Acta Neurologica Belgica (2021) 121:1823–1830
https://doi.org/10.1007/s13760-020-01552-7

ORIGINAL ARTICLE

The correlation between carbamazepine and valproic acid monotherapy with serum adiponectin and carnitine

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Received: 19 February 2020 / Accepted: 10 November 2020 / Published online: 26 November 2020

Abstract

Antiepileptic drugs may cause systemic and metabolic side effects. The aim of our study was to investigate the effects of valproic acid and carbamazepine monotherapy used in the treatment of epilepsy patients on serum adiponectin and carnitine levels. The study included 60 patients, of which 30 patients receiving valproic acid monotherapy and 30 patients receiving carbamazepine monotherapy, who were followed up by the epilepsy outpatient clinic with the diagnosis of idiopathic epilepsy, and 30 healthy volunteers. Patients, who used drugs for at least 6 months, were selected. Venous blood samples were collected from the patients and healthy volunteers after their consent was obtained. Serum carnitine and adiponectin levels in the collected samples were measured using the ELISA method. Serum carnitine levels were 5166.55 ng/ml (±1954.92) in patients receiving carbamazepine, 4224.56 ng/ml (±2055.54) in patients using valproic acid, and 5802.64 ng/ml (±3422.57) in the control group. Serum adiponectin levels were 13,606.51 ng/ml (±5915.92) in patients using carbamazepine, 11,986.58 ng/ml (±5367.82) in patients receiving valproic acid, and 14,033.43 ng/ml (±5646.34) in the control group. In both groups, both serum carnitine and serum adiponectin levels were lower than the control group. There was a negative but insignificant correlation between the duration and dose of carbamazepine and valproic acid drug use and serum adiponectin and carnitine levels. There is a need for more extensive studies with larger sample size to investigate the effect of antiepileptic drugs used on serum adiponectin and carnitine levels.

Keywords Epilepsy · Valproic acid · Carbamazepine · Adiponectin · Carnitine

Introduction

Today, numerous antiepileptic drugs are used and they are known to have different systemic side effects [1]. Continuous administration of antiepileptic drugs results in long standing complications such as psychiatric disorders, metabolic disorder, endocrine disorders, idiosyncratic reactions and drug interaction effects in some cases [2]. Valproic acid (VPA) and carbamazepine (CBZ) are commonly used antiepileptic drugs. VPA may cause gastrointestinal side effects such as nausea, anorexia, dyspepsia, diarrhea and constipation, as well as weight gain, thrombocytopenia, skin rash, hair loss, tremor and sedation [3]. One of the important side effects of VPA is hepatotoxicity. Weight gain associated with insulin resistance and metabolic disorder is a complication of the treatment with VPA [4]. The incidence of weight gain reported in the studies varies between 10 and 70% [5]. The major side effects seen during the use of CBZ include gastrointestinal symptoms such as nausea, vomiting, dyspepsia, abdominal pain, loss of appetite, diarrhea and constipation. Weight gain has also been associated with CBZ treatment [6]. It has been reported that adiponectin levels decrease with VPA monotherapy [7]. Adiponectin is a plasma protein synthesized by adipose tissue. It has been reported that plasma adiponectin levels decrease with obesity, insulin resistance, type 2 diabetes, metabolic syndrome, dyslipidemia, cardiovascular diseases, hypertension, carbohydrate-rich diet, while it increases with weight loss, anorexia, kidney failure, heart failure, fat-rich diet and the use of certain

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drugs. [8]. Adipocytokines play a major role in the development of insulin resistance and other metabolic complications [9]. Adiponectin mitigates weight gain and plays an important role in regulating insulin sensitivity [10]. There are not enough studies investigating the correlation between serum adiponectin level and VPA and CBZ monotherapy in adult epilepsy patients.

The correlation between antiepileptic drugs and antioxidants has been analyzed and remarkable results have been reported [11, 12]. Epilepsy and antiepileptic drugs may cause oxidative stress by affecting the formation of free radicals [13]. The nervous system is especially susceptible to oxidative stress-induced damage due to its polyunsaturated fatty acid content [14]. Polyunsaturated fatty acids prone to lipid peroxidation may therefore cause neuronal deterioration due to the increase in free radicals [15]. Long-term treatment with antiepileptic drugs is associated with high levels of systemic inflammation, as well as oxidative stress [16]. Especially in epileptic patients receiving antiepileptic drug treatment, the components of metabolic syndrome have been identified. Oxidative stress and associated complications play a role in the development of metabolic syndrome. Carnitine, an antioxidant synthesized in vivo or taken with diet, is of great importance because of its neuromodulator, neuroprotective and cytoprotective properties [17]. Although a decrease has been reported in serum carnitine levels with antiepileptic drugs in the literature, there are not enough studies on adult patient group [18, 19]. Although valproic acid is mainly associated with hypocarnitinemia, some studies have shown that other antiepileptic drugs, especially carbamazepine, phenytoin, and phenobarbital, may lead to carnitine deficiency [20, 21].

