Circulating levels of adipokines are altered in patients with temporal lobe epilepsy

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ABSTRACT

Objective: A persistent low-grade inflammatory state has been described in patients with temporal lobe epilepsy (TLE) in the interictal period. Adipokines are cytokines produced by the adipose tissue that can influence inflammatory response. The purpose of this study was to evaluate the plasma levels of adipokines in patients with TLE in comparison with controls. In addition, we sought to investigate whether the levels of adipokines were associated with clinical parameters in TLE.
Methods: Forty patients with TLE and 40 controls were enrolled in this study. All participants were subjected to clinical assessment that included the Mini International Neuropsychiatric Interview (MINI) and the Hamilton Depression Rating Scale (HAM-D). Peripheral blood was drawn, and plasma levels of adipokines (adiponectin, leptin, and resistin) were measured by enzyme-linked immunoassay (ELISA).
Results: People with TLE presented higher leptin and lower adiponectin and resistin levels in comparison with controls. The levels of these adipokines correlated negatively with illness length but not with other clinical parameters. In a binary logistic regression model, higher leptin and lower adiponectin levels remained as significant predictors of TLE diagnosis.
Conclusions: These results corroborate the view that TLE is a multisystemic condition associated with low-grade inflammation.

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1. Introduction

A great body of evidence suggests the involvement of peripheral and central nervous system (CNS) inflammation in the pathogenesis of epilepsy [1–6]. Inflammatory changes are particularly evident in ictal and periictal phases, with a limited number of studies addressing persistent and/or interictal immune changes [7–9]. In this regard, our group described an exacerbated proinflammatory profile in CD4^{+} and CD8^{+} T lymphocytes of individuals with temporal lobe epilepsy (TLE) during the interictal period [4].

The adipose tissue is an important source of inflammatory cytokines, such as tumor necrosis factor (TNF), interleukin (IL)-1β and IL-6 [10,11], and adipokines. Adipokines are adipose tissue-derived cytokines that regulate energetic metabolism [11,12]. Besides playing a pivotal role in energetic metabolism, adipokines can modulate innate and adaptive immunity, with leptin and resistin exerting proinflammatory effects and adiponectin presenting antiinflammatory actions [13–15]. The role of adipokines in epilepsy has been explored in experimental models. For instance, adiponectin reduced hippocampal excitotoxicity after kainic acid-induced seizures in mice [16]. In humans, cerebrospinal fluid (CSF) and plasma levels of leptin decreased while adiponectin levels increased 24 h after tonic–clonic seizures [17]. To the best of our knowledge, no previous study has evaluated adipokines in patients with TLE.

Psychiatric comorbidities, especially depression, are common in patients with TLE. There is a well-established bidirectional association between epilepsy and depression [18–20]. Interestingly, depression has been consistently associated with a chronic low-grade systemic inflammation [4,21–23], including changes in the circulating levels of adipokines [24–26]. Changes in inflammatory parameters, including adipokine levels, might reflect shared mechanisms between epilepsy and depression.

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In this scenario, the aim of this study was to examine plasma levels of adipokines in patients with TLE in comparison with controls and to evaluate whether adipokine levels are associated with clinical parameters, mainly depression, in TLE.

2. Methods and materials

2.1. Subjects and clinical evaluation

This is an exploratory cross-sectional study involving 40 patients with TLE who were consecutively recruited at the Epilepsy Outpatient Clinic, UFMG University Hospital. In addition, we recruited 40 age- and sex-matched controls from the local community.

Patients with TLE older than 18 years who were seizure-free for at least 72 h were enrolled in the study. The definition of 'seizure-free' period was based on the reports of patients and/or their relatives. If patients or family members expressed any doubt regarding the date of the last seizure (less than 72 h), such individuals were not included in the study. Temporal lobe epilepsy diagnosis was based on seizure semiology, ictal/interictal electroencephalography (EEG), and neuroimaging (magnetic resonance imaging) exams. Patients were excluded if i) they had any epileptic seizures within 3 days of research assessment; ii) they had any other neurological diseases (such as dementia or stroke), inflammatory diseases, or cancer; iii) they had used any immunosuppressive or immunomodulatory medication in the six weeks prior to the study; iv) they had any surgery or major trauma in the month prior to the study; v) they presented renal or hepatic impairment or pregnancy. The 72-hour period without seizures was chosen in order to exclude the potential influence of seizures on the circulating levels of inflammatory mediators [27,28].

