Serum Leptin Levels in Epileptic Patients Treated with Topiramate and Valproic Acid

Topiramat ve Valproik Asit ile Tedavi Edilen Epilepsi Hastalarında Serum Leptin Düzeyleri

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ÖZET

Amaç: Leptin, vücut ağırlığını ve enerji dengesini düzenleyen bir sinyal molekülüdür. Serum leptin düzeyi, beden kitle indeksi ve vücut yağ oranı ile korelasyon göstermektedir. Bu çalışmada epileptik hastalarda valproik asit (VPA) ve topiramat (TPM) ile ilişkili beden kitle değişikliklerinde leptinin rolü araştırılmıştır.

Hastalar ve Yöntem: Elli altı epilepsi hastası (40 VPA kullanan, 16 VPA ve TPM kullanan hasta) ve 40 sağlıklı gönüllüde beden kitle indeksi hesaplanmış ve serum leptin ve insülin düzeyleri ölçülmüştür.

Bulgular: Sadece VPA kullanan hastaların 21 (%52.5)'i, kontrol hastalarının 15 (%37.5)'i obez iken, VPA ve TPM'yi birlikte kullanan hastalardan sadece 1 (%6.3)'i obezdir. Beden kitle indeksi VPA ve TPM'yi birlikte kullanan hastalarda daha düşüktür ($p< 0.001$). Serum leptin düzeyleri, beden kitle indeksi ile korelasyon göstermektedir ($r= 0.49$, $p< 0.001$). Serum leptin düzeyleri obezlerde ($p< 0.001$) ve kadınlarda ($p< 0.001$) daha yüksek, VPA ve TPM kombinasyonu ile tedavi edilen hastalarda daha düşüktür ($p< 0.05$).

Yorum: Çalışmamızda VPA kullanan hasta grubunda yüksek, VPA ve TPM'yi birlikte kullanan hasta grubunda ise anlamlı düzeyde düşük leptin konsantrasyonlarının bulunmuş olması, VPA ve TPM ile indüklenen beden kitlesi değişikliklerinin serum leptin değişiklikleri ile ilişkili olduğu hipotezini desteklemektedir.

Anahtar Kelimeler: Leptin, valproik asit, topiramat, obezite, epilepsi.

ABSTRACT

Serum Leptin Levels in Epileptic Patients Treated with Topiramate and Valproic Acid

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Objective: Leptin is considered to be a signal factor that regulates body weight and energy expenditure, and there is a strong correlation between serum leptin concentrations, body mass index (BMI) and body fat mass in humans. Our aim in this study was to evaluate the role of leptin in valproic acid (VPA) and topiramate (TPM) related weight changes in epileptic patients.

Patients and Methods: BMI was calculated and serum leptin and insulin levels were measured in 56 patients with epilepsy (40 patients taking VPA and 16 patients taking VPA and TPM) and in 40 healthy control subjects.

Results: Obesity was seen in 21 (52.5%) patients in the VPA-treated group, in 15 (37.5%) patients in the control group and in only 1 (6.3%) male in the VPA-TPM-treated group. BMI was lower in the group treated with VPA and TPM ($p< 0.001$). Serum leptin concentrations were correlated with the BMI ($r= 0.49$, $p< 0.001$) and were significantly higher in obese subjects ($p< 0.001$) and in females ($p< 0.001$). Serum leptin levels were significantly lower in patients treated with both VPA and TPM ($p< 0.05$).

Conclusion: High levels of serum leptin in patients taking VPA and significantly low levels of serum leptin in patients taking VPA and TPM in our study are in agreement with the hypotheses that weight changes induced with VPA and TPM are related to the alterations in serum leptin levels.

Key Words: Leptin, valproic acid, topiramate, obesity, epilepsy.

INTRODUCTION

Leptin is a peptide hormone encoded by the *ob* (obese) gene and expressed in adipose tissue (1). Leptin is one of the main regulatory molecules in energy balance, but it is also involved in multiple immunologic and endocrine processes and is seen in several diseases like Alzheimer's disease, osteoporosis, reproductive abnormalities, and epilepsy (1-3). Leptin's role in energy expenditure and the pathogenesis of obesity is in the afferent loop of the negative feedback system signaling the adipose tissue mass to the brain. Leptin circulates in the blood and when fat mass decreases, plasma leptin concentrations decrease, which stimulates appetite and suppresses energy expenditure. When fat mass increases, plasma leptin concentrations increase, which suppresses appetite. This system maintains the homeostatic control of adipose tissue mass (1).

Valproic acid (VPA) is a first-line and widely used antiepileptic agent, with a very broad spectrum of activity against both generalized and partial seizures in adults and children. It is also increasingly used for other indications, such as bipolar psychiatric disorder and migraine prophylaxis (4-6). Weight gain during VPA treatment is a frequent side effect occurring in 49-59% of patients taking VPA and leads to several endocrine and psychiatric consequences (7-9). Possible mechanisms underlying VPA-induced weight gain, such as the effect of VPA on the hypothalamus, VPA-induced hyperinsulinemia and insulin resistance, genetic factors, the interaction between VPA and adiponectin, and VPA-induced hyperleptinemia and leptin resistance have been studied, but unsolved problems remain and the real pathogenetic mechanism is still unclear (7).

Topiramate (TPM) is a structurally novel broad-spectrum antiepileptic drug containing a sulfamate moiety, synthesized from D-fructose, and it exerts not only anticonvulsant but also analgesic and mood-stabilizing activities with complex biochemical and pharmacologic actions. TPM has been trialed for various central nervous system indications other than epilepsy, including neuropathic pain, bipolar disorder and migraine prophylaxis (10). Most antiepileptic drugs, particularly those which potentiate γ-aminobutyric acid inhibitory transmission such as VPA, benzodiazepine and vigabatrin, promote weight gain (4). In contrast, TPM can lower body weight and body weight gain by reducing food intake and energy deposition and by stimulating energy expenditure. The mechanisms by which an antiepileptic drug such as TPM controls energy metabolism require further investigations (11). Recent data suggest that TPM may affect body fat mass by altering leptin secretion, metabolism or requirement. However, the mechanism of TPM-induced body weight loss is still unclear (12).