In our study, we aimed to investigate the effects of VPA and CBZ, some of the commonly used antiepileptic drugs, on serum levels of adiponectin and carnitine with antioxidant properties, which are important in terms of metabolic complications.

Materials and methods

Patients between 18 and 50 years old who were followed up by our Neurology Outpatient Clinic between June 2012 and January 2014 and diagnosed with epilepsy were evaluated. The ILAE 1989 classification was used for the epilepsy types of the patients. Carbamazepine and valproic acid monotherapy were selected. Those aged < 18 and > 50 years, those with the diagnoses of hypertension, hyperlipidemia, endocrine disease, diabetes mellitus, acute/chronic cardiovascular, lung, liver and kidney disease, rheumatologic disease and those who receive multiple antiepileptic treatment, those who used multiple antiepileptics within the last 6 months, those with the diagnoses of central nervous system or other malignant diseases, smokers, alcoholics, and subjects presented with symptoms of infection, patients with head injury and pregnant or lactating women were excluded from the study. Those with a body mass index (BMI) of > 25 kg/m^2 and those who were found to have endocrine disorders (diabetes mellitus, thyroid dysfunction) in laboratory tests were excluded from the study. Using the determined criteria, the study was conducted until 30 patients in each of the VPA and CBZ groups were reached. The dose and duration of drug use were recorded in all patients. The control group consisted of 30 healthy volunteers in line with the criteria determined for the patient group. Informed consent form was obtained from the patients participated in the study. The approval for the study was obtained from the local ethics committee (17/3/24.05.2012).

Collection and study of serum samples

For adiponectin and carnitine levels, 10 ml of venous blood sample was taken from the antecubital region of the patients and healthy volunteers in the morning following 12 h of fasting and centrifuged at 3000 rpm for 10 min. The serums were placed in two separate Eppendorf tubes and stored at − 80 °C until the study. Before the study, the samples were kept at − 20 °C for one night and at + 4 °C for another night. The serum samples and study kits were kept at room temperature for approximately 2 h on the day of study. Blood samples were collected only after the subjects had been free from seizures for at least 1 week.

Adiponectin was studied using the Enzyme-Linked Immuno Sorbent Assay (ELISA) method (BioVendor, Lot: RD191023100, Czech Republic). The analysis results were calculated as ng/ml according to the manufacturer's instructions.

Carnitine was studied using the ELISA method (CUSABIO, lot: CSB-E 13606 h, China). The analysis results were calculated as ng/ml according to the manufacturer's instructions.

Statistical analysis

The normality of the data was checked by the Kolmogorov–Smirnov test, and the parametric methods of Student *t* test and one-way analysis of variance (ANOVA) and the non-parametric methods of Mann–Whitney *U* test were used as statistical tests to compare the difference between two independent means. Numerical variables were expressed as mean ± SD, minimum–maximum, and categorical variables *n* (%). The Spearman's rank-order correlation was used to analyze the correlation between drug dose, duration of drug use, and carnitine and adiponectin levels. A two-way *p* value of < 0.05 was considered significant. All analyses were

performed in the computer environment using the SPSS 21.0 statistical software package.

