



Measurement of Irisin, Adiponectin, and Leptin Levels in Patients with Idiopathic Epilepsy

İdiopatik Epilepsili Hastalarda İrisin, Adiponektin ve Leptin Düzeylerinin Ölçülmesi

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ABSTRACT

Objective: Epilepsy is a common childhood neurological disorder in which neuroinflammatory and metabolic mechanisms may contribute to epileptogenesis. Adipomyokines such as irisin, leptin, and adiponectin have been suggested to influence neuroinflammation, energy metabolism, and neuronal excitability. This study aimed to evaluate serum adipomyokine levels in children with idiopathic epilepsy and investigate their association with treatment response.

Methods: This case-control study included 68 children with idiopathic epilepsy (15 drug-resistant, 53 drug-responsive) and 66 healthy controls. Serum irisin, leptin, and adiponectin levels were measured using ELISA. After one-to-one matching based on body mass index (BMI), age, and sex, 58 epilepsy patients and 58 controls were included in the final analyses. For subgroup analyses, 15 drug-resistant patients were compared

Öz

Amaç: Epilepsi, çocukluk çağında sık görülen ve nöroenflamasyon ile metabolik süreçlerin epileptogenezde rol oynadığı düşünülen kronik bir nörolojik hastalıktır. İrisin, leptin ve adiponektin gibi adipomyokinlerin nöroenflamasyon, enerji metabolizması ve nöronal uyarılabilirlik üzerinde etkili olabileceği düşünülmektedir. Bu çalışmada idiyopatik epilepsili çocuklarda serum adipomyokin düzeylerinin değerlendirilmesi ve bu moleküllerin tedavi yanıtı ile ilişkilerinin araştırılması amaçlandı.

Yöntemler: Bu olgu-kontrol çalışmasına 68 idiyopatik epilepsili çocuk (15'i ilaç dirençli, 53'ü ilaç yanıtı) ve 66 sağlıklı kontrol dahil edildi. Serum irisin, leptin ve adiponektin düzeyleri ELISA yöntemiyle analiz edildi. Vücut kitle indeksi (VKİ), yaş ve cinsiyete göre birebir eşleştirme sonrası 58 epilepsi hastası ve 58 kontrol değerlendirmeye alındı. Alt grup analizlerinde 15 ilaç dirençli hasta ile VKİ uyumlu 15 ilaç yanıtı hasta karşılaştırıldı.

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ABSTRACT

with 15 BMI-matched drug-responsive patients. Correlation, logistic regression, and receiver operating characteristic analyses were performed.

Results: After matching, serum irisin levels were significantly lower in epilepsy patients compared to controls ($p=0.032$). Leptin and adiponectin levels did not differ significantly between epilepsy and control groups. In subgroup analyses, leptin and adiponectin levels were significantly higher in drug-responsive patients than in drug-resistant patients ($p=0.043$ and $p=0.024$, respectively). Irisin levels did not differ between epilepsy subgroups. Logistic regression analyses showed that leptin and adiponectin were associated with treatment response.

Conclusion: The findings suggest that irisin may be involved in epilepsy-related mechanisms, whereas leptin and adiponectin may be associated with treatment response. Although adipomyokines appear to have limited diagnostic utility for differentiating epilepsy subtypes, they may represent potential biomarkers for predicting treatment response in pediatric epilepsy.

Keywords: Epilepsy, adipomyokines, irisin, leptin, adiponectin, drug resistance

ÖZ

Korelasyon, lojistik regresyon ve alıcı işletim karakteristiği analizleri yapıldı.

Bulgular: Eşleştirme sonrası epilepsi grubunda serum irisin düzeyleri kontrol grubuna göre anlamlı olarak daha düşük bulundu ($p=0,032$). Leptin ve adiponektin düzeyleri açısından epilepsi ve kontrol grupları arasında anlamlı fark saptanmadı. Alt grup analizlerinde leptin ve adiponektin düzeyleri ilaç yanıtı grupta ilaç dirençli gruba göre anlamlı olarak daha yüksekti (sırasıyla $p=0,043$ ve $p=0,024$). Irisin düzeyleri açısından alt gruplar arasında fark izlenmedi. Lojistik regresyon analizinde leptin ve adiponektin tedavi yanıtı ile ilişkili bulundu.

Sonuç: Bulgular, irisinin epilepsi ile ilişkili mekanizmalarda rol oynayabileceğini, leptin ve adiponektinin ise tedavi yanıtı ile ilişkili olabileceğini düşündürmektedir. Adipomyokinlerin epilepsi alt tiplerini ayırt etmede sınırlı tanılabilir değeri olmakla birlikte, çocukluk çağı epilepsisinde tedavi yanıtının öngörülmesinde potansiyel biyobelirteçler olabileceği düşünülmektedir.