The inclusion criteria for the control group were age older than 18 years and the absence of any neurological disease or unstable medical condition. All participants agreed in participating in our study and provided written informed consent. The local Ethics Committee approved our protocol.

After reading and signing the informed consent, all participants underwent a clinical interview performed by an experienced physician and had their peripheral blood drawn.

All participants were subjected to a structured assessment composed of a sociodemographic and medical history inventory and the Mini International Neuropsychiatric Interview (MINI) [29,30] for psychiatric evaluation. In addition, the Mini Mental State Examination (MMSE) [31,32] and the Hamilton Depression Rating Scale (HAM-D) [33–35] were applied for the assessment of global cognition and depressive symptoms, respectively.

2.2. Adipokine assessment

After clinical evaluation, 10 mL of venous blood were drawn in vacuum tubes containing sodium heparin. Blood samples were then centrifuged at 3000 rpm, 4 °C, for 10 min for plasma obtaining. Plasma samples were stored at −70 °C until analysis. Plasma samples were thawed for the analysis of adipokines (adiponectin, leptin, and resistin) by enzyme-linked immunoassay (ELISA) sandwich kit, following the manufacturer's instructions (R&D Systems, Minneapolis, MN, USA).

The analyses were performed blinded and in duplicate. The detection limit of the assays was 15 pg/mL. The concentrations values are expressed as ng/mL.

2.3. Statistics

Categorical variables were analyzed by the Chi-square test or the Fisher's exact test, when appropriate. All continuous variables were tested for normality using the Shapiro–Wilk test. Two groups of continuous variables were compared using the Student's t test or the Mann–Whitney U test when variables were determined to follow or not a normal distribution. Spearman's correlation analyses were performed to examine the relationship between clinical variables and plasma levels of adipokines.

Binary logistic regression models were used to verify differences in adipokine levels controlling for major depressive episode diagnosis.

A multivariate analysis was performed to ascertain the effects of adipokine levels, cognitive performance, and severity of depressive symptoms on the likelihood of TLE diagnosis. More specifically, a binary logistic regression using a backward elimination approach was performed, and the following variables were included in the initial

Table 1
Sociodemographic and clinical characteristics of patients with temporal lobe epilepsy and controls.

	Controls (N = 40)		Patients with TLE (N = 40)		
	N/mean (SD)	Proportion (%)/median (range)	N/mean (SD)	Proportion (%)/median (range)	p value
Sex					0.823[a]
Male	20	50%	21	52.5%	
Female	20	50%	19	47.5%	
Age in years	41.7 (9.4)	43 (24–65)	41.3 (11.5)	39.5 (19–55)	0.923[c]
Educational level in years	10.05 (5.3)	11 (1–25)	7.9 (3.9)	10 (0–15)	0.099[c]
Marital status					**<0.001**[b]
Single	9	22.5%	24	60.0%	
Married/stable union	27	67.5%	12	30.0%	
Divorced/separated	4	10.0%	3	7.5%	
Widowed	0	0%	1	2.50%	
Employment					**<0.001**[b]
Employee	37	92.5%	8	20.0%	
Unemployed	1	2.5%	17	42.5%	
Retired (age or length of service)	1	2.5%	1	2.5%	
Retired (due to illness)	1	2.5%	14	35.0%	
BMI	27 (5.2)	26.1 (18–44.9)	26.1 (5.9)	25.4 (18.3–41.9)	0.507[c]
Major depressive episode	8	20%	18	45.0%	**0.017**[a]
MMSE	28.1 (2.5)	28.5 (19–30)	25.4 (3.7)	26.5 (15–30)	**0.001**[c]
HAM-D	6.23 (8.3)	3 (0–33)	12.1 (11.3)	9 (0–45)	**0.001**[c]

