25.3 IU/L (min:8 , max:259), GGT was 32.5±38.9 mg/dl (min:8 , max:292) and uric acid was 5.4±1.7 mg/dl (min:0.6 , max:11.3).

Mean body weights were 79.1 kg for women and 85.2 for men on admission whereas 78.2 kg and 83.9 kg on the last visit respectively. There was a significant difference between first and last body weights (p=0.005). After the therapy, 27.7% of the cases had been lost, 12.1% gained and 60% unchanged their body weight. Although changes in the body weight were statistically significant, it was not clinically remarkable.

Mean waist circumferences were 100.1 cm for women and 102.8 cm for men on admission whereas 97.3 cm and 100.2 cm on the last visit respectively. Even though the difference was statistically significant ($p<0.0001$), clinically central obesity criterion for diagnosis of metabolic syndrome, remained positive in the cases.

Mean BMIs were 33.3 for women and 30.8 for men on admission whereas 33.0 and 30.4 on the last visit respectively. There was no significant difference between first and last BMIs ($p>0.05$).

Cases were evaluated in point of being used antihypertensive drugs. On admission, 116 cases (82.2%) were taking antihypertensive drugs. Of those, 89 (76.7%) were using angiotensin converting enzyme inhibitors (ACEi), 27 (23.2%) were using other medications. On the last visit, 136 of 141 cases (96.4%) were using antihypertensive drugs which mostly consisted of ACEi and angiotensin receptor blockers (ARB) (126 of 136, 92%).

When all cases were considered, there was a marked reduction in both systolic and diastolic blood pressure between first and last visit. There was approximately 23 mm/Hg decrease in systolic and 12 mm/Hg decrease in diastolic blood pressure. Both of these differences were highly significant ($p<0.0000$, $p<0.0000$ respectively). Results were shown in Table 2.

Table 2: *Anthropometric values and blood pressure status on admission and last visit*

Parameter (n=141)	**Admission (mean ±SD)**	**Last visit (mean ±SD)**	**p**
Weight (kg)	81,2±13,0	80,1± 12,8	0,005
BMI (kg/m2)	32,5±5,3	32,1±5,1	AD
Waist circumference (cm)	101,0±10,6	98,2±10,6	<0,0001
SystolicBP (mmHg)	155,3±26,6	132,0±15,3	<0,0000
Diastolic BP (mmHg)	95,0±15	82,6±9,9	<0,0000
Antihypertensive drug (s)	1,7±1,1	2,6±1,0	<0,0000

Sixty eight of 93 women (73.1%) were in postmenopausal period. Of those cases 33 (48.5%) had had NASH on admission and this rate raised to 58.8% on the last visit. During the study, the rate of fatty liver disease increased 10.3% in postmenopausal women while 18% increment was seen in premenopausal ones. There was no significant difference between pretreatment and post treatment periods ($p>0.05$). In addition, there was no significant difference between the rates of fatty liver in premenopausal and postmenopausal women.

Thirty five cases had type 2 DM as accompanying disease. In the subgroup analysis; 57% of those had been shown having hepatosteatosis in initial ultrasonographic evaluation while this rate was 60% after therapy. There

was also no significant difference between the rates of pretreatment and posttreatment periods (p>0.05).

Dyslipidemia was existed in 100 cases (71%). In this group, 38 cases (38%) were usingstatin, 18 (18%) fibrate and 2 (2%) both. There was no significant difference between dyslipidemia groups with regard to NAFLD distribution in initial (p:0.242) and last (p:0.843) visits. There was also no significant difference between statin using and non-statin using cases with regard to NAFLD distribution in initial (p:0.523) and last (p:0.633) visits.
A comparison was also performed between cases with and without NAFLD in point of reduction rate in total cholesterol and LDL cholesterol from admission to last visit. Significantly better response to antihyperlipidemic therapy was observed in patients without NAFLD than with NAFLD ones (for both total and LDL-cholesterol p<0.0001). Additionally, HDL-cholesterol level was also significantly more elevated in cases without NAFLD than with NAFLD ones (p:.0004).