Anahtar Kelimeler: Epilepsi, adipomyokin, irisin, leptin, adiponektin, ilaç direnci

Introduction

Epilepsy is a common neurological disorder characterized by recurrent unprovoked seizures and remains a significant cause of morbidity in children (1,2). According to the 2017 classification of the International League Against Epilepsy (ILAE), epilepsy arises from multiple etiologies, including structural, genetic, metabolic, infectious, and immune-related mechanisms (3). Increasing evidence suggests that neuroinflammation plays a key role in epileptogenesis, contributing to neuronal hyperexcitability and seizure persistence (4,5).

Adipose tissue and skeletal muscle function as endocrine organs that secrete bioactive molecules known as adipomyokines, which regulate energy metabolism, inflammation, and neuronal function (6,7). Among these, leptin, adiponectin, and irisin have attracted attention due to their potential roles in neuroprotection and modulation of neuronal excitability (8,9). Emerging evidence suggests that these molecules may also be involved in epileptogenesis, although their exact role remains unclear (6).

Despite growing interest, studies investigating adipomyokines in epilepsy are limited and show inconsistent findings, particularly in pediatric populations. Moreover, the relationship between adipomyokine levels and treatment response, especially drug-resistant epilepsy, has not been adequately explored.

Therefore, this study aimed to evaluate serum levels of irisin, leptin, and adiponectin in children with idiopathic epilepsy, to compare these levels between drug-responsive

and drug-resistant patients, and to investigate their association with current drug responsiveness.

Methods**Study Design and Participants**

This case-control study included 68 children aged 2-10 years with idiopathic epilepsy, recruited from the Pediatric Neurology Clinic of Bezmialem Vakıf University Hospital between October 2020 and March 2021. Fifteen children met the ILAE 2010 criteria for drug-resistant epilepsy (10), and 53 were classified as drug-responsive. The control group consisted of 66 healthy children without chronic diseases who attended the pediatric outpatient clinic for routine examination. All participants were in the prepubertal stage, as determined by Tanner criteria.

To minimize the potential confounding effect of body composition on adipomyokine levels, body mass index (BMI)-based matching was performed separately for the primary case-control analysis and for the subgroup analysis.

For the primary case-control analysis, patients with epilepsy and healthy controls were matched using a one-to-one optimal matching approach with a predefined BMI caliper of $\pm 1.5 \text{ kg/m}^2$. Matching was based only on BMI. Age and sex were not used as matching variables; however, they were compared after matching to evaluate the comparability of the groups. This procedure yielded 58 matched patients with epilepsy and 58 matched healthy controls (Figure 1).

For the subgroup analysis, a separate BMI-based matching procedure was performed to compare drug-resistant

and drug-responsive patients. Because this analysis did not include healthy controls, all available drug-resistant patients were considered as the reference group. Fifteen drug-responsive patients with eligible BMI values were selected for comparison, yielding 15 drug-resistant and 15 drug-responsive patients. Participants who could not be matched within the predefined BMI caliper were excluded only from the corresponding matched analysis (Figure 1).

Inclusion criteria were: prepubertal status, absence of structural brain lesions or genetic diagnoses, and no history of hypoxic/traumatic brain injury or chronic systemic illness. Exclusion criteria were: obesity (BMI $\geq$ 95th percentile for age and sex) (11), use of medications known to affect adipokine levels (other than anti-seizure drugs), recent acute illness, or abnormal brain magnetic resonance imaging. Patients with

a genetic diagnosis were also excluded. Only prepubertal patients were included because serum irisin and leptin levels are known to increase during puberty (12).

Epilepsy Classification

Epilepsy and seizure types were classified according to the ILAE 2017 criteria, which categorize seizures by onset (focal, generalized, unknown) and epilepsy as focal, generalized, combined focal and generalized, or unknown etiology (3). Drug responsiveness was determined according to the ILAE 2010 definition, where drug-resistant epilepsy is defined as the persistence of seizures despite appropriate use of at least two tolerated and appropriately chosen anti-seizure medications (10). Selection of anti-seizure drugs was based on patient age, seizure etiology, and electroencephalography (EEG) findings.