BMI — body mass index; MMSE — Mini Mental State Examination; HAM-D — Hamilton Depression Rating Scale; SD — standard deviation; TLE — temporal lobe epilepsy.
Bold values indicate statistical significance.
[a] Chi square.
[b] Fisher's exact test.
[c] Mann–Whitney U test.

model: plasma levels of adiponectin, leptin, and resistin, MMSE, and HAM-D scores. The backward stepwise selection was automatically performed using the Statistical Package for the Social Sciences (SPSS) software version 25.0 (SPSS Inc., Chicago, IL, USA), and the removal testing was based on the probability of the likelihood-ratio statistic based on conditional parameter estimates. The goodness of fit of the logistic regression model was assessed by the Hosmer–Lemeshow test as well as a receiver operating characteristic (ROC) curve.

All statistical tests were two-tailed and were performed using a significance level of $\alpha = 0.05$. Statistical analyses were performed using the SPSS software version 25.0 (SPSS Inc., Chicago, IL, USA), as well as GraphPad Prism 5.0 (GraphPad Software, Inc., La Jolla, California, USA).

3. Results

3.1. Demographic and clinical characteristics

Sociodemographic and clinical characteristics of both patients with TLE and controls are shown in Tables 1 and 2. There were no significant differences in sociodemographic characteristics such as sex, age, level of education, and body mass index (BMI) between groups. The frequency of current major depressive episode was higher in patients (45%) than in controls (20%) (Table 1).

Most patients with TLE had a long-standing condition (28.84 ± 14.84 years) and exhibited on average 2 seizures per month. There was a high frequency of hippocampal sclerosis (87.5%), and 95% of patients were in use of 2 or more antiepileptic drugs (AEDs) (Table 2). Regarding the type of AED, 25 were taking carbamazepine (62.5%), 15 lamotrigine (37.5%), 11 topiramate (27.5%), 9 valproate (22.5%), 4 phenobarbital (10%), 3 oxcarbazepine (7.5%), and 3 phenytoin (7.5%). Twelve patients were taking antidepressants.
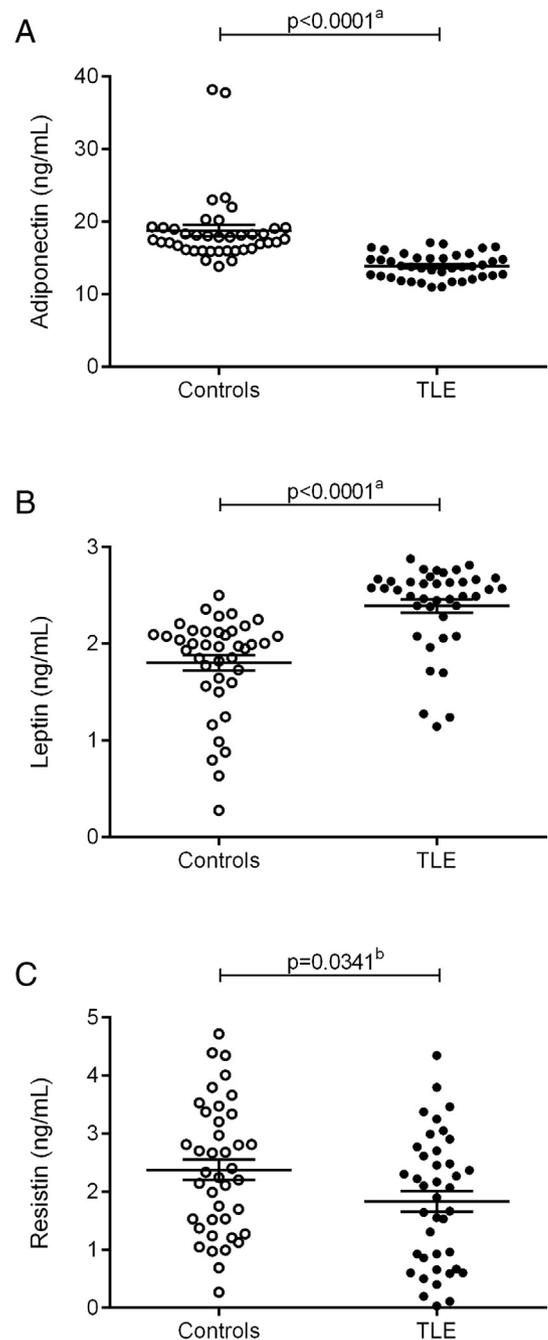
3.2. Levels of adipokines