Although blood glucose level was significantly decreased from admission to last visit in cases with DM and impaired glucose tolerance (p<0.0001), the rate of NAFLD increased in this group during the observation period. Results were shown on Table 3.

Table 3: *Biochemical parameters on admission and last visit*

Parameter (n=141)	**Admission (mean±SD)**	**Last visit (mean±SD)**	**p**
Fasting glucose (mg/dl)	106.9±20.7	99.5±13.4	<0.0001
Insulin (µU/ml)	11.4±8.0	11.2±6.8	NS
Total cholesterol (mg/dl)	215.7±43.9	197.5±43.6	<0.0001
Triglyceride (mg/dl)	162.0±90.2	139.5±67.8	0.0002
HDL-cholesterol (mg/dl)	46.8±10.7	49.8±13.0	0.0004
LDL-cholesterol (mg/dl)	136.6±38.3	120.9±35.8	<0.0001
Creatinine (mg/dl)	1.0±0.4	0.9±0.4	0.01
Microalbuminuria(mg/gün)	53.5±106.7	47.7±165.7	NS
AST (IU/L)	26.0±17.2	23.9±13.0	NS
ALT (IU/L)	30.5±30.9	27.2±25.3	NS
GGT (mg/dl)	42.9±51.1	32.5±38. 9	0.004
Uric Acid (mg/dl)	5.3±3.5	5.4±1.7	NS

NS: non-significant

In the initial evaluation of 93 woman cases, 44 (47.3%) were diagnosed as having NAFLD whereas this rate was 57% on the last visit. On the other hand, 48 male cases which half of them had been diagnosed as having NAFLD on admission, 22 (45.8%) were still having NAFLD on the last visit. Although, the rate of NAFLD was showing increasing tendency in women and decreasing tendency in men, the difference was not significant (p>0.05).

In order to diagnose metabolic syndrome (MS) two different guidelines were used. According to NCEP/ATP III and IDF 2005 guidelines 80.1% and 82.2% of the cases were diagnosed as metabolic syndrome respectively. Results were shown in the Table 4. For both guidelines, the rate of metabolic syndrome was significantly higher in women than men (p<0.001). When compared to non-MS ones, cases with MS were significantly high proportion of NAFLD both on admission and on the last visit (p:0.006 and p:0.001 respectively).

Table 4: *The distribution of metabolic syndrome diagnosis according to NCEP/ATP III and IDF 2006 guidelines (10)*

Metabolic Syndrome	**NCEP ATP III guideline**		**IDF 2006 guideline**	
	N	**Rate (%)**	**N**	**Rate (%)**
No	28	19,9	25	17,8
Yes	113	80,1	116	82,2
Aggregate	141	100,0	141	100,0

Discussion

Non Alcoholic Steatohepatitis (NASH) had been considered as benign disorder for a long time. However, currently by the view of increasing number of published case series and studies, it is accepted that NASH is not a benign disorder and a part of patients can progress to cirrhosis. Natural course of NASH is still not known completely (11).

Because of it is known that this disorder can progress to cirrhosis in its natural course, therapeutic interventions have been come into consideration. In addition to weight loss by dietary regulation and exercise programs, several medications have been used in this issue. Antidiabetic drugs, lipid lowering agents, antioxidants and hepato protective agents had been tested (12,13,14,15). Unfortunately, there is no agent accepted to be effective in this disorder.

The most important causes of NAFLD is included; obesity, type 2 DM and dyslipidemia. Insulin resistance is also an important factor in the Pathogenesis. By this reason, there are several reports evaluating the effectiveness of insulin resistance correcting agents (13,14,15). These studies have mostly been conducted on small sized samples and response to therapy has been evaluated without histopathological confirmation. In this study, the effectiveness of antihypertensive, antidiabetic and antihyperlipidemic therapy along with dietary regulations and exercise in the management of NAFLD was investigated. It was showen that although some amount of weight loss have been achieved and BMI values lowered; especially in male cases, there was no significant improvement in NAFLD. A possible reason may be due to the failure to achieve target weight loss.