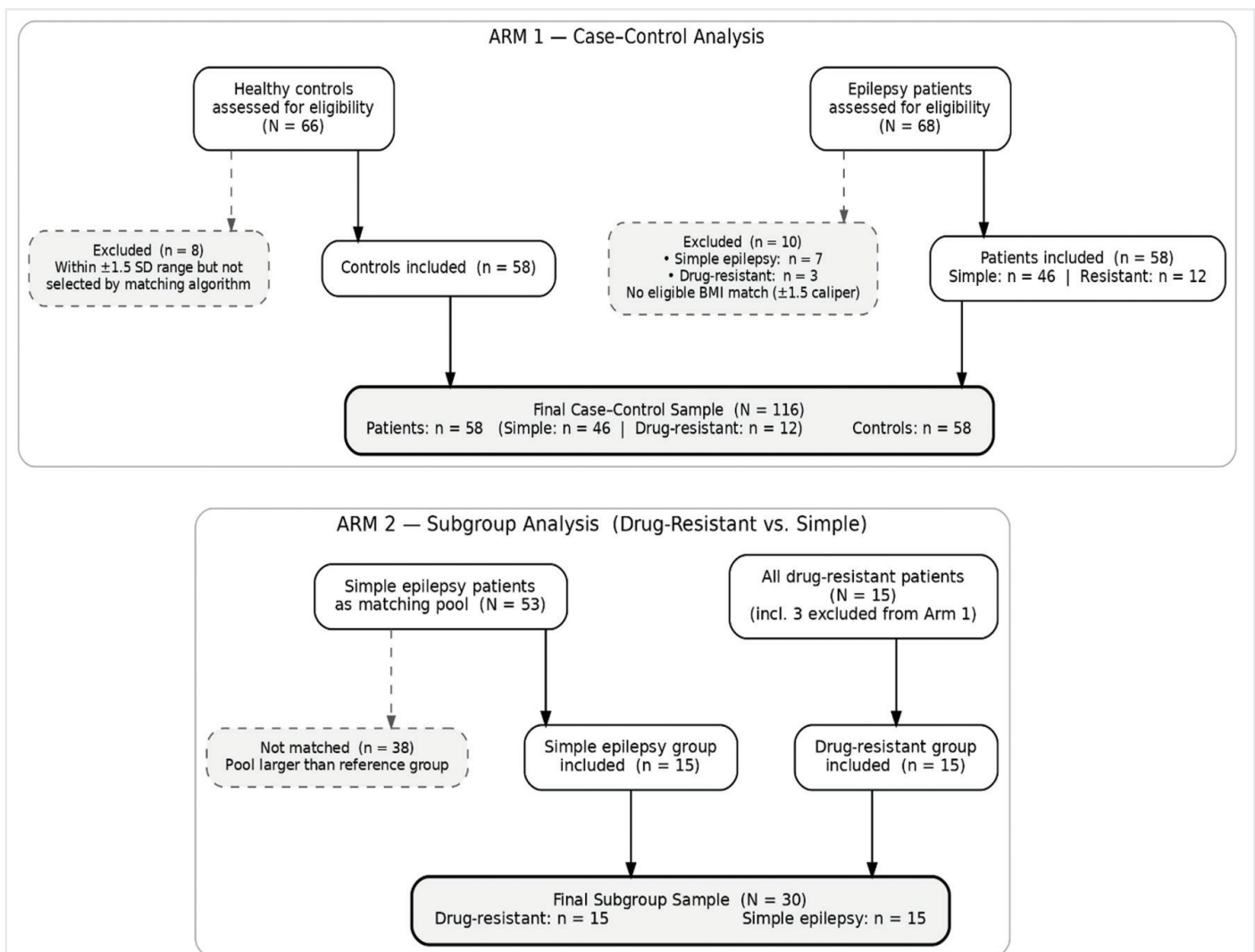


Figure 1. Flow diagram illustrating participant selection and BMI-matching procedures for the primary case-control analysis and the separate BMI-matched subgroup analysis. BMI matching was performed independently for each analysis. Consequently, three drug-resistant patients who were not included in the primary BMI-matched case-control analysis were included in the separate subgroup analysis, in which all 15 drug-resistant patients served as the reference group

BMI: Body mass index, SD: Standard deviation

Ethical Considerations

The study was approved by the Bezmialem Vakıf University Ethics Committee (decision no: 7/36, approval date: 22/07/2020, approval number: 8546). Written informed consent was obtained from the parents of all participants in accordance with the principles of the Declaration of Helsinki.

Clinical and Demographic Data

Patient histories were obtained from children and their caregivers, including sociodemographic characteristics, age at seizure onset, seizure types, disease duration, medication history, and seizure frequency. Physical and neurological examinations were performed by the same pediatric neurologist.

Anthropometric Measurements

BMI, arm circumference, and triceps skinfold thickness were measured by a single trained dietician. Arm circumference was measured at the midpoint between the acromion and olecranon processes using a non-stretchable tape. Triceps skinfold thickness was measured with a skinfold caliper over the triceps muscle.

Mid-arm circumference and triceps skinfold thickness measurements were available only for a subset of participants because these assessments were performed only when a trained dietitian was available during the recruitment period. Therefore, analyses involving these variables were based on the available data and should be interpreted with caution.

Blood Sampling Protocol

Venous blood samples were collected between 8:00-9:00 a.m., after an overnight fast of at least 8 hours, to minimize circadian and dietary influences. All participants refrained from strenuous physical activity for at least 24 hours before sampling. Where available, the time since the last seizure was recorded; if unavailable, this was noted as a study limitation. EEG was recorded during the interictal period using a 32-channel Nihon Kohden 1200 digital EEG device with the international 10–20 electrode placement system.

