

The Evaluation of Liver Steatosis with Transient Elastography in Metabolic Syndrome and the Relationship Between Serum Endorphin Levels

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ABSTRACT

Objective: Studies in recent times researching the correlation between serum endorphin level and Type 2 DM have focused on the association of fatty liver with metabolic syndrome. This study aims to research the correlation between serum endorphin levels, defined as a marker of metabolic dysregulation, with nonalcoholic fatty liver in metabolic syndrome patients, with increasing prevalence.

Methods: Our prospective study included 40 patients (24 females and 16 males) with metabolic syndrome attending the internal medicine clinic and 20 healthy volunteers (ten females and ten males). Evaluation of patients in terms of liver steatosis used transabdominal ultrasonography with a Toshiba 500 Aplio brand model ultrasound device with 10 MHz convex probe with transient elastography method. Fatty Liver Index and Hepatic Steatosis Index (HSI) were calculated on the basis sample analyses. The endorphin levels were studied with a Sunred enzyme-linked immunosorbent assay kit.

Results: Endorphin levels were found to be lower in the group with metabolic syndrome compared to the healthy group and results were statistically significant different ($p<0.001$). When the mean elastography results for the groups (in m/s and kPa) are compared, there were statistically significant differences found ($p=0.001$, $p<0.001$). There were statistically significant differences between HSI score with serum insulin levels and homeostasis model assessment results.

Conclusion: In our study, a correlation was not found between endorphin levels and fatty liver. Endorphin is a parameter with newly discovered effects and is being researched for applicability and reliability in clinical practice.

INTRODUCTION

Metabolic syndrome is a complex of risk factors associated with each other causing cardiovascular disease and diabetes. These risk factors include dysglycemia, increased blood pressure, high triglyceride levels, low high-density lipoprotein (HDL) levels, and obesity (especially abdominal obesity). In recent times, researches about possible diagnostic criteria have focused on the associations of the connecting factor of insulin resistance in spite of uncertain pathogenesis.^[1] Liver steatosis may form for a variety of reasons;

however, it is mostly associated with the obesity, insulin resistance, and hyperlipidemia which are components of metabolic syndrome.^[2] Studies have shown close associations of insulin resistance in the majority of patients with body mass index (BMI), lipid distribution, and prediabetes independent of the presence of non-alcoholic fatty liver disease (NAFLD).^[3] Endorphin is a small protein formed by degradation of collagen VI produced for renewal of structural support and vital growth factors in adipocytes.^[4] In addition to playing an important role in formation of chemo-resistance against cancer progression and tumor

cells, it appears to be one of the most important factors in collagen VI-associated signal paths encompassing profibrotic structure and chemoattractant features for macrophages.^[5] Endotrophin is mainly produced by fat tissue and induces transforming growth factor beta increase, fibrosis in fat tissue, angiogenesis, and inflammation.^[6] In animal models, it was shown to negatively change metabolic functions such as insulin susceptibility, nutrient intake, energy balance, and fat tissue inflammation. These findings support that endotrophin levels in blood may be useful in classification and monitoring of patients with metabolic dysfunction.^[7] Studies in recent times researching the correlation between serum endotrophin level and Type 2 DM have focused on the association of fatty liver with metabolic syndrome. This study aims to research the correlation between serum endotrophin levels, defined as a marker of metabolic dysregulation, with nonalcoholic liver fattening in metabolic syndrome patients, with increasing prevalence.

MATERIALS AND METHODS

Clinical data

Our prospective study included 40 patients (24 females and 16 males) with metabolic syndrome attending the internal medicine clinic and 20 healthy volunteers (ten females and ten males). The study was approved by the Taksim Training and Research Hospital Ethics Committee (date: April 4, 2018, decision no: 70). The principles of the Declaration of Helsinki were observed throughout this research. Each participant provided written, informed consent.

The presence of metabolic syndrome was defined as the presence of at least one of diabetes mellitus, impaired glucose tolerance or insulin resistance and at least two of hypertension (systolic blood pressure >130, diastolic blood pressure >85 mmHg or using antihypertensive), dyslipidemia (triglyceride [TG] level >150 mg/dL or HDL level <40 mg/dL in males or <50 mg/dL in females), and abdominal obesity (BMI >30 kg/m² or waist circumference >94 cm in males or >80 cm in females). Patients with chronic liver diseases (chronic viral hepatitis, alcoholic hepatitis, autoimmune hepatitis, toxic hepatitis, etc.), carriers of hepatitis B, or those with chronic alcohol use (>20 g/day in males or >10 g/day in females) were not included in the study.^[8] Patients included in the study had prospective and observational data recorded including demographic data (age, sex, and chronic disease), BMI, waist circumference measurements (at central point of the anterior superior distance between arcus costarum and spina iliaca), and systolic and diastolic blood pressure.