The present study was undertaken to evaluate the frequency of weight changes in epileptic patients treated with VPA and TPM and to assess whether VPA and TPM affect serum leptin levels, thereby testing the hypothesis that VPA and TPM alter body weight via serum leptin levels. We also aimed to expand our knowledge about the metabolic effects of these two commonly used antiepileptic drugs.

PATIENTS and METHODS

This study was carried out in the Outpatient Service of the Department of Neurology at Izmir Tepecik Training and Research Hospital, Turkey, with the approval of the Hospital Ethics Committee. The subjects provided written informed consent before participation. Patients eligible for the study were at least 18 years of age and diagnosed with epilepsy. A total of 40 patients (23 males, 17 females) taking VPA monotherapy, 16 patients (9 males, 7 females) taking VPA and TPM (VPA-TPM) and 40 control subjects (14 males, 26 females) matched for age, gender and socioeconomic status participated in the study.

None of the subjects was taking any medication in addition to VPA and TPM or had any evidence of metabolic disease, and all reported that their body weight had been stable for at least three months before the study. None of

the subjects abused alcohol, or was pregnant or lactating. All patients had been taking VPA or TPM for at least six months before study entry.

The medical history of each patient was obtained by interview and examination of hospital records. Epilepsy type was classified according to recommendations of the International League Against Epilepsy (13). At clinical examination, weight, height, and waist and hip circumferences were measured, and body mass index (BMI, weight in kilograms divided by the square of height in meters) and waist-hip ratio (WHR, waist circumference in centimeters divided by hip circumference in centimeters) were assessed. A BMI of 25.0-29.9 kg/m^2 was classified as overweight, 30.0-34.9 kg/m^2 as class I obesity, 35.0-39.9 kg/m^2 as class II obesity and > 40.0 kg/m^2 as class III obesity according to the definition of the World Health Organization (WHO) (14). In this study, patients with a BMI > 25 kg/m^2 were considered obese and patients with a BMI < 25 kg/m^2 were considered lean in statistics and tables. Central obesity is diagnosed when WHR is > 0.90 in females and > 0.85 in men and/or BMI is > 30 kg/m^2 (15). Serum triglyceride (TG), cholesterol (CHO) and high-density lipoprotein (HDL) levels were determined by enzymatic method using commercially available kits (Clinical Chemistry by Abbott Diagnostics, IL, USA for TG and CHO; Sentinel by Abbott Diagnostics, IL, USA for HDL). Low-density lipoprotein (LDL) levels were calculated by the method of Friedewald et al. (16). Normal serum lipid profile was defined as follows: TG < 150, CHO < 200, HDL ≥ 39 in females and ≥ 35 in males and LDL < 130 (15).

Serum insulin was analyzed by a radioimmunoassay (RIA) technique with double antibody-polyethylene glycol (CIS Bio International, Gif-sur-Yvette, France). Hyperinsulinism was defined according to WHO criteria (≥ 20 mU/L) (15).

Blood samples for serum leptin assays were obtained at 8 a.m. after an overnight fast and the serum was frozen at -80°C until analysis.

Serum leptin concentrations were analyzed with Enzyme Amplified Sensitivity Immunoassay (EASIA) method, using semi-automatic Enzyme-Linked Immunosorbent Assay (ELISA) analyzer from Biotech and commercial leptin EASIA kits (KAP2281) from Biosource. The limit of sensitivity for the human leptin assay was 0.1 ng/mL and the intra-assay standard coefficient of variation was 5.2%.

The distribution of the data was non-Gaussian, so non-parametric Kruskal-Wallis test was performed for the analysis. Spearman correlation was used to analyze the relationship between the variables. Statistical Package for the Social Sciences (SPSS) 17.0 software was used, and if the p value was less than 0.05, statistical significance was considered.

RESULTS

The demographic and clinical characteristics of the patients are presented in Table 1. The mean age was 36.7 ± 8.3 (21-58) in the control group, 35.9 ± 13.7 (19-64) in the VPA group and 28.5 ± 13.3 (11-58) in the VPA-TPM group. In the VPA-treated group, generalized seizure types were primarily generalized tonic-clonic seizures in 19 patients, myoclonic seizures in 2 patients and absence seizures in 1 patient. Five patients in the VPA-treated group had partial seizures, being complex partial in 2 and simple partial in 3. In the group taking VPA-TPM, 5 patients had secondarily generalized tonic-clonic seizures, 1 patient had absence seizures and 10 patients had simple partial seizures.

All patients showed relatively good seizure control with antiepileptic drugs. The seizure frequency was 5.6 ± 15.7 (0-96) seizure/year in the group taking VPA and 9.8 ± 12.2 (0-36) seizure/year in the group taking VPA-TPM. Patients on monotherapy were taking 995 ± 242.5 (500-1500) mg/day VPA and patients on combined therapy were taking 1200 ± 507.9 (600-2500) mg/day VPA and 234.4 ± 88.9 (100-400) mg/day TPM. The mean serum VPA concentrations were 77.0 ± 26.0 µg/mL in the VPA group and 80.3 ± 25.8 µg/mL in the VPA-TPM group.

The main results are presented in Tables 2-8.

Obesity was observed in 21 patients (10 females, 11 males) in the VPA-treated group (52.5% of the group), in 15 patients (8 females, 7 males) in the control group (37.5% of the group) and in only 1 male in the VPA-TPM-treated group (6.3% of the group) (Table 2).

BMI was lower in the group treated with VPA-TPM (mean 19.5 ± 5.6 kg/m^2) than in the group treated with VPA only (mean 25.9 ± 5.0 kg/m^2) and the control group (mean 23.8 ± 3.3 kg/m^2) (p< 0.001) (Table 2).