Biochemical Analysis

Blood was collected into plain gel separator vacutainer tubes and allowed to clot for 2 hours at room temperature (23 °C). Samples were centrifuged at 1000× g for 20 minutes, and the serum supernatant was aliquoted and stored at -80°C until analysis, strictly avoiding repeated freeze-thaw cycles. To minimize lot-to-lot variability, all samples were analyzed within a single batch. Serum irisin, leptin, and adiponectin concentrations were measured using commercially available ELISA kits (Human Irisin, Cat No: E-EL-H5735; Human LEP, Cat No: E-EL-H6017; Human ADP/Acrp30, Cat No: E-EL-H6122; all from Elabscience,

Houston, TX, USA) according to the manufacturer's protocols. Patient samples were assayed in singlicate.

The analytical characteristics of the kits were as follows: for irisin, the detection range was 78.13-5000 pg/mL with a sensitivity of 46.88 pg/mL; for leptin, the detection range was 15.63-1000 pg/mL with a sensitivity of 9.38 pg/mL; and for adiponectin, the detection range was 0.16-10 ng/mL with a sensitivity of 0.1 ng/mL. The intra-assay and inter-assay coefficients of variation for all three parameters were reported as <10%.

Statistical Analysis

All statistical analyses were performed using Jamovi (version 2.7.15; The jamovi project, 2025), which interfaces with R (Version 4.5; R Core Team, 2025). Normality of continuous variables was assessed using the Shapiro-Wilk test, and homogeneity of variances was evaluated with Levene's test.

For between-group comparisons, Student's independent samples t-test was applied when both normality and homogeneity of variance assumptions were satisfied; Welch's t-test was used when normality was met but variances were unequal; and the Mann-Whitney U test was employed when the normality assumption was violated. Categorical variables were compared using Pearson's chi-squared test or Fisher's exact test, the latter applied when expected cell frequencies fell below five.

Associations between continuous variables were examined using Spearman's rank correlation coefficient, given the non-normal distribution of several variables. To evaluate the association of irisin and adiponectin for group membership, separate univariable binary logistic regression models were fitted, with model fit evaluated using the likelihood ratio chi-squared statistic and McFadden's pseudo- R^2 .

Discriminative performance was quantified using the area under the receiver operating characteristic (ROC) curve (AUC). The statistical significance threshold was set at $\alpha=0.05$ for all analyses.

Due to the high proportion of censored leptin values (>1,000 pg/mL) in both groups, leptin was excluded from logistic regression and ROC analyses; it is reported descriptively only and findings should be considered exploratory.

Results

Participants

A total of 116 participants were included in the primary case-control analysis, comprising 58 patients with epilepsy and 58 healthy controls. The epilepsy group consisted of 46 patients with drug-responsive epilepsy and 12 with drug-resistant epilepsy after BMI-based matching.

Following one-to-one matching based on BMI, the patient and control groups were comparable with respect to age ($p=0.390$), sex distribution ($p=0.350$), and BMI ($p=0.754$), indicating successful matching (Table 1).

For the subgroup analysis, a separate BMI-matched cohort was constructed to compare drug-resistant and drug-responsive patients. This analysis included all 15 drug-resistant patients and 15 BMI-matched drug-responsive patients. The two subgroups did not differ significantly in age, sex, or BMI (all $p>0.05$), confirming the comparability of the matched subgroup (Table 2).

The participant selection and BMI-matching procedures for the primary case-control and subgroup analyses are illustrated in Figure 1.

Comparison Between Epilepsy and Control Groups

Among the available measurements, no statistically significant differences were observed in mid-arm circumference or triceps skinfold thickness between the epilepsy and control groups. However, these analyses were based on a limited number of participants and should therefore be interpreted with caution (Table 1).

Table 1. Comparison of demographic and biochemical variables between patient and control groups

Variable	Patient group (n=58)	Control group (n=58)	Test statistic	p-value
Sex, n (%)				
Male	23 (40%)	28 (48%)	$\chi^2=0.87$	0.350
Anthropometric measurements, mean $\pm$ SD ^a				
Mid-arm circumference (cm) (n=11/22)	15.93 $\pm$ 2.82	15.74 $\pm$ 1.92	t (31)=0.23	0.820
Triceps skinfold thickness (mm) (n=11/22)	10.30 $\pm$ 2.99	9.49 $\pm$ 2.17	t (31)=0.89	0.381
Continuous variables, median (IQR) ^b				
Age (years)	6.46 (4.4)	6.25 (2.9)	U=1526	0.390
BMI (kg/m ²)	16.15 (2.2)	16.00 (1.7)	U=1607	0.679
Irisin (pg/mL) ^c	14.90 (15.5)	27.83 (81.1)	U=515	0.032
Leptin (pg/mL) ^d	1000.00 (995.0)	89.89 (995.0)	U=1421	0.117
Adiponectin (μ g/mL)	2.12 (1.3)	1.17 (1.4)	U=1332	0.073