Results

The mean age of the patients receiving CBZ was 34 (±10.4) years, the mean age of the patients receiving VPA 35.03 (±8.9) years, the mean age of the control group was 34.93 (±7.5) years, and there was no statistically significant difference between the three groups in terms of mean age ($p > 0.05$). Fifty percent of the patients using CBZ ($n = 15$) were female, 60% ($n = 18$) of the patients using VPA were female, 53.6% ($n = 16$) of the control group were female, and there was no statistically significant difference between the groups ($p = 0.73$). The most common seizure type was generalized tonic clonic seizure in the VPA group, while it was complex partial seizure in the CBZ group. The mean serum carnitine level was 5166.55 ng/ml (±1954.92) in the patients using CBZ, 4224.56 ng/ml (±2055.54) in the patients using VPA, 5802.64 ng/ml (±3422.57) in the control group and serum carnitine level was lower in the groups using both drugs than in the control group (Table 1). The mean serum adiponectin level was 13,606.51 ng/ml (±5915.92) in the patients using CBZ, 11,986.58 ng/ml (±5367.82) in the patients using VPA, 14,033.43 ng/ml (±5646.34) in the control group and serum adiponectin level was lower in the groups using both drugs than in the control group. There was no statistically significant difference in the decrease in serum adiponectin and serum carnitine level between the patients receiving CBZ and VPA and the control group ($p = 0.780$, $p = 0.163$ and $p = 0.384$, $p = 0.360$, respectively). (Fig. 1). There was a negative but insignificant correlation between drug dose and serum adiponectin and serum carnitine level in the patients receiving VPA ($p = 0.268$, $r = –0.209$ and $p = 0.054$, $r = –0.356$, respectively). (Fig. 2). There was a negative but insignificant correlation between drug dose and serum adiponectin and serum carnitine level in the patients receiving CBZ ($p = 0.205$, $r = –0.238$ and $p = 0.347$, $r = –0.178$, respectively). (Fig. 3). There was a negative but insignificant correlation between duration of drug use and serum adiponectin and serum carnitine level

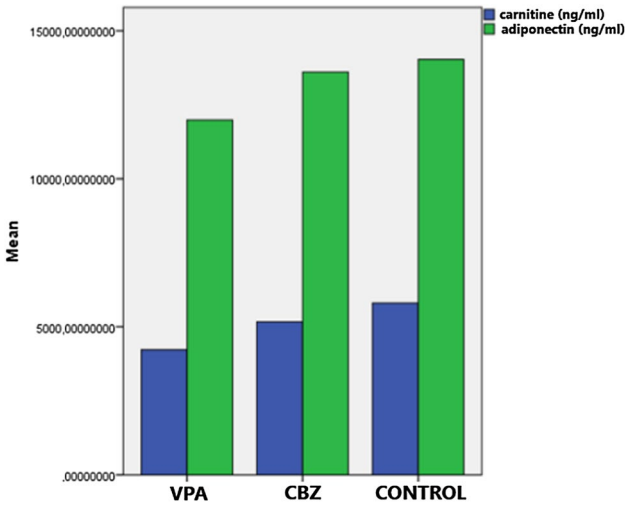

Fig. 1 Mean serum carnitine and adiponectin levels of therapy groups and control group

Table 1 Demographic and clinical characteristics of patient and control groups

	CBZ ($n = 30$)	VPA ($n = 30$)	Control ($n = 30$)
Age*	34 ± (10,4)	35,03 ± (8,9)	34,93 ± (7,5)
Gender**			
Female	15	18	16
Male	15	12	14
Seizure type			
Generalized tonic clonic seizure	2	24	
Compleks partial seizure	26	1	
Absence	0	1	
Myoclonic	0	3	
Simple partial seizure	2	1	
Drug dose (mean) mg/day	801,7 ± 326 (400–1500)	725 ± 399,3 (200–1500)	
Drug use time			
Median (min–max) month	12 (6–240)	21 (6–360)	
BMI kg/m^2***	21.9 ± 3.6	22.1 ± 3.7	21.7 ± 3.7
Adiponectin ng/ml	13,606,5 ± 5915,9	11,986,6 ± 5367,9	14,033,4 ± 5646,3
Carnitine ng/ml	5166,6 ± 1954,9	4224,6 ± 2055,5	5802,6 ± 3422,6