Serum leptin levels were significantly lower in the combined therapy group (4.6 ± 4.4 µg/mL in the VPA group, 2.7 ± 2.8 µg/mL in the VPA-TPM group and 5.1 ± 4.1 µg/mL in the control group; p= 0.012 when comparing the VPA-TPM group with the VPA-only group and p= 0.026 when comparing the VPA-TPM group with control subjects) (Table 2). Serum leptin concentrations were correlated with BMI (r= 0.49, p< 0.001).

Patients taking VPA-TPM demonstrated higher levels of HDL than the patients taking VPA (p= 0.007) and the control subjects (p= 0.017) (54.9 ± 13.3 mg/dL vs. 45.1 ± 11.5 mg/dL and 45.0 ± 11.1 mg/dL, respectively). Serum TG, CHO and LDL levels were higher in the VPA group (p> 0.05) (Table 3).

Obese subjects showed significantly higher levels of insulin (10.4 ± 7.8 mU/L vs. 7.7 ± 11.9 mU/L) (p= 0.001),

Tablo 1. The demographic and clinical characteristics of the patients

	Patients taking VPA	Patients taking VPA and TPM
n	40	17/23
F/M	17/23	7/9
Age (mean ± SD, range)	35.9 ± 13.7 19-64	28.5 ± 13.3 11-58
Type of epilepsy (G/P)	35/5	6/10
EEG (N/Ga/Fa)	33/3/4	10/1/5
MRI (N/A)	28/12	12/4
Duration of epilepsy (years, mean ± SD, range)	12.7 ± 9.2 3-39	18.1 ± 12.7 5-49
Age at onset of the illness (years, mean ± SD, range)	23.3 ± 15.7 3-57	10.4 ± 11.8 0.1-46
Duration of medication (years, mean ± SD, range)	8.3 ± 4.7 3-19	7.4 ± 5.3 3-19
Seizure frequency (seizure/year, mean ± SD, range)	5.6 ± 15.7 0-96	9.8 ± 12.2 0-36
VPA dose (mg/day, mean ± SD, range)	995 ± 242.5 500-1500	1200 ± 507.9 600-2500
TPM dose (mg/day, mean ± SD, range)	-	234.4 ± 88.9 100-400
Serum VPA levels (µg/mL, mean ± SD, range)	77.0 ± 26 22-125	80.3 ± 25.8 24-120

VPA: Valproic acid, TPM: Topiramate, n: Number of patients, F: Female, M: Male, SD: Standard deviation, G: Generalized, P: Partial, EEG: Electroencephalography, N: Normal, GA: Generalized abnormality, FA: Focal abnormality, MRI: Magnetic resonance imaging, A: Abnormal.

leptin (6.7 ± 4.7 µg/L vs. 3.1 ± 3.1 µg/L) (p< 0.001), TG (132.1 ± 102.8 mg/dL vs. 95.7 ± 52.0 mg/dL) (p= 0.038), CHO (193.4 ± 41.4 mg/dL vs. 175.6 ± 32.0 mg/dL) (p= 0.031), and LDL (121.9 ± 34.9 mg/dL vs. 105.6 ± 30.8 mg/dL) (p= 0.018) and lower levels of HDL (42.3 ± 9.1 mg/dL vs. 49.5 ± 13.0 mg/dL) (p= 0.005) than the lean subjects (Table 4). Within the VPA monotherapy group and control group, leptin levels were higher in obese subjects than in lean subjects (6.6 ± 5.3 µg/L in obese patients taking VPA vs. 2.4 ± 1.4 µg/L lean patients taking VPA and 6.6 ± 3.9 µg/L in obese control subjects vs. 5.1 ± 4.1 µg/L in lean control subjects) (p= 0.001 and p= 0.028, respectively) (Table 2).

In sex-based analyses, we observed significantly higher levels of serum leptin in females (5.9 ± 4.6 µg/L vs. 3.0 ± 2.9 µg/L) (p< 0.001). WHR (0.79 ± 0.07 vs. 0.89 ± 0.06) (p< 0.001) and serum TG (99.5 ± 81.7 mg/dL vs. 120.8 ± 71.4 mg/dL) (p= 0.021) and LDL (105.1 ± 26.9 mg/dL vs. 119.3 ± 37.9 mg/dL) (p= 0.048) levels were also lower and serum HDL levels (49.8 ± 11.9 mg/dL vs. 43.4 ± 11.5 mg/dL) (p= 0.007) were higher in females (Table 4). High levels of leptin (6.6 ± 5.2 µg/L in females of the VPA group vs. 3.1 ± 3.1 µg/L in males of the VPA group) and HDL (49.2 ± 11.8 mg/dL in females of the VPA group vs. 42.1 ± 10.6 mg/dL in males of the VPA group) and low WHR (0.79 ± 0.08 in females of the VPA group vs. 0.91 ± 0.06 in males of the VPA group) and LDL levels (105.8 ± 26.8 mg/dL in females of the VPA group vs. 133.2 ± 41.6 mg/dL in males of the VPA group) in females were also present within the VPA group (p= 0.004, p= 0.027, p< 0.001 and p= 0.022, respectively). Within the VPA-TPM treated group, only LDL levels were higher in males (92.3 ± 17.6 mg/dL in females in the VPA-TPM group vs. 116.7 ± 30.5 mg/dL in males of the VPA-TPM group) (p= 0.030). In control subjects, BMI (23.1 ± 3.4 kg/m^2 in females of the control group vs. 25.1 ± 2.6 kg/m^2 in males of the control group) and WHR (0.79 ± 0.06 in females of the control group vs. 0.88 ± 0.004 in males of the control group) were lower and leptin levels (6.4 ± 4.4 µg/L in females of the control group vs. 2.7 ± 2.2 µg/L in males of the control group) were higher in females (p= 0.050, p< 0.001 and p= 0.005, respectively) (Table 5-8).