Bold p-values indicate statistical significance at $p<0.05$
 BMI: Body mass index, IQR: Interquartile range (Q3-Q1), SD: Standard deviation
^a: Mid-arm circumference and triceps skinfold thickness: normality confirmed by Shapiro-Wilk test ($p=0.160$ and 0.104 , respectively); Levene's test for equality of variances was non-significant. Student's t-test applied
^b: Normality assumption violated (Shapiro-Wilk $p<0.05$) for all remaining continuous variables; Mann-Whitney U test applied
^c: Levene's test also significant for irisin ($p=0.019$), indicating unequal variances in addition to non-normality. Mann-Whitney U test applied
^d: A substantial proportion of leptin values reached the upper assay limit (1000 pg/mL); therefore, leptin findings should be interpreted cautiously

Table 2. Comparison of demographic and biochemical variables between resistant and simple patient subgroups

Variable	Resistant group (n=15)	Simple group (n=15)	Test statistic	p-value
Sex, n (%)				
Male	7 (47%)	6 (40%)	$\chi^2=0.14$	0.710
Continuous variables, mean $\pm$ SD ^a				
Age (years)	6.79 $\pm$ 2.18	6.70 $\pm$ 2.55	t (28)=0.10	0.925
Adiponectin (μ g/mL)	1.61 $\pm$ 0.72	2.20 $\pm$ 0.60	t (27)=-2.40	0.024
Continuous variables, median (IQR) ^c				
BMI (kg/m ²)	17.10 (5.4)	17.20 (4.7)	U=111.5	0.983
Irisin (pg/mL)	16.27 (85.1)	23.30 (108.7)	U=52.0	1.000
Leptin (pg/mL)	224.40 (958.6)	1000.00 (0.0)	U=68.0	0.043

BMI: Body mass index, IQR: Interquartile range (Q3-Q1), SD: Standard deviation
^a: Normality confirmed (Shapiro-Wilk $p\geq 0.05$) and Levene's test non-significant: Student's t-test applied. Age: SW $p=0.065$; adiponectin: SW $p=0.110$.
^c: Normality assumption violated (Shapiro-Wilk $p<0.05$) for BMI, irisin, and leptin: Mann-Whitney U test applied
Note: Leptin IQR for the simple group is 0.0, reflecting a highly right-skewed distribution in which both Q1 and Q3 were at the upper detection limit (1,000.0 pg/mL). A substantial proportion of values in both groups were censored at this limit (57% of patients, 43% of controls), rendering statistical inference unreliable. All leptin findings are exploratory and must not be used for inferential conclusions

Among adipomyokines, irisin levels were significantly lower in the epilepsy group compared to controls (median: 14.90 vs. 27.83 pg/mL, $p=0.032$) (Table 1).

In contrast, no statistically significant differences were observed in leptin or adiponectin levels between the groups ($p=0.117$ and $p=0.073$, respectively). Because leptin measurements were affected by a substantial ceiling effect, this finding should be interpreted with caution (Table 1).

Comparison Between Drug-responsive and Drug-resistant Epilepsy

In the BMI-matched subgroup analysis, adiponectin levels were significantly higher in the drug-responsive group compared to the drug-resistant group (2.20 ± 0.60 vs. 1.61 ± 0.72 $\mu\text{g/mL}$, $p=0.024$) (Table 2).

Leptin values were also higher in the drug-responsive group (median: 1000.00 vs. 224.40 pg/mL). However, because a substantial proportion of leptin measurements reached the assay upper limit of quantification, these findings were considered exploratory and were not used for inferential conclusions (Table 2).

However, irisin levels did not differ significantly between the two subgroups ($p=1.000$) (Table 2).

Correlation Analyses

Spearman correlation analyses demonstrated a strong positive association between leptin and adiponectin levels ($\rho=0.84$, $p<0.001$).

In the full sample, mid-arm circumference was negatively correlated with both leptin ($\rho=-0.43$, $p=0.013$) and adiponectin ($\rho=-0.54$, $p=0.001$) levels, while BMI was positively associated with triceps skinfold thickness ($\rho=0.52$, $p=0.002$).

Within the epilepsy group, exploratory analyses showed that leptin level was positively associated with age at seizure onset ($\rho=0.31$, $p=0.019$) and negatively associated with treatment duration ($\rho=-0.35$, $p=0.008$). Adiponectin also showed a negative correlation with treatment duration ($\rho=-0.35$, $p=0.008$).

No significant correlations were observed between irisin levels and anthropometric or clinical variables.

Clinical Characteristics of Epilepsy Subgroups

There were no statistically significant differences between drug-responsive and drug-resistant groups in terms of clinical and demographic characteristics, including age at onset, gestational age, treatment duration, seizure type, EEG findings, or family history (all $p>0.05$) (Table 3).