Laboratory testing and measurements

Blood samples were taken after 8 h fast. Fasting blood sugar (FBS), HbA1c, insulin, aspartate transaminase (AST), alanine transaminase (ALT), Gamma-Glutamyl Transpeptidase (GGT), total cholesterol, TG, low-density lipoprotein (LDL), HDL, C-reactive protein (CRP), and serum endotrophin

levels were measured. Serum cholesterol, TG, and HDL levels were measured with kits using the enzymatic colorimetric method (COBAS 311, Roche Diagnostics GmbH, Mannheim, Germany). LDL was calculated according to the Friedewald formula (LDL = Total cholesterol – (Very low-density lipoprotein [VLDL] + HDL), VLDL = TG/5). Serum glucose measurements were identified using the enzymatic route with the hexokinase method (Roche Diagnostics GmbH, Mannheim, Germany). HbA1c levels were measured with a COBAS 311 analyzer using the particle-supported immunoturbidometric method (Roche Diagnostics GmbH, Mannheim, Germany). HbA1c results are stated as percentage of total Hb in accordance with the Diabetes Control and Complication Trial/National Glycohemoglobin Standardization Program. CRP was measured with the particle-supported immunoturbidometric method with a Behring Nephelometer BN-100 (Behring Diagnostic, Frankfurt, Germany). The sensitivity of the test was 0.1 mg/L. Insulin levels were measured with electrochemiluminescence immunoassay (Roche Diagnostics, Mannheim, Germany) on an automated Roche Cobas E 411 (Roche Diagnostics). Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) index was calculated using fasting blood glucose and fasting serum insulin levels in the formula $HOMA-IR = \text{Fasting glucose (mg/dL)} \times \text{Fasting insulin (uIU/mL)} / 405$. In addition to these tests, blood samples were taken in a citrate tube for endotrophin levels, centrifuged in the biochemistry laboratory of our hospital and stored in cold storage. The stored samples were studied with a Sunred enzyme-linked immunosorbent assay kit. The kit has intra and inters assay variability of 10% and 12%, respectively. The minimum value of detectable endotrophin is 1.398 ng/mL.

Fatty Liver Index (FLI) and Hepatic Steatosis Index (HSI) calculation

$HSI = 8 * ALT/AST + BMI + 2$, if diabetes mellitus; + 2, if female; with values <30 ruling out and values ≥ 36 ruling in steatosis.^[9]

$FLI = \text{logistic}(0.953 * \ln(TG) + 0.139 * BMI + 0.718 + \ln(GGT) + 0.053 * \text{waist } 15.745) * 100$, where $\text{logistic}(x) = 1/(1 + e^{-x})$ denotes the logistic function and \ln the natural logarithm. Values <30 rule out, and values ≥ 60 rule in steatosis.^[10]

Equipment and methods

Evaluation of patients in terms of liver steatosis used transabdominal ultrasonography with a Toshiba 500 Aplio brand model ultrasound device with 10 MHz convex probe with transient elastography method. Patients included in the study were taken for shear wave elastography evaluation after 8 h fasting.

Measurements were made in supine position on the right lobe of the liver. Measurements were taken at least 1 cm below the liver capsule in an area at least 3×3 cm away from the vascular-biliary tract. A 1 cm diameter circle was drawn and data were statistically analyzed for comparison with results for healthy volunteers.

Statistical analysis

In our study, descriptive statistics were used to describe continuous variables (mean, standard deviation, minimum, median, and maximum). Comparison of two independent variables with normal distribution used the Student's *t* test. Comparison of two independent variables without normal distribution used the Mann-Whitney U-test. With the aim of investigating the correlation between categorical variables, the Chi-square (or if appropriate Fisher exact test) test was used. With the aim of investigating the effect of the independent variables on the continuous dependent variable, multiple linear regression analysis was applied. Spearman's rho correlation analysis was used to analyze the correlation between two continuous variables not abiding by normal distribution. Statistical significance was determined as 0.05. Analyses were completed using the MedCalc Statistical Software version 12.7.7.