Matthews et al conducted a study in order to evaluate the effects of MS, obesity and insulin resistance on ALT level. In this study; 3091 cases which were diagnosed as NAFLD by ultrasonography, evaluated in point of existence of MS criteria, anthropometric parameters, fasting insulin, CRP and ALT levels. As a consequence of this study; older age, male gender, increased levels of fasting blood glucose, triglyceride, insulin and CRP, enlarged waist circumference, high BMI values, high diastolic blood pressure and decreased levels of HDL cholesterol were suggested to be related to increase in ALT activity that associated with NAFLD (16). Whereas; in the current study, no significant differences in AST, ALT, uric acid and microalbuminuria neither between cases with and without MS, nor between pretreatment and post treatment periods was found. A possible explanation for this inconsistence may be due to small sample size included in our study.

Ueno et al showed that dietary regulations and exercise resulted in significant improvement in enzyme levels and grade of hepatosteatosis (17). In this study, BMI was reported to be significantly decreased in study group while unchanged in control group. Similar results have been also observed in animal studies which were reported that low-calorie diet resulted in significantly reduction in ALT levels and hepatosteatosis whereas no improvement in inflammation (18). Although, case-controlled studies with large series are not available in the literature, diet and exercise is recommended in the treatment of NAFLD.

Weight loss with dietary regulation and exercise should be crucial in all subgroups of patients. Body mass index is an independent risk factor for NAFLD. Tetri-Neuschwanderet al conducted a study on diabetic patient population. They showed that antidiabetic therapy with certain drugs resulted in weight gain and increase in BMI from 34.1 kg/m^2 pretreatment value to 36.4 kg/m^2 posttreatment value (19). Antidiabetic therapy without dietary regulations and exercise is usually leads to Increase in BMI due to reduced calorie losing (especially via reduced urinary glucose). Due to the fact that BMI is an independent risk factor for NAFLD, this situation can make evaluation of drug effectiveness quite problematic. There are several similar studies conducted with different treatment modalities and some of them did not take into account post treatment BMI values (14,20). So, evaluation of drug effectiveness may be debatable by these studies.

In above mentioned studies; the rate of diabetic patients was high whereas in ours, this rate was only 24%. In evaluation of NAFLD between initial and last visit, we found no significant change in BMI indicating that dietary regulations and exercise let us to make true comparison between different agents

İpekci et al. suggested that ALT levels show fluctuations in NAFLD and serum ALT levels may not be a reliable marker for therapeutic response (21). Results in the study, are supporting this hypothesis. After therapy, ultrasonographic and histopathologic evidences consistent with hepatosteatosis were not correlated with ALT levels. By this reason, when investigating effectiveness of certain drugs in patients with NAFLD, other risk factors should be remained unchanged and if possible histopathological evaluation should be involved. But, because of natural course of NAFLD is slow and patients are usually asymptomatic, achieving this goal seems to be difficult. Diagnosing NAFLD by ultrasonographic evaluation is quite subjective and highly user-dependent. If histopathological evaluation was done, more reliable results would be obtained.

As expected, study showed that cases with MS have greater tendency of developing NAFLD possibly due to the existence of obesity, insulin resistance and dyslipidemia. The limitations of our study include; evaluation method for diagnosis and grading hepatosteatosis and small sample size for each subgroups. By these reasons, even aimed therapeutic goals could be reached; the difference was not statistically significant. Although, total risk was reduced, no improvement was achieved in terms of rate and grade of hepatosteatosis. It is possible that a number of different etiological factors can take part in the pathogenesis of NAFLD and therapy should be directed to these factors.

As a consequence, our study suggested that dietary regulations and exercise demonstrate no superior results over antidiabetic, antihyperlipidemic and antihypertensive therapy. Additionally, blood glucose regulation, lipid regulation and blood pressure normalization seems no effective on reducing NAFLD frequency and grade.

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