As seen in Table 5, females of the group treated with VPA-TPM were leaner than in the two other gro-

Table 2. Body mass index, waist/hip ratio, central obesity, serum insulin levels, hyperinsulinemia, and serum leptin levels in obese and lean subjects

	Patients taking VPA			Patients taking VPA and TPM			Control subjects		
	Obese (n= 21)	**Lean (n= 19)**	**All (n= 40)**	**Obese (n= 1)**	**Lean (n= 15)**	**All (n= 16)**	**Obese (n= 15)**	**Lean (n= 25)**	**All (n= 40)**
BMI	29.6 ± 3.9	21.9 ± 2.2	25.9 ± 5.0	35.8	18.4 ± 3.7	19.5 ± 5.6[b]	27.2 ± 1.5	21.7 ± 2.1	23.8 ± 3.3
(kg/m^2)	25.1-40.3	17.6-24.9	17.6-40.3		12.4-24.5	12.4-35.8	25.1-30.1	18.7-25.0	18.7-30.1
WHR	0.88 ± 0.09	0.83 ± 0.08	0.86 ± 0.09	0.80	0.83 ± 0.07	0.82 ± 0.06	0.85 ± 0.05	0.80 ± 0.08	0.82 ± 0.07
	0.61-1	0.68-1	0.61-1.0		0.67-0.90	0.67-0.90	0.76-0.91	0.68-0.94	0.68-0.94
CO n (%)	16	7	23	1	5	6	6	5	11
	76.2	36.8	57.5	100	33.3	37.5	40	20	27.5
Insulin	9.4 ± 5.6	7.3 ± 5.5	8.4 ± 5.6	12.9	5.0 ± 3.7	5.5 ± 4.1	11.6 ± 10.3	9.7 ± 17.4	10.4 ± 15.0
(mU/L)	2.0-23.0	2.0-23.4	2.0-23.4		2.0-16.3	2.0-16.3	2.6-44.6	2.0-90.0	2.0-90.0
HI n (%)	1	1	2	0	0	0	2	2	4
	4.8	5.3	5				13.3	8	10
Leptin	6.6 ± 5.3[a]	2.4 ± 1.4	4.6 ± 4.4	10.3	2.2 ± 1.9	2.7 ± 2.7[c]	6.6 ± 3.9[d]	4.2 ± 4.1	5.1 ± 4.1
(µg/L)	1.4-17.1	1.1-6.2	1.1-17.1		0.6-7.3	0.6-10.3	0.6-15.7	0.1-15.4	0.1-17.1

[a] p= 0.001 when compared to the lean subjects of the same group.

[b] p< 0.001 when compared to the other two groups.

[c] p= 0.012 and p= 0.026, respectively, when compared to the first and the third groups.

[d] p= 0.028 when compared to the lean subjects of the same group.

VPA: Valproic acid, TPM: Topiramate, n: number of subjects, BMI: Body mass index, WHR: Waist-hip ratio, CO: Central obesity, HI: Hyperinsulinemia.

BMI, WHR, insulin and leptin values expressed as mean ± standard deviation in the first line and range values in the second line.

Table 3. Serum lipid profile in obese and lean subjects

	Patients taking VPA			Patients taking VPA and TPM			Control subjects		
	Obese (n= 21)	**Lean (n= 19)**	**All (n= 40)**	**Obese (n= 1)**	**Lean (n= 15)**	**All (n= 16)**	**Obese (n= 15)**	**Lean (n= 25)**	**All (n= 40)**
TG	140.4 ± 128.7 36-569	90.7 ± 44.1 24-174	116.8 ± 100.1 24-569	142	78.0 ± 34.6 41-165	82.0 ± 37.1 41-165	119.7 ± 57.2 34-201	110.1 ± 62.8 36-278	113.7 ± 60.2 34-278
High TG levels, n (%)	4 19	3 15.8	7 17.5	0	1 6.7	1 6.3	5 33.3	6 24	11 27.5
CHO	196.3 ± 42.7 122-308	183.3 ± 38.8 130-295	190.1 ± 40.9 122-308	213	176.4 ± 25.4 134-218	178.7 ± 26.2 134-218	188 + 41.6 125-246	169.3 ± 29.6 131-221	176.4 ± 35.2 125-246
High CHO levels, n (%)	10 47.6	7 36.8	17 42.5	1 100	3 20	4 25	5 33.3	4 16	9 22.5
HDL	41.9 ± 7.6 29-61	48.7 ± 14.1 32-82	45.1 ± 11.5 29-82	33	56.3 ± 12.4 39-79	54.9 ± 13.3[a] 33-79	43.5 ± 11.0 22-64	45.9 ± 11.3 23-64	45.0 ± 11.1 22-64
Low HDL levels, n (%)	7 33.3	4 21.1	11 27.5	1 100	0	1 6.26	3 20	6 24	9 22.5
LDL	126.3 ± 38.1 66-233	116.4 ± 38.6 67-218	121.6 ± 38.2 66-233	152	102.9 ± 25.8 53-144	106.0 ± 27.8 53-152	113.9 ± 30.0 65-170	99.0 ± 25.4 58-147	104.6 ± 27.8 58-170
High LDL levels, n (%)	9 42.9	7 36.8	16 40	1 100	3 20	4 25	4 26.7	4 16	8 20

[a] p= 0.007 and p= 0.017 when compared to the first and the third groups.

VPA: Valproic acid, TPM: Topiramate, n: number of subjects, TG: Triglyceride, CHO: Cholesterol, HDL: High-density lipoprotein, LDL: Low-density lipoprotein.

TG, CHO, HDL and LDL values expressed in mg/dL as mean ± standard deviation in the first line and range values in the second line.