RESULTS

The study included a total of 40 patients and 20 healthy volunteers. The patient group comprised 60% females (n=24) and 40% males (n=16) with mean age of 54.05±9.09

years. The healthy volunteers comprised ten female and ten males with mean age of 52.5±7.98 years. When parameters obtained from those with metabolic syndrome and healthy volunteers are compared, there were statistically significant differences in terms of systolic blood pressure, weight, waist circumference, BMI, FBS, HbA1c, insulin, HOMA, TG, HDL, ALT, GGT, CRP, FLI, and HSI distributions ($p<0.05$). Endotrophin levels were found to be lower in the group with metabolic syndrome compared to the healthy group and results were statistically significant ($p<0.001$). When the mean elastography results for the groups (in m/s and kPa) are compared, there were statistically significant differences found ($p=0.001$, $p<0.001$) (Table 1). There were no statistically significant correlations identified between endotrophin with the other parameters in the patient group (Spearman's rho, $p>0.05$) (Table 2).

When elastography measurements (in m/s and kPa) are compared with metabolic syndrome criteria, demographic data and HSI-FLI scores, there was a statistically significant correlation identified with FLI score ($p=0.020$ and $p=0.037$) (Table 3).

When the elastography measurements in both m/s and

Table 1. Clinical and biochemical characteristics of MS and controls

	MS group (n=40)	Control group (n=20)	p
	Mean±SD/n (%)	Mean±SD/n (%)	
Age (years)	54.05±9.09	52.5±7.98	
Gender			
Male	16 (40)	10 (50)	
Female	24 (60)	10 (50)	
Body mass index (kg/m ²)	31.62±4.65	25.58±3.67	**
Waist circumference(cm)	109.72±11.73	85.05±11.79	**
Systolic pressure (mmHg)	132.05±21.08	117.5±9.25	**
Diastolic pressure (mmHg)	73.97±11.99	71.25±8.72	
Endotrophin (ng/mL)	57.07±39.83	129.52±59.77	**
Fasting blood glucose (mg/dl)	171.59±96.09	91.2±12.48	**
Fasting insulin (μU/ml)	22.89±29.83	7.71±5.93	**
HOMA-IR	8.9±9.88	1.72±1.33	**
HbA1c (%)	8.42±2.76	5.55±0.46	**
Triglyceride (mg/dl)	250.05±198.03	115.1±57.96	**
Total cholesterol (mg/dl)	211.1±49.91	207.1±35.89	
Low-density lipoprotein (mg/dl)	119.56±36.27	129.1±30.31	
High-density lipoprotein (mg/dl)	46.1±10.81	54.95±14.92	*
C-reactive protein (mg/l)	6.1±3.87	2.3±2.02	**
Aspartate transaminase (U/L)	27.38±17.34	19.75±3.67	
Alanine transaminase (U/L)	32.49±25.53	19.05±5.92	*
Gamma-glutamyl transpeptidase (U/L)	40.33±31.72	20.6±8.59	**
Fatty liver index	51.52±24.7	6.57±35.23	**
Hepatic steatosis index	33.9±29.6	17.6±7.1	**
Mean Elastography (m/sn)	1.75±0.25	1.54±0.15	**
Mean Elastography (kPa)	9.8±2.97	7.38±1.41	**

Mann-Whitney U, Student *t*, Fisher's Exact Statistical significance: * $p<0.05$, ** $p<0.01$. MS: Metabolic syndromes; HOMA-IR: Homeostasis model assessment of insulin resistance; SD: Standard deviation.

Table 2. Correlation between other parameters and endotrophin in MS

	MS group	
	r	p
Endotrophin and waist circumference	-0.021	0.902
Endotrophin and BMI	-0.195	0.234
Endotrophin and FBG	-0.044	0.790
Endotrophin and HbA1c	-0.072	0.663
Endotrophin and HOMA-IR	-0.075	0.649
Endotrophin and T. cholesterol	-0.164	0.318
Endotrophin and Triglyceride	-0.085	0.609
Endotrophin and LDL	0.017	0.918
Endotrophin and HDL	0.006	0.972
Endotrophin and FLI	-0.128	0.443
Endotrophin and HSI	-0.043	0.793
Endotrophin and Mean Elastography (m/sn)	0.016	0.091
Endotrophin and Mean Elastography (kPa)	-0.006	0.970
Endotrophin and CRP	-0.110	0.506

Spearman's rho, Statistical significance: *p<0.05, **p<0.01. MS: Metabolic syndromes; BMI: Body mass index; FBG: Fasting blood glucose; HOMA-IR: Homeostasis model assessment of insulin resistance; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; FLI: Fatty liver index; HSI: Hepatic steatosis index; CRP: C-reactive protein.

Table 3. Correlation between other parameters and elastography in MS

	MS group	
	r	P
Mean Elastography (m/sn) and FLI	0.377	0.020*
Mean Elastography (kPa) and FLI	0.340	0.037*
Mean Elastography (m/sn) and HSI	0.275	0.091
Mean Elastography (m/sn) and HSI	0.210	0.201

Spearman's rho, Statistical significance: *p<0.05, **p<0.01. MS: Metabolic syndromes; FLI: Fatty liver index; HSI: Hepatic steatosis index.