Logistic Regression and ROC Analyses

In the case-control comparison, neither irisin nor adiponectin level was significantly associated with group membership in the univariable logistic regression analyses

(all $p>0.05$). Among these, irisin level showed the highest, although non-significant, discriminative performance (AUC: 0.643).

In the subgroup analysis, higher adiponectin levels were significantly associated with drug responsiveness (odds ratio: 3.67, $p=0.031$). Irisin level was not significantly associated with subgroup status. Because of the marked ceiling effect observed in leptin measurements, leptin was excluded from logistic regression and ROC analyses.

ROC curves for irisin and adiponectin in subgroup analyses are presented in Figure 2.

Discussion

The present study investigated the relationship between serum adipomyokine levels and treatment response in children with idiopathic epilepsy. The main findings were that irisin levels were significantly lower in patients with epilepsy than in healthy controls, whereas adiponectin levels were significantly higher in drug-responsive than in drug-resistant patients. Exploratory analyses also suggested higher leptin levels in the drug-responsive group; however, these findings should be interpreted with caution because of the marked ceiling effect observed in leptin measurements. These findings suggest that adipomyokines may be associated not only with epileptogenesis but also with differences in current drug responsiveness.

The pathophysiology of epilepsy involves multiple mechanisms, and increasing evidence highlights the role of inflammation in epileptogenesis. The inclusion of immune etiology in the ILAE classification and the demonstration of neuronal damage induced by pro-inflammatory mediators have further emphasized the importance of inflammation in epilepsy (3,4). This has increased interest in identifying immune-related molecules that may improve our understanding of disease mechanisms and potentially contribute to future research on disease monitoring and therapeutic strategies.

Recent reviews have further emphasized the interaction between metabolic pathways, neuroinflammation, and epileptogenesis, suggesting that adipokines may influence seizure susceptibility through oxidative stress, glucose metabolism, and blood-brain barrier regulation (6).

Leptin is a hormone primarily synthesized in adipocytes and is involved in energy balance, immune regulation, and neuronal function. It has been shown to influence hippocampal neuronal activity, synaptic plasticity, and neurotrophic processes (6,8,13,14). Previous studies have reported both proconvulsive and anticonvulsive effects of leptin, indicating that its effects may vary according to disease stage, receptor distribution, and metabolic conditions (15). Experimental studies have shown that leptin deficiency may increase seizure susceptibility, whereas leptin administration may exert neuroprotective effects (16,17).

Table 3. Clinical and demographic characteristics of resistant and simple epilepsy subgroups

Variable	Resistant group (n=15)	Simple group (n=15)	Test statistic	p-value
Continuous variables, median (IQR) ^a				
Age at onset (years)	4.00 (5.0)	5.50 (4.5)	U=81.0	0.197
Gestational age (weeks)	38.00 (0.0)	38.00 (0.0)	U=105.0	0.577
Treatment duration (years)	2.00 (3.1)	1.50 (1.5)	U=79.5	0.177
Categorical variables, n (%)				
Age at onset category			$\chi^2(2)=2.71$	0.269
Infant (1-24 months)	6 (40%)	5 (33%)		
Preschool (25-60 months)	5 (33%)	2 (13%)		
School-age (6-11 years)	4 (27%)	8 (53%)		
Gestational age				
Term	15 (100%)	13 (87%)	Fisher	0.483
Preterm	0 (0%)	2 (13%)		
Consanguineous marriage				
No	12 (80%)	14 (93%)	Fisher	0.598
Yes	3 (20%)	1 (6.7%)		
Mode of delivery				
NSD	13 (87%)	14 (93%)	Fisher	>0.999
C-section	2 (13%)	1 (6.7%)		
NICU admission history				
No	14 (93%)	14 (93%)	Fisher	>0.999
Yes	1 (6.7%)	1 (6.7%)		
Seizure type ^b				
Focal	5/13 (38%)	8/15 (53%)	$\chi^2(1)=0.62$	0.431
Generalised	8/13 (62%)	7/15 (47%)		
Epilepsy type ^c			$\chi^2(2)=3.66$	0.111
Focal	5/14 (36%)	8/11 (73%)		
Generalised	8/14 (57%)	3/11 (27%)		
Focal and generalised	1/14 (7.1%)	0/11 (0%)		
EEG finding ^d				
Focal	5/11 (45%)	7/10 (70%)	Fisher	0.387
Generalised	6/11 (55%)	3/10 (30%)		
History of febrile seizures				
No	12 (80%)	12 (80%)	Fisher	>0.999
Yes	3 (20%)	3 (20%)		
Family history of epilepsy				
No	10 (67%)	12 (80%)	$\chi^2(1)=0.68$	0.682
Yes	5 (33%)	3 (20%)		
Special education				
No	13 (87%)	14 (93%)	Fisher	>0.999
Yes	2 (13%)	1 (6.7%)		
Drug allergy	0 (0%)	0 (0%)	-	-
Genetic diagnosis	0 (0%)	0 (0%)	-	-
Additional disease				
No	15 (100%)	14 (93%)	Fisher	>0.999
Yes	0 (0%)	1 (6.7%)		