Patients with TLE exhibited lower plasma levels of adiponectin and resistin, while higher levels of adiponectin in comparison with controls [mean ± SD (median) values are given as follows: i) adiponectin = 13.89 ± 1.72 (13.82) ng/mL and 18.76 ± 4.92 (17.75) ng/mL, for patients with TLE and controls, respectively (p < 0.0001, Mann–Whitney test); ii) resistin = 1.83 ± 1.12 (1.98) ng/mL and 2.38 ± 1.12 (2.29)

Table 2
Clinical characteristics of patients with temporal lobe epilepsy.

	Patients with TLE (n = 40)	
	No. or mean (SD)	Proportion (%) or median (range)
Type of crisis		
Simples focal	10	25%
Complex focal	40	100%
Secondary generalization	18	45%
Epilepsy early age, in years	5.9 (8.7)	2.5 (0–42)
Duration of epilepsy in years	28.8 (14.8)	26.5 (2–57)
Frequency of seizures per month	2.1 (3.6)	1 (0–22)
Seizure-free for 12 months or more	7	17.5%
MR		
WMTS	5	12.5%
RMTS	14	35.0%
LMTS	17	42.5%
BMTS	4	10.0%
AEDs		
1 AED	2	5%
2 AEDs	15	37.5%
3 or 4 AEDs	23	57.5%

MR — nuclear magnetic resonance; WMTS — without mesial temporal sclerosis; RMTS — right mesial temporal sclerosis; LMTS — left mesial temporal sclerosis; BMTS — bilateral mesial temporal sclerosis; AEDs — antiepileptic drugs; TLE — temporal lobe epilepsy; SD — standard deviation.

Fig. 1. Plasma levels of adipokines in patients with temporal lobe epilepsy (TLE) and controls. Patients with TLE presented decreased levels of adiponectin (A) and resistin (C) and increased levels of leptin (B) in comparison with controls. Horizontal bars indicate the mean and the standard deviation of the mean. [a]Mann–Whitney test. [b]Student's t test. A p value <0.05 was considered significant.

ng/mL, for patients with TLE and controls, respectively (p = 0.0341, Student's t test); iii) leptin = 2.39 ± 0.44 (2.56) ng/mL and 1.80 ± 0.51 (1.98) ng/mL, for patients with TLE and controls, respectively (p < 0.0001, Mann–Whitney test)]. Fig. 1 shows the plasma levels of adipokines in patients with TLE and in controls. The differences found for adiponectin and leptin, but not for resistin, remained statistically significant after controlling for current major depressive episode diagnosis.

In patients with TLE, leptin levels correlated positively with BMI (rho = 0.387; p = 0.038), and both leptin and adiponectin levels correlated negatively with TLE duration (rho = −0.363; p = 0.021; rho =

Table 3
Final logistic regression model (step 02) to predict temporal lobe epilepsy.

Predictive variable	B	SE	Wald	df	p value	Odds ratio	95% CI for odds ratio	
							Lower	Upper
Resistin	−0.001	0.001	2.927	1	0.087	0.999	0.998	1.000
Adiponectin	**−0.001**	**0.000**	**11.066**	**1**	**0.001**	**0.999**	**0.998**	**0.999**
Leptin	**0.004**	**0.002**	**6.416**	**1**	**0.011**	**1.004**	**1.001**	**1.008**
MMSE	−0.277	0.154	3.228	1	0.072	0.758	0.561	1.025

Variable(s) entered on step 1: Resistin, adiponectin, leptin, MMSE, and HAM-D24.
Abbreviations: CI = confidence interval; df = degrees of freedom; HAM-D = Hamilton Depression Rating Scale; MMSE = Mini Mental State Examination; SE = standard error.
Bold values indicate statistical significance.