Table 4. Correlation between other parameters and FLI-HSI scores in MS

	MS group	
	r	p
FLI and insulin	0.232	0.161
FLI and HOMA-IR	0.137	0.413
FLI and AST	0.322	0.049*
HSI and insulin	0.996	0.000**
HSI and HOMA-IR	0.850	0.000**
HSI and AST	-0.090	0.587

Spearman's rho, Statistical significance: *p<0.05, **p<0.01. MS: Metabolic syndromes; FLI: Fatty liver index; HSI: Hepatic steatosis index; HOMA-IR: Homeostasis model assessment of insulin resistance; AST: Aspartate transaminase.

kPa are examined in those with high FLI score, they were found to be high. There were no statistically significant differences identified for the other parameters. Correlations of HSI and FLI scores with other parameters are given in Table 4. HSI scores were correlated with serum insulin levels and HOMA results. FLI scores were correlated with waist circumference, BMI, TG, and GGT, found in the formula, along with serum AST level and elastography measurements.

DISCUSSION

Endotrophin, a surplus product of collagen VI produced by fat tissue, plays an important role in systemic insulin resistance associated with obesity which activates chronic inflammation and fibrosis in fat tissue.^[5] Animal studies have identified that endotrophin has strong chemoattractant activity causing pro-inflammatory microenvironment in fat tissue and this appears to trigger systemic insulin resistance with pro-fibrotic and pro-inflammatory effects.^[11,12] In addition, local fibrosis caused by endotrophin limits intake and esterification of non-esterified fat acids by fat tissue.

Fat tissue with high endotrophin level disrupts circulation of triacylglycerol and non-esterified fat acids which leads to fattening of the liver.^[12] Lipids beginning to accumulate in other tissues trigger the formation of insulin resistance.^[13,14]

In our study, serum endotrophin level was found to be lower in the group with metabolic syndrome compared to the control group. Kai Sun et al.^[6] in a study of mice with induced insulin resistance identified that endotrophin levels increased. The same study observed that obese subjects with higher insulin resistance had clearly higher serum endotrophin levels compared to those with normal insulin resistance. Considering insulin resistance is a criterion for metabolic syndrome, this result contradicts our study. As endotrophin is collagen VI metabolic waste, it is associated with the fibrotic and inflammatory processes. Considering this situation and the other components of metabolic syndrome, we suggest that the presence of comorbid chronic diseases or inflammatory status in individuals in the patient group may affect serum endotrophin levels. Some of those in our patient group were receiving antihypertensive, antihyperlipidemic, and antidiabetic treatment. This is another situation that should be considered and could affect the results. In the study by Kai Sun et al., animal subjects with only insulin resistance were used; as a result, there were no other pathologies that could have affected the results such as medications or comorbid diseases. This situation may explain the differences in results obtained by the two studies.

HIS and FLI are scores for the prediction of fatty liver which are also used to ensure convenience in diagnosis and management of NAFLD.^[15,16] We found that HSI and FLI values were higher in the metabolic syndrome group compared to the healthy control group which is similar

to the data of a study on polycystic ovarian syndrome in 2014.^[17] They identified significantly high values in terms of waist circumference, BMI, FBS, insulin, HOMA, TG, HDL, ALT, and GGT in patients of polycystic ovarian syndrome. Both studies proved that individuals with metabolic syndrome have high risk of liver steatosis. In addition, liver elastography measurements were found to be high in those with metabolic syndrome. In other words, according to our data, the results of indices such as HSI and FLI and also elastographic measurements indicate fatty liver in those with metabolic syndrome.

When the correlations between serum endotrophin levels in the patient group with metabolic syndrome criteria are investigated in our study, there were no significant differences identified between waist circumference, BMI, TG, and HDL levels, FBS, HbA1c, and HOMA with endotrophin levels. Although the data of serum endotrophin in patients with metabolic syndrome are new for literature, endotrophin levels were found to be correlated with adipose tissue mass, insulin resistance, and FLI in patients with Type 2 DM previously.^[7] They found no correlation between FBS and HbA1c levels, similar to our data. They suggested that elevated serum endotrophin levels indicate good response to Ppar γ agonists. Accordingly, suppression of serum endotrophin ameliorates insulin sensitivity in animal models.^[6,18,19] However, serum endotrophin levels were found to be low in patients with metabolic syndrome in our study which can be explained by the antidiabetic medication history of our patients.