*$p > 0,05$, **p = 0,73, ***p = 0.308

CBZ carbamazepine, *VPA* Valproic acit, *BMI* Body mass index

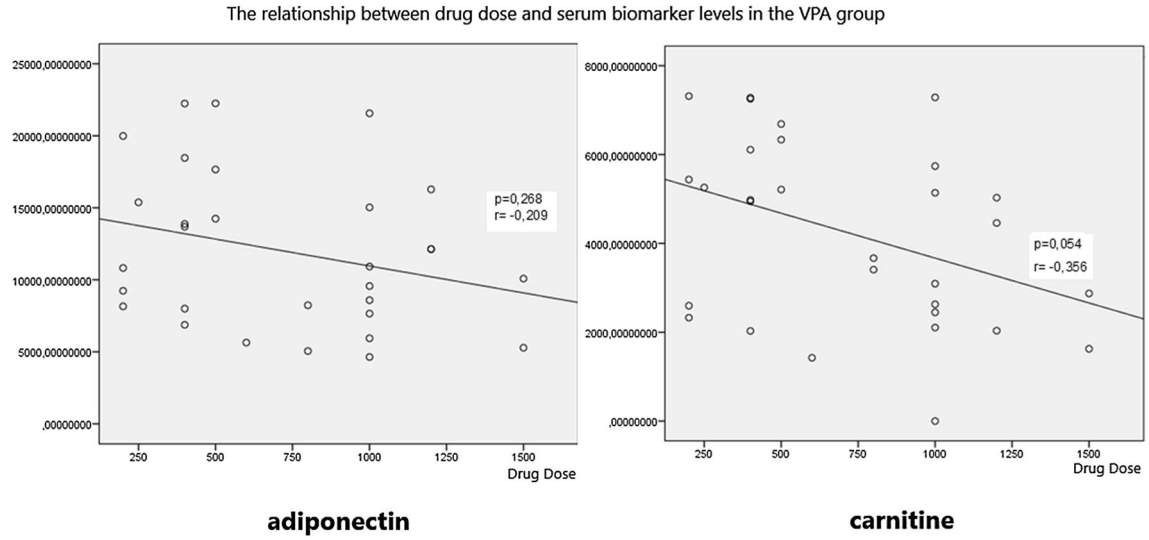

Fig. 2 Serum carnitine and adiponectin level – VPA therapy duration correlation graphic. X-axis shows serum carnitine and adiponectin levels in µmol/l and y-axis shows drug dose of VPA treatment of patients. Every single dot represents a patient in the graphic. There was a negative but insignificant correlation between drug dose and serum adiponectin level in the patients receiving VPA ($p=0.268$, $r=–0.209$). There was a negative but insignificant correlation between drug dose and serum carnitine level in the patients receiving VPA ($p=0.054$, $r=–0.356$)