Table 3. Continued

Variable	Resistant group (n=15)	Simple group (n=15)	Test statistic	p-value
Autism features ^e				
No	14/15 (93%)	13/14 (93%)	Fisher	>0.999
Yes	1/15 (6.7%)	1/14 (7.1%)		
ADHD ^f				
No	13/14 (93%)	12/14 (86%)	Fisher	>0.999
Yes	1/14 (7.1%)	2/14 (14%)		

ADHD: Attention-deficit/hyperactivity disorder, IQR: Interquartile range (Q3-Q1), NICU: Neonatal intensive care unit, NSD: Normal spontaneous delivery, EEG:

Electroencephalography

^a: Mann-Whitney U test applied to all continuous variables; data are presented as median (IQR)

^b: Two patients in the resistant group had missing seizure-type data (analysed n=13/15)

^c: Five patients had missing epilepsy-type data (resistant n=14/15; simple n=11/15)

^d: Nine patients had missing EEG data (resistant n=11/15; simple n=10/15)

^e: One patient in the simple group had missing data (analysed n=14/15)

^f: Two patients had missing ADHD data (resistant n=14/15; simple n=14/15)

Note: No statistically significant between-group differences were detected for any variable (all p>0.05). Fisher's exact test was applied when expected cell frequencies were below 5; Pearson's chi-squared test was used otherwise

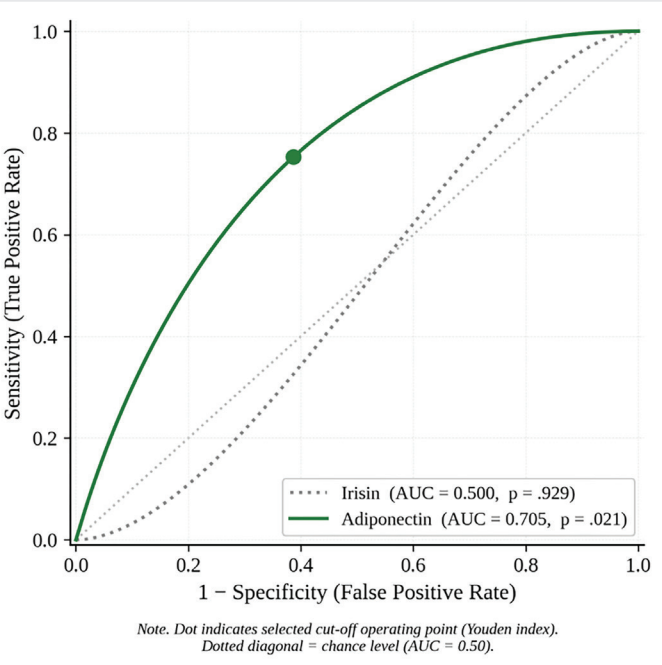


Figure 2. Receiver operating characteristic curves of irisin and adiponectin levels for discrimination between drug-responsive and drug-resistant epilepsy groups. Adiponectin demonstrated the highest discriminative performance among the evaluated adipomyokines

AUC: Area under the curve

In our study, leptin levels did not differ significantly between patients with epilepsy and healthy controls. Exploratory analyses suggested higher leptin levels in drug-responsive patients than in drug-resistant patients; however, these findings should be interpreted with caution because a substantial proportion of leptin measurements reached the upper limit of quantification of the assay. Therefore, no definitive conclusions regarding the association between leptin and current drug responsiveness can be drawn

from the present data. In addition, leptin levels showed a negative correlation with treatment duration, suggesting that circulating leptin concentrations may decrease during long-term treatment. Similar treatment-related alterations in leptin levels have been reported previously (18).

Adiponectin is another adipomyokine involved in energy homeostasis, neurogenesis, and synaptic plasticity. It has been shown to reduce oxidative stress, prevent neuronal injury, and preserve blood-brain barrier integrity after seizures (19,20). Several studies have demonstrated that adiponectin levels may be affected by antiepileptic drugs and ketogenic diet therapy (21-23). However, findings regarding its role in epilepsy remain inconsistent.

In the present study, adiponectin levels did not differ between patients with epilepsy and healthy controls but were significantly higher in drug-responsive than in drug-resistant patients. This finding suggests an association between higher adiponectin levels and current drug responsiveness in this cohort. In contrast to studies reporting lower adiponectin levels in drug-resistant epilepsy (24), our findings may reflect differences in study populations, treatment regimens, and methodological approaches.

Irisin is a recently identified adipomyokine with anti-inflammatory and neuroprotective properties. Previous studies have shown that irisin may contribute to neurogenesis and cognitive functions and may play a role in several neurological disorders (25,26). Several factors, including physical activity and metabolic status, are known to influence irisin levels (27).