Table 4. Body mass index, waist/hip ratio, central obesity, serum insulin levels, hyperinsulinemia, serum leptin levels, and serum lipid profile in obese, lean, female and male subjects

	Obese (n= 37)	Lean (n= 59)	Female (n= 50)	Male (n= 46)	All (n= 96)
BMI	28.8 ± 3.5	20.9 ± 3.0	23.6 ± 5.3	24.4 ± 4.6	24.0 ± 5.0
(kg/m^2)	25.1-40.3	12.4-25.0	12.5-40.3	12.4-35.8	12.4-40.3
WHR	0.87 ± 0.08	0.82 ± 0.08	0.79 ± 0.07[c]	0.89 ± 0.06	0.84 ± 0.08
	0.61-1	0.67-1	0.61-0.92	0.78-1	0.61-1
CO, n (%)	23	17	15	25	40
	62.2	28.8	30	54.3	41.7
Insulin (mU/L)	10.4 ± 7.8[a]	7.7 ± 11.9	7.2 ± 5.2	10.4 ± 14.1	8.8 ± 10.5
	2-44.6	2-90	2-23.4	2-90	2-90
HI, n (%)	3	3	2	4	6
	8.1	5.1	4	8.7	6.3
Leptin (µg/L)	6.7 ± 4.7[b]	3.1 ± 3.1	5.9 ± 4.6[c]	3.0 ± 2.9	5.0 + 4.1
	0.6-17.1	0.1-15.4	0.8-17.2	0.1-16.1	0.1-17.1
TG (mg/dL)	132.1 ± 102.8[a]	95.7 ± 52.0	99.5 ± 81.7[d]	120.8 ± 71.4	109.7 ± 77.3
	43-569	24-278	24-569	34-440	24-569
High TG levels, n (%)	9	10	7	12	19
	24.3	16.9	14	26.1	19.8
CHO (mg/dL)	193.4 ± 41.4[a]	175.6 ± 32.0	175.5 ± 32.1	190.0-40.2	182.5 ± 36.7
	122-308	130-295	122-247	125-308	122-308
High CHO levels, n (%)	16	14	9	21	30
	43.2	23.7	18	45.7	31.3
HDL (mg/dL)	42.3 ± 9.1[a]	49.5 ± 13.0	49.8 ± 11.9[d]	43.3 ± 11.5	46.7 ± 12.1
	22-64	23-82	25-82	22-72	22-82
Low HDL levels, n (%)	11	10	8	13	21
	29.7	16.9	16	28.3	21.9
LDL (mg/dL)	121.9 ± 34.9[a]	105.6 ± 30.8	105.1 ± 26.9[d]	119.3 ± 37.9	111.9 ± 33.2
	65-233	53-218	58-170	53-233	53-233
High LDL levels, n (%)	14	14	10	18	28
	37.8	23.7	20	39.1	29.2

[a] p= 0.001, p= 0.038, p= 0.031, p= 0.005 and p= 0.018, respectively, when compared to the lean subjects.
[b] p< 0.001 when compared to the lean subjects.
[c] p< 0.001 when compared to males.
[d] p= 0.021, p= 0.007 and p= 0.048, respectively, when compared to males.
n: Number of subjects, BMI: Body mass index, WHR: Waist-hip ratio, CO: Central obesity, HI: Hyperinsulinemia, TG: Triglyceride, CHO: Cholesterol, HDL: High-density lipoprotein, LDL: Low-density lipoprotein.
BMI, WHR, insulin, leptin, TG, CHO, HDL and LDL values expressed as mean ± standard deviation in the first line and range values in the second line.

ups (BMI 18.4 ± 4.0 kg/m^2 vs. 26.5 ± 6.4 kg/m^2 in females in VPA monotherapy and 23.1 ± 3.4 kg/m^2 in female control subjects) (p= 0.008) and had lower serum leptin levels (2.3 ± 1.7 µg/L vs. 6.6 ± 5.2 µg/L in the VPA monotherapy group and 6.4 ± 4.4 µg/L in control subjects) (p= 0.017 and p= 0.012 for the comparison between the females taking VPA and the female control subjects, respectively). Lower BMI was seen in both the females and males of the group treated with VPA-TPM (BMI 20.3 ± 6.7 kg/m^2 vs. 25.5 ± 3.9 kg/m^2 in the males of the VPA monotherapy group and 25.1 ± 2.6 kg/m^2 in the male control subjects) (p= 0.003 and p= 0.008, respectively). Males in the VPA-TPM group also showed lower WHR than the VPA-only group (0.85 ± 0.05 vs. 0.91 ± 0.06) (p= 0.015) (Table 7). Serum lipid profiles of the females were not statistically different between the three groups, but in males, LDL levels were higher in the VPA monotherapy group than in the control group (133.2 ± 41.6 mg/dL vs. 98.1 ± 25.6 mg/dL) (p= 0.008) (Tables 6 and 8).

Table 5. Body mass index, waist/hip ratio, central obesity, serum insulin levels, hyperinsulinemia, and serum leptin levels in female subjects

	Female patients taking VPA			Female patients taking VPA and TPM	Female control subjects		
	Obese (n= 10)	Lean (n= 7)	All (n= 17)	Lean (n= 7)	Obese (n= 8)	Lean (n= 18)	All (n= 26)
BMI	30.8 ± 4.3	20.3 ± 2.1	26.5 ± 6.4	18.4 ± 4.0[a]	27.2 ± 1.7	21.3 ± 2.1	23.1 ± 3.4
(kg/m^2)	25.5-40.3	17.6-23.4	17.6-40.3	12.5-24.4	25.1-30.1	18.7-25.0	18.7-30.1
WHR	0.81 ± 0.08	0.77 ± 0.08	0.79 ± 0.08	0.80 ± 0.08	0.83 ± 0.05	0.77 ± 0.06	0.79 ± 0.06
	0.61-0.90	0.68-0.89	0.61-0.90	0.67-0.88	0.76-0.88	0.68-0.92	0.68-0.92
CO, n (%)	6	2	8	2	4	1	5
	60	28.6	47.1	28.6	50	5.6	19.2
Insulin (mU/L)	8.9 ± 5.3	7.5 ± 7.6	8.3 ± 6.1	4.4 ± 2.0	9.1 ± 4.6	6.5 ± 5.0	7.3 ± 5.0
	2.7-18.7	2.0-23.4	2.0-23.4	2.0-6.9	2.6-16.1	2.0-21.3	2.0-21.3
HI, n (%)	0	1	1	0	0	1	1
		14.3	5.9			5.6	3.8
Leptin (µg/L)	9.3 ± 5.2	2.8 ± 1.4	6.6 ± 5.2	2.3 ± 1.7[b]	9.0 ± 3.5	5.3 ± 4.3	6.4 ± 4.4
	3.0-17.1	1.7-5.4	1.7-17.1	0.8-5.2	4.3-15.7	0.8-15.4	0.8-15.7

[a] p= 0.008 when compared to the females in the first and the third groups.