Transient elastograph was identified to be a useful noninvasive method for identification of liver fibrosis and measurement of hardness.^[20,21] In light of this data, comparison of elastography measurements (in m/s and kPa) with metabolic syndrome criteria, demographic data and HSI and FLI scores only identified a statistically significant correlation with FLI score. A study by Cantero et al.,^[9] including NAFLD cases, identified high elastography measurements in those with high FLI values, similar to our data. However, they found a positive correlation between insulin levels and HOMA score with elastography measurements. This study included 127 obese non-alcoholic fatty liver patients. Our patient group had BMI values varying from 23 to 43. This situation may explain the differences in the results obtained for insulin resistance and HOMA values.

Limitations of our study are led by the low number of patients. In addition, the patient group included those receiving antihypertensive, antihyperlipidemic, and antidiabetic treatment and in this situation, we cannot exclude the effect of medications in our results. As endotrophin is a marker with newly-discovered effects, there are insufficient studies in the literature.

CONCLUSION

In our study, a correlation was not found between endotrophin levels and fatty liver. Our study is the first in the literature investigating the associations between en-

dotrophin and metabolic syndrome. Endotrophin is a parameter with newly-discovered effects and is being researched for applicability and reliability in clinical practice. Biopsy is still the gold standard for diagnosis of liver diseases; there is a need for a reliable, repeatable, and non-invasive method. Among these methods, transient elastography comes to the fore. For both endotrophin and transient elastography to finalize their places in clinical practice, there is a need for larger, broad scope, and prospective studies investigating their applicability for this topic.

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Ethics Committee Approval

The study was approved by the Taksim Training and Research Hospital Ethics Committee (date: April 4, 2018, decision no: 70).

Peer-review

Internally peer-reviewed.

Authorship Contributions

Concept: B.B., S.İ.Ç.; Design: S.G., S.İ.Ç.; Supervision: B.B.; Fundings: E.B., O.M.; Materials: S.İ.Ç.; Data: E.B., S.İ.Ç.; Analysis: B.B.; Literature search: B.B., O.M.; Writing: S.İ.Ç.; Critical revision: B.B., O.M.

Conflict of Interest

None declared.

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Metabolik Sendromlularda Karaciğer Yağlanması Transient Elastografi ile Değerlendirilmesi ve Serum Endotrofin Seviyeleri Arasındaki İlişki

Amaç: Son zamanlarda serum endotrofin seviyesi ile tip 2 Diyabetes Mellitus (DM) arasındaki ilişkiyi araştıran çalışmalar, yağlı karaciğer ile metabolik sendrom arasındaki ilişkiye odaklanmıştır. Bu çalışmada, metabolik sendromlu hastalarda metabolik disregülasyonun bir belirteci olarak tanımlanan serum endotrofin düzeyi ile non-alkolik yağlı karaciğer arasındaki ilişkinin artan prevalansla araştırılması amaçlanmıştır.

Gereç ve Yöntem: İleriye yönelik çalışmamıza dahiliye kliniğine başvuran metabolik sendromlu 40 hasta (24 kadın ve 16 erkek) ve 20 sağlıklı gönüllü (10 kadın ve 10 erkek) dahil edildi. Hastaların karaciğer steatozu açısından değerlendirilmesi, geçici elastografi yöntemi ile 10 MHz konveks problu Toshiba 500 Aplio marka model ultrason cihazı ile transabdominal ultrasonografi kullanıldı. FLI ve HSI temel numune analizlerine göre hesaplanmıştır. Endotrofin seviyeleri bir Sunred ELISA kiti ile çalışıldı.

Bulgular: Endotrofin düzeyleri, metabolik sendromlu grupta sağlıklı gruba göre daha düşük bulundu ve sonuçlar istatistiksel olarak anlamlı farklılık gösterdi ($p < 0.001$). Gruplar için ortalama elastografi sonuçları (m/s ve kPa cinsinden) karşılaştırıldığında istatistiksel olarak anlamlı farklılıklar bulundu ($p = 0.001$, $p < 0.001$). HSI skoru ile serum insülin seviyeleri ve HOMA sonuçları arasında istatistiksel olarak anlamlı farklılıklar saptandı.

Sonuç: Çalışmamızda endotrofin seviyeleri ile yağlı karaciğer arasında bir ilişki bulunmadı. Endotrofin, yeni keşfedilen etkilere sahip bir parametredir; klinik uygulamada uygulanabilirlik ve güvenilirlik açısından araştırılmaktadır.

Anahtar Sözcükler: Endotrofin; geçici elastografi; metabolik sendrom.