In our study, irisin levels were significantly lower in epilepsy patients than in controls, suggesting a possible association between irisin and epilepsy-related mechanisms. However, no significant difference was observed between drug-responsive and drug-resistant groups. These findings are consistent with some previous studies reporting no

difference in irisin levels between epilepsy subgroups (15), although other studies reported elevated irisin levels in uncontrolled seizures (28). Differences in study populations, seizure types, and timing of blood sampling may explain these conflicting findings.

Emerging evidence suggests that irisin may act as a compensatory neuroprotective molecule during neuroinflammatory processes; however, its clinical significance in epilepsy has not yet been established (6).

In addition, irisin levels decreased with longer treatment duration in our study. This finding may be related to metabolic adaptations occurring during long-term treatment, although the underlying mechanisms remain unclear. Similar temporal changes have also been reported in experimental epilepsy models (29).

Correlation analyses revealed a strong positive association between leptin and adiponectin levels. However, because leptin measurements were affected by a substantial ceiling effect, this finding should be interpreted cautiously. Previous studies have also demonstrated interactions between adipomyokines, suggesting coordinated regulation of these molecules, although these relationships may vary depending on metabolic and disease-related conditions (30).

In the subgroup analysis, higher adiponectin levels were significantly associated with current drug responsiveness, whereas irisin showed no significant association. Because leptin measurements were substantially affected by the assay ceiling effect, leptin level was excluded from the logistic regression and ROC analyses, and no conclusions regarding its association with drug responsiveness can be drawn from these analyses. Overall, these findings suggest that adiponectin level may be associated with the current drug responsiveness status in this cohort, although confirmation in prospective studies is required. Consistent with previous reports, adipomyokines appear to have limited utility in distinguishing epilepsy subgroups (15,31).

Current evidence increasingly suggests that adipokines may be involved in mechanisms related to treatment response and disease progression rather than serving as diagnostic markers, particularly in pediatric epilepsy, where inflammatory and metabolic pathways may differ from those in adult (6).

To reduce the potential confounding effects of body composition on adipokine levels, BMI-matched analyses were performed in the present study. This approach may have contributed to a more reliable evaluation of the

relationship between adipomyokines and epilepsy-related variables.

Study Limitations

This study has several limitations. First, the relatively small sample size, particularly in the subgroup analyses, may have limited the statistical power to detect subtle between-group differences. Second, the lack of information regarding seizure activity within 24 hours before blood sampling may have influenced adipokine levels. Third, although medications affecting adipokine levels were excluded, factors such as physical activity and diet were not fully controlled. In addition, mid-arm circumference and triceps skinfold thickness measurements were available only for a subset of participants because these assessments could only be performed when a trained dietitian was available during the recruitment period. Therefore, findings related to these anthropometric variables should be interpreted with caution. Finally, because of the cross-sectional design, causal relationships cannot be established, and longitudinal studies are needed to clarify temporal changes in adipomyokines during the course of epilepsy and treatment. In addition, the marked ceiling effect observed for leptin measurements limited the interpretation of leptin-related findings, which should therefore be considered exploratory.

Conclusion

In conclusion, this study demonstrated that serum irisin levels were lower in children with idiopathic epilepsy than in healthy controls, whereas adiponectin levels were higher in drug-responsive than in drug-resistant patients. Exploratory analyses also suggested higher leptin levels in the drug-responsive group; however, these findings should be interpreted with caution because of the marked ceiling effect observed in leptin measurements. These findings suggest that adipomyokines may be associated not only with epilepsy-related inflammatory and metabolic mechanisms but also with differences in current drug responsiveness.

Although adipomyokines showed limited ability to distinguish between the study groups in this cohort, the observed association between adiponectin and current drug responsiveness warrants further investigation. Because of the cross-sectional design, these findings should not be interpreted as evidence of predictive performance. Prospective longitudinal studies with larger cohorts are needed to clarify the clinical significance of adipomyokines in pediatric epilepsy.

Ethics

Ethics Committee Approval: The study was approved by the Bezmialem Vakıf University Ethics Committee (decision no: 7/36, approval date: 22/07/2020, approval number: 8546).

Informed Consent: Written informed consent was obtained from the parents of all participants in accordance with the principles of the Declaration of Helsinki.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Ş.S.Ş., T.U.Ş., Z.E.Ç., S.D., Ş.S., D.F.İ., Concept: Ş.S.Ş., T.U.Ş., T.Y., Ş.S., D.F.İ., A.İ., Design: Ş.S.Ş., T.U.Ş., T.Y., Ş.S., D.F.İ., A.İ., Data Collection or Processing: Ş.S.Ş., T.U.Ş., T.Y., Z.E.Ç., S.D., Ş.S., Analysis or Interpretation: Ş.S.Ş., T.U.Ş., T.Y., Z.E.Ç., Ş.S., D.F.İ., Literature Search: Ş.S.Ş., Writing: Ş.S.Ş., D.F.İ.

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