[b] p= 0.017 and p= 0.012, respectively, when compared to the females in the first and the third groups.

VPA: Valproic acid, TPM: Topiramate, n: Number of subjects, BMI: Body mass index, WHR: Waist-hip ratio, CO: Central obesity, HI: Hyperinsulinemia.

BMI, WHR, insulin and leptin values expressed as mean ± standard deviation in the first line and range values in the second line.

Table 6. Serum lipid profile in female subjects

	Female patients taking VPA			Female patients taking VPA and TPM	Female control subjects		
	Obese (n= 10)	Lean (n= 7)	All (n= 17)	Lean (n= 7)	Obese (n= 8)	Lean (n= 18)	All (n= 26)
TG	138.7 ± 154.9 47-569	65.4 ± 24.5 24-99	108.5 ± 122.9 24-569	58.3 ± 17.1 41-86	122-9 ± 53.8 50-201	96.7 ± 52.1 36-193	104.8 ± 52.9 36-201
High TG levels, n (%)	2 20	0	2 11.8	0	2 25	3 16.7	5 19.2
CHO	181.8 ± 37.1 122-247	169.7 ± 20.6 142-204	176.8 ± 31.2 122-247	168.9 ± 20.9 137-189	194-8 ± 42.4 140-245	168.4 ± 30.2 131-221	176.5 ± 35.7 131-245
High CHO levels, n (%)	3 30	1 14.3	4 23.5	0	3 37.5	2 11.1	5 19.2
HDL	43.6 ± 7.1 37-61	57.1 ± 13.1 46-82	49.2 ± 11.8 37-82	59.7 ± 13.4 49-79	45.3 ± 11.3 25-64	48.6 ± 10.5 30-64	47.5 ± 10.6 25-64
Low HDL levels, n (%)	3 30	0	3 17.6	0	1 12.5	4 22.2	5 19.2
LDL	110.4 ± 26.8 66-145	99.3 ± 27.3 67-141	105.8 ± 26.8 66-145	92.3 ± 17.6 80-128	125.0 ± 28.8 90-170	100.5 ± 26.0 58-147	108.0 ± 28.7 58-170
High LDL levels, n (%)	3 30	1 14.3	4 23.5	0	3 37.5	3 16.7	6 23.1

VPA: Valproic acid, TPM: Topiramate, n: Number of subjects, TG: Triglyceride, CHO: Cholesterol, HDL: High-density lipoprotein, LDL: Low-density lipoprotein.

TG, CHO, HDL and LDL values expressed in mg/dL as mean ± standard deviation in the first line and range values in the second line.

Table 7. Body mass index, waist/hip ratio, central obesity, serum insulin levels, hyperinsulinemia, and serum leptin levels in male subjects

	Male patients taking VPA			Male patients taking VPA and TPM			Male control subjects		
	Obese (n= 11)	**Lean (n= 12)**	**All (n= 23)**	**Obese (n= 1)**	**Lean (n= 8)**	**All (n= 9)**	**Obese (n= 7)**	**Lean (n= 7)**	**All (n= 14)**
BMI	28.5 ± 3.4	22.8 ± 1.7	25.5 ± 3.9	35.8	18.4 ± 3.6	20.3 ± 6.7[a]	27.2 ± 1.2	23.0 ± 1.7	25.1 ± 2.6
(kg/m^2)	25.2-34.1	19.8-24.5	19.8-34.1		12.4-24.5	12.4-35.8	25.6-29.0	20.1-24.8	20.1-29.0
WHR	0.94 ± 0.04	0.87 ± 0.06	0.91 ± 0.06	0.80	0.85 ± 0.05	0.85 ± 0.05[b]	0.88 ± 0.03	0.89 ± 0.05	0.88 ± 0.04
	0.89-1	0.79-1	0.79-1		0.78-0.90	0.78-0.90	0.84-0.91	0.81-0.94	0.81-0.94
CO, n (%)	10	5	15	1	3	4	2	4	6
	90.9	41.7	65.2	100	37.5	44.4	28.6	57.1	42.9
Insulin (mU/L)	10.0 ± 6.0	7.1 ± 4.3	8.5 ± 5.3	12.9	5.6 ± 4.9	6.4 ± 5.2	14.5 ± 14.4	18.0 ± 32.0	16.2 ± 24.0
	2.0-23.0	2.8-16.1	2.0-23		2.0-16.3	2.0-16.3	4.8-44.6	2.0-90.0	2.0-90.0
HI, n (%)	1	0	1	0	0	0	2	1	3
	9.1		4.3				28.6	14.3	21.4
Leptin (µg/L)	4.1 ± 4.1	2.2 ± 1.4	3.1 ± 3.1	10.3	2.1 ± 2.2	3.0 ± 3.4	3.9 ± 2.3	1.5 ± 1.3	2.7 ± 2.2
	1.4-16.1	1.1-6.2	1.1-16.1		0.6-7.3	0.6-10.3	0.6-8.0	0.1-2.9	0.1-8.0

[a] p= 0.003 and p= 0.008, respectively, when compared to males of the first and the third groups.

[b] p= 0.015 when compared to males of the first group.

VPA: Valproic acid, TPM: Topiramate, n: Number of subjects, BMI: Body mass index, WHR: Waist-hip ratio, CO: Central obesity, HI: Hyperinsulinemia.

BMI, WHR, insulin and leptin values expressed as mean ± standard deviation in the first line and range values in the second line.