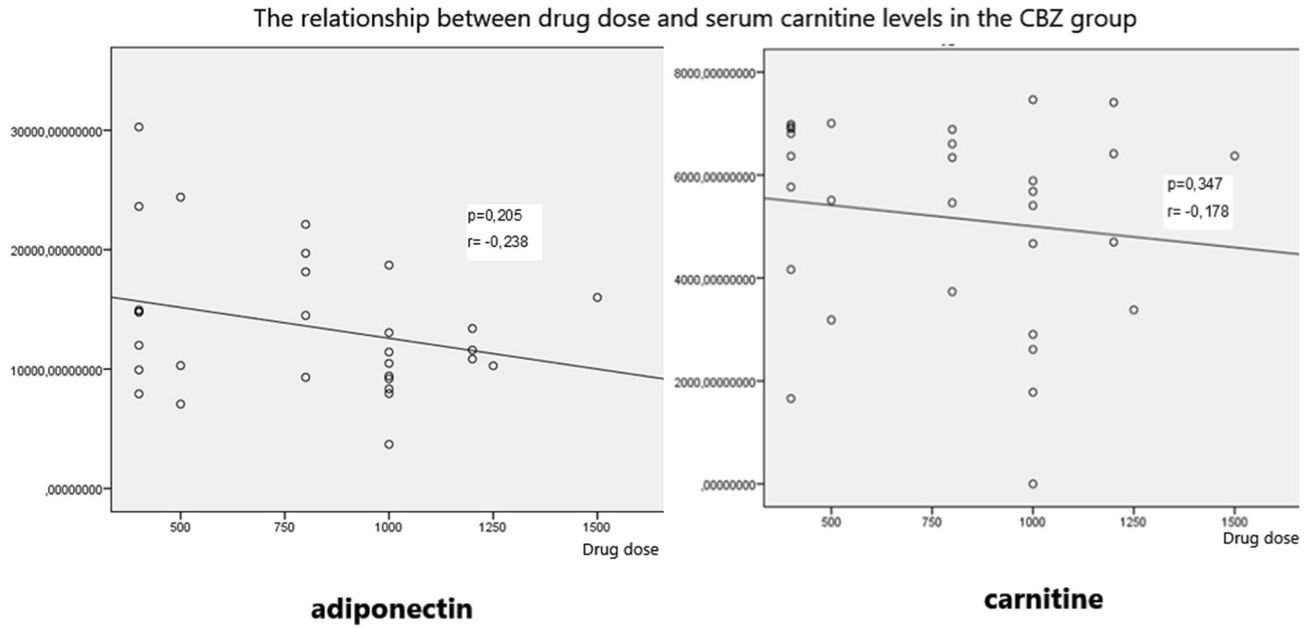

Fig. 3 Serum carnitine and adiponectin level – CBZ therapy duration correlation graphic. X-axis shows serum carnitine and adiponectin levels in µmol/l and y-axis shows drug dose of CBZ treatment of patients. Every single dot represents a patient in the graphic. There was a negative but insignificant correlation between drug dose and serum adiponectin level in the patients receiving CBZ ($p=0.205$, $r=–0.238$). There was a negative but insignificant correlation between drug dose and serum carnitine level in the patients receiving CBZ ($p=0.347$, $r=–0.178$)

in the patients receiving VPA ($p=0.305$, $r=–0.194$ and $p=0.618$, $r=–0.095$, respectively). (Fig. 4). There was a negative but insignificant correlation between duration of drug use and serum adiponectin and serum carnitine level in the patients receiving CBZ ($p=0.526$, $r=–0.120$ and $p=0.782$, $r=–0.053$, respectively) (Fig. 5).

In the patients receiving CBZ and VPA, there was no significant difference in serum adiponectin and carnitine

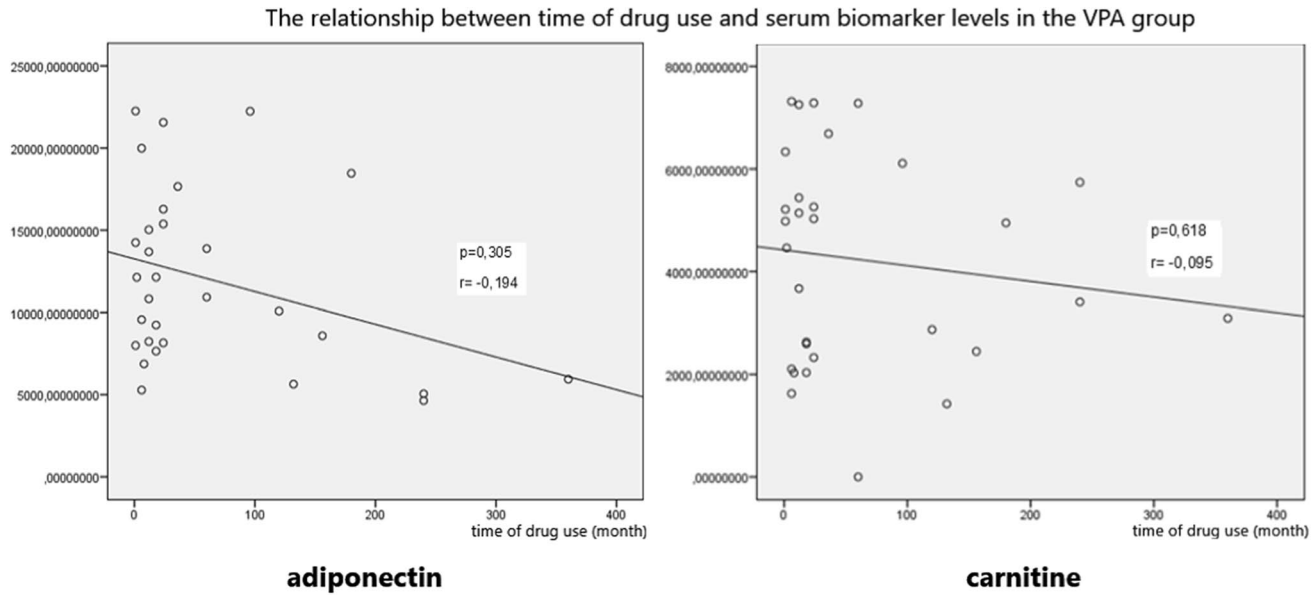

Fig. 4 Serum carnitine and adiponectin level – VPA therapy duration correlation graphic. X-axis shows serum free carnitine levels in µmol/l and y-axis shows duration of VPA treatment of patients in months. Every single dot represents a patient in the graphic. There was a negative but insignificant correlation between duration of drug use and serum adiponectin level in the patients receiving VPA ($p=0.305$, $r=–0.194$). There was a negative but insignificant correlation between duration of drug use and serum carnitine level in the patients receiving VPA ($p=0.618$, $r=–0.095$)