−0.478, p = 0.002; respectively). We did not find any correlation between adipokine levels and MMSE or HAM-D scores or the levels of AED.

A binary logistic regression was performed to ascertain the effects of adipokine levels, MMSE, and HAM-D scores on the likelihood of TLE diagnosis. The final model included MMSE score, leptin, adiponectin, and resistin levels. Lower adiponectin levels and higher leptin levels remained as significant predictors of TLE diagnosis (Table 3). The logistic regression model can be considered excellent since the predicted variability resulted in an area under the curve (AUC) of 0.987 in the ROC analysis (Supplementary Fig. 1).

4. Discussion

In the current study, we showed that plasma levels of adipokines are altered in patients with TLE in comparison with controls. After controlling for depression diagnosis, adiponectin and leptin levels remained significantly different in patients with TLE in comparison with controls. Corroborating these findings, lower plasma levels of adiponectin and higher levels of leptin remained as significant predictors of TLE diagnosis in a logistic binary regression model with excellent accuracy (AUC = 0.987).

It is worth emphasizing that although depression is frequently comorbid with TLE and is associated with low-grade inflammation [18], the observed results could not be explained by this comorbidity. The presence of depressive symptom in the patients with TLE or controls did not change the results regarding adiponectin and leptin. This is the first study to investigate adipokine levels in patients with epilepsy controlling for depression.

This is also an important study that evaluated plasma levels of adipokines specifically in TLE. A negative correlation between the frequency of generalized tonic–clonic seizures and leptin levels in women was previously reported [17]. The same study described an increase in adiponectin and decrease in leptin levels within 24 h after the seizure, possibly indicating an 'antiinflammatory reaction' to the seizure [17]. We noticed changes in the opposite direction during the interictal period. Accordingly, the changes toward an antiinflammatory profile that follow the seizures seem to be transient, with the persistence of a proinflammatory profile. This may occur because of continuous CNS cell activation (especially astrocytes and microglia) [5,36] and possibly recruitment of peripheral leukocytes, enhancing local and systemic inflammatory mechanisms [1,6,9,37–39]. Interestingly, we observed that TLE duration was negatively correlated with leptin and adiponectin plasma levels.

Patients with TLE had increased leptin and decreased adiponectin levels in comparison with controls. Based on the pro- and antiinflammatory actions exerted by leptin and adiponectin, respectively, our findings corroborate the view that TLE is associated with a persistent low-grade chronic inflammation as shown by elevated circulating levels of proinflammatory cytokines [9,40] and active immune cells [4]. Temporal lobe epilepsy-related chronic systemic inflammation could aggravate epileptogenesis [41] and increase the risk of clinical

comorbidities [42]. Indeed, studies have shown that epilepsy is not only associated with psychiatric disorders but also systemic conditions, such as hypertension, gastrointestinal, cardiovascular, cerebrovascular and pulmonary diseases [43–45]. Accordingly, our current findings also support the concept of TLE as a systemic condition.

Our results might be interpreted considering the study limitations. First, the cross-sectional design does not allow causal or temporal assumptions regarding the relationship between adipokines and TLE. Second, all patients were medicated. Antiepileptic drugs have shown to increase leptin and decrease adiponectin levels, especially valproate and topiramate [46–51].

5. Conclusion

Plasma levels of adiponectin and leptin are independently associated with TLE, having no influence of sex, age, or depression diagnosis. These data suggest that adipokines may play a role in TLE pathophysiology. The changes of adipokines are in line with a low-grade inflammation status in TLE.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yebeh.2018.11.023.

Conflict of interest

The authors have no conflict of interest to declare.

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