Table 8. Serum lipid profile in male subjects

	Male patients taking VPA			Male patients taking VPA and TPM			Male control subjects		
	Obese (n= 11)	**Lean (n= 12)**	**All (n= 23)**	**Obese (n= 1)**	**Lean (n= 8)**	**All (n= 9)**	**Obese (n= 7)**	**Lean (n= 7)**	**All (n= 14)**
TG	142.0 ± 107.3 36-440	105.5 ± 47.1 41-174	123.0 ± 81.8 36-440	142.0	95.3 ± 37.6 55-165	100.4 ± 38.5 55-165	116.1 ± 65.1 34-198	144.6 ± 78.5 56-278	130.3 ± 70.8 34-278
High TG levels, n (%)	2 18.2	3 25	5 21.7	0	1 12.5	1 11.1	3 42.9	3 42.9	6 42.9
CHO	209.5 ± 44.7 155-308	191.3 ± 45.3 130-295	200.0 ± 44.0 130-308	213	183.0 ± 28.6 134-218	186.3 ± 28.5 134-218	180.3 ± 42.5 125-246	171.9 ± 30.1 131-208	176.1 ± 35.7 125-246
High CHO levels, n (%)	7 63.6	6 50	13 56.5	1 100	3 37.5	4 44.4	2 28.6	2 28.6	4 28.6
HDL	40.4 ± 8.1 29-57	43.8 ± 12.6 32-72	42.1 ± 10.6 29-72	33	53.4 ± 11.5 39-70	51.1 ± 12.7 33-70	41.6 ± 11.2 22-57	39.0 ± 11.2 23-51	40.4 ± 10.8 22-57
Low HDL levels, n (%)	4 36.4	4 33.3	8 34.8	1 100	0	1 11.1	2 28.6	2 28.6	4 28.6
LDL	140.7 ± 42.1 95-233	126.3 ± 41.7 69-218	133.2 ± 41.6[a] 69-233	152	112.3 ± 29.3 53-144	116.7 ± 30.5 53-152	101.1 ± 27.7 65-148	95.1 ± 25.2 69-139	98.1 ± 25.6 65-148
High LDL levels, n (%)	6 54.5	6 50	12 52.2	1 100	3 37.5	4 44.4	1 14.3	1 14.3	2 14.3

[a] p= 0.008 when compared to males of the third group.

VPA: Valproic acid, TPM: Topiramate, n: Number of subjects, TG: Triglyceride, CHO: Cholesterol, HDL: High-density lipoprotein, LDL: Low-density lipoprotein.

TG, CHO, HDL and LDL values expressed in mg/dL as mean ± standard deviation in the first line and range values in the second line.

DISCUSSION

VPA treatment is associated with weight gain in approximately half of the patients (17). Dinesen et al. reported weight gain in 57% of 63 adult epileptic patients treated with VPA (17). Isojärvi et al. found that VPA therapy for epilepsy is associated with weight gain during treatment in 59% of female patients, especially when the medication was started before the age of 20 years (8). Increased weight gain was noted in 44 of 100 epileptic children treated with VPA, and the increase in BMI can occur as early as 3 months of age (18,19). Consistent with previous reports, 52.5% of the patients treated with VPA were obese in our study. Obesity and central obesity were more frequent and BMI was higher in the VPA- treated group than the VPA-TPM-treated group ($p< 0.001$), as well as the control group ($p> 0.05$) (Table 1).

Weight loss is recorded in more than 80% of patients taking TPM and has also been observed in patients receiving TPM for conditions other than epilepsy (20-22). Storey et al. observed weight loss in 50% of patients taking TPM for migraine prevention (21). In the study by Chengappa et al., all 20 patients with bipolar disorder who started on TPM lost weight in five weeks (23). TPM-related weight loss continued for at least one year after the commencement of treatment and is more pronounced in obese patients (24). In our study, BMI in the VPA-TPM-treated group was significantly lower than in the VPA-treated group and the control group ($p< 0.001$), and there was only one obese patient in the VPA-TPM-treated group (Table 2).

The protein product of the adipocyte-specific ob gene is leptin, a circulating protein that regulates body weight (25). It is now well-established that serum leptin concentrations are correlated with the percentage of body weight and that obese subjects have higher serum leptin concentrations than normal-weight subjects (9,26-29). We found in our study that serum leptin levels were increased in obese subjects and that serum leptin levels were correlated with BMI. The mean serum leptin concentrations were 6.7 ± 4.7 µg/mL in obese subjects and 3.1 ± 3.1 µg/mL in normal-weight subjects ($p< 0.001$) (Table 4). Serum leptin values for normal-weight subjects were recently reported as 3.1 ± 0.9 µg/L by Pylvänen et al., 7.5 ± 9.3 ng/mL by Considine et al. and 9.0 ± 2.1 ng/mL by Verrotti et al. (9,26,27). In obese subjects, mean serum leptin concentrations were reported as 6.9 ± 3.6 µg/L in the study of Pylvänen et al., which is in accordance with our results, and 31.3 ± 24.1 ng/mL in the study of Considine et al. (9,26). Higher leptin levels in obese subjects were also present within the VPA and control groups ($p< 0.05$) (Table 2).

We found significantly higher levels of leptin in women than in men ($p< 0.001$) (Table 4). A sexual dimorphism for leptin has been reported in a number of investigations (30-33). In the study of Plaisance et al., serum leptin levels were higher in female subjects (34). Pylvänen et al. also observed higher serum leptin levels in women (9). Rosenbaum et al. reported high levels of leptin in women, especially in the premenopausal period (35). Ellis et al. found that gender differences in serum leptin concentrations were already evident in prepubertal ages and suggested that there are differences in the clearance of leptin from the blood or in the transport system to the brain's leptin receptor site (29). In our study, the significantly high levels of leptin in women were also present within the VPA and control groups ($p< 0.05$, Table 5,6); therefore, the sexual difference in serum leptin concentrations in our study reflects not only the sexual dimorphism for leptin but also a tendency in women to gain weight during VPA therapy, as in the study of El-Khatib et al., who suggested that women are more prone to gain weight during VPA therapy due to leptin resistance and higher frequency of carbohydrate craving (36).

The main goal of the present study was to compare serum leptin levels in VPA-treated, VPA- TPM-treated and control subjects and to enrich our knowledge about the metabolic effects of these drugs and the mechanism by which they induce weight changes. We found significantly low levels of leptin in the VPA-TPM-treated group ($p< 0.05$) (Table 2). In the VPA group, serum leptin levels were higher ($p> 0.05$) (Table 2). VPA- and TPM-induced weight changes are thought to be related to influences of VPA and TPM on serum leptin levels (37). The study by Verrotti et al. demonstrated that after treatment with VPA, patients who became obese showed increased serum leptin levels, and this led to the suggestion that VPA affects the serum levels of leptin (27). Greco et al. suggested that the high leptin levels in patients taking VPA could be the result of obesity due to increased production of leptin by the adipose tissue (38). Lagace et al. also hypothesized that the increase in serum leptin associated with weight gain after VPA therapy may be a consequence of the increase in adipose tissue, but they also raised the possibility that VPA may directly affect the leptin secretion from adipose tissue (39). The finding that VPA stimulates pancreatic cells ex vivo supported the effect of VPA in adipocytes (40). Another mechanism proposed for VPA-induced weight gain and hyperleptinemia is a state of leptin resistance or leptin insensitivity provoked by VPA (26,28). VPA is shown to be capable of developing this kind of leptin resistance by the regulation of hypothalamic gene expression in vitro (41). In contrast to these studies supporting the influence of VPA on serum leptin le-

vels, Pylvänen et al. found increased leptin levels in obese subjects taking VPA as well as in obese control subjects, and Lagace et al. reported that VPA paradoxically inhibits adipogenesis in vitro (9,39).

Leptin levels reduce during TPM treatment, and the greater the weight loss, the greater the reduction in serum leptin, although the role of leptin in TPM-induced weight loss is still not clear (22,24,37,42,43). In the study by Li et al., serum levels in the TPM group were remarkably lower than those of the corresponding control group in rats (37). In children, Li et al. suggested that there was no significant difference in leptin before and after the TPM treatment and that the change in leptin would not be a key mechanism for a weight loss after TPM treatment (22). Lalonde demonstrated in rats that the effects of TPM were not prevented or potentiated with leptin but that the effects of TPM and leptin were additive (24). Husum et al. found in rats that single injections of TPM reduced leptin in controls that are more obese but that TPM had no effect on leptin levels in depressed rats with lower BMI (42). Kim et al. observed increased serum levels of leptin in 12 VPA-treated patients compared to 11 TPM-treated patients (43).

Our results are also similar to those of Kim et al. with the significantly low levels of leptin in our TPM-VPA-treated group, but the high levels of leptin in our VPA-treated group were statistically insignificant (Table 2) (43). Thus, while the results are inconclusive regarding the role of leptin in the pathogenesis of VPA-induced weight changes, they support a leptin-associated mechanism for the TPM-induced weight loss. Leptin and insulin are both catabolic peripheral hormones that are recognized by the brain for regulation of food intake and energy expenditure. Although they are unrelated structurally, and their receptors are different, they influence each other at the central and peripheral levels, and serum leptin concentrations are correlated with fasting insulin concentrations (44-48). The weight gain during VPA treatment is associated with hyperinsulinemia but the mechanism remains unclear (8,19,49). Several possible mechanisms are the increase in the availability of local free fatty acids, in the activity of the sympathetic nervous system and in the plasma level of gamma aminobutyric acid (36,40,50-54). Hyperinsulinemia in VPA therapy seems also to be correlated with weight gain and the increase in the serum leptin levels (9,19,53,55). On the other hand, TPM has been observed to decrease insulin levels, increase insulin sensitivity, improve glucose tolerance, and lower glucose levels in rats (11,12,20,56). Li et al. reported low levels of insulin with TPM in rats, but the relationship and the correlation between weight loss and serum insulin and leptin levels in TPM therapy in humans is not clear (37). In our study, patients treated only with VPA showed increased levels of leptin, but we did not observe significantly high levels of insulin or hyperinsulinemia in the VPA-treated group (Table 2). In the group taking VPA-TPM, serum insulin levels and the rate of hyperinsulinemia were lower than in the two other groups, but these findings were not statistically significant ($p > 0.05$) (Table 2). VPA causes metabolic syndrome in some patients, but this effect may be associated with the weight gain rather than VPA itself (43,48,57). We found increased levels of TG, CHO and LDL in the VPA-treated group ($p > 0.05$) (Table 3) like in other studies, suggesting a tendency towards metabolic syndrome with VPA (43). In contrast, TPM has been shown to reduce plasma levels of CHO and TG (11,20). In our study, there was no significant change in serum CHO and TG levels in the group taking VPA-TPM, similar to the findings by Richard et al. which suggested that TPM does not alter serum TG levels (12). However, we found that serum HDL levels were higher in the VPA-TPM group ($p < 0.05$) (Table 3).

In conclusion, our main results are the low BMI and low leptin levels in patients treated with VPA-TPM. In our study, high leptin levels in the VPA-treated group were not significant; therefore, it is not possible to conclude on the basis of our results that the effects of VPA on BMI are related to the alterations in serum leptin levels. Nevertheless, our findings support the hypothesis that TPM-induced weight loss is associated with changes in serum leptin. On the other hand, serum leptin levels are correlated with BMI, and the serum leptin changes in our patient groups can simply be the result of weight changes rather than their causes. However, despite the significant correlation between BMI and leptin, the changes in the serum leptin seemed more impressive than the changes in BMI, especially in the group treated with VPA-TPM. Despite the limitations of this study, like the small sample size and the lack of a group of patients in TPM monotherapy, this study demonstrates that an increase in BMI and serum insulin can be present in epileptic patients receiving VPA treatment and that the add-on treatment with TPM can reverse these effects. VPA treatment inducing obesity, hyperinsulinemia and insulin resistance may also be associated with a tendency to metabolic syndrome, which can benefit from TPM. We suggest that the combination of weight loss and metabolic improvements seen with TPM could be a valid reason to choose this drug in epileptic patients with metabolic syndrome or in add-on treatment of patients taking VPA or other drugs with metabolic side effects.

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