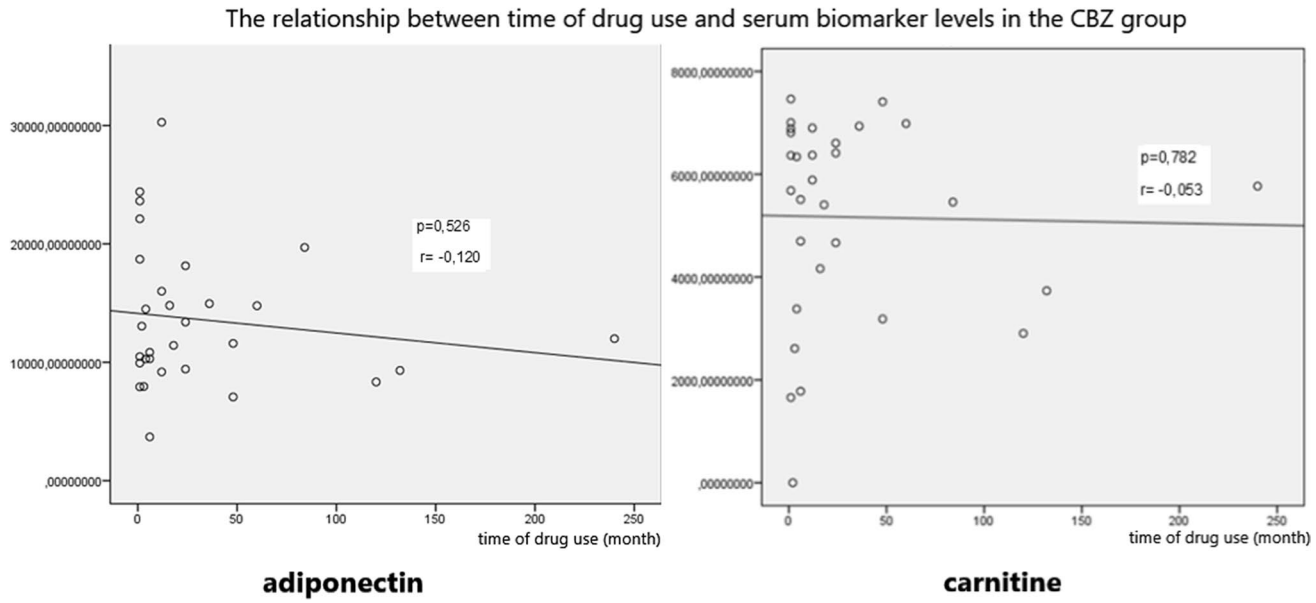

Fig. 5 Serum carnitine and adiponectin level – CBZ therapy duration correlation graphic. X-axis shows serum free carnitine levels in µmol/l and y-axis shows duration of CBZ treatment of patients in months. Every single dot represents a patient in the graphic. There was a negative but insignificant correlation between duration of drug use and serum adiponectin level in the patients receiving CBZ ($p=0.526$, $r=–0.120$). There was a negative but insignificant correlation between duration of drug use and serum carnitine level in the patients receiving CBZ ($p=0.782$, $r=–0.053$)

levels between genders ($p=0.373$, $p=0.724$ and $p=0.068$, $p=0.295$, respectively).

Discussion

In our study, no significant difference was found between the epilepsy patients on VPA and CBZ monotherapy and the healthy control group in terms of serum adiponectin and carnitine levels. There was also no significant correlation between duration of drug use and dose of both drugs and adiponectin and carnitine levels.

All current data indicate that VPA treatment is associated with a significant increase in body weight [22, 23]. VPA-induced weight gain is associated with basal hyperinsulinemia and insulin resistance (23). It has been reported that serum levels of an adipose-derived hormone adiponectin [24, 25], which plays a role in insulin sensitivity and energy hemostasis, decreased in VPA-related obesity [26, 27]. Various studies have shown that the levels of adiponectin, leptin and insulin increase and LDL (low-density lipoprotein) decreases in underweight individuals using VPA compared to similar control groups [28, 29]. Some studies have shown an inverse correlation between adiponectin level and body weight [28]. In a study conducted on mice, it was shown that body weight and epididymal adipose tissue decreased with adiponectin expression [30]. In the same study, it was reported that VPA slowed down the gene expression of adiponectin in a dose- and time-dependent manner [30]. In a different study, it was found that serum adiponectin levels were lower in patients who gained weight as a result of using VPA compared to those without weight gain [28]. In our study, we found that serum adiponectin levels were lower in the patients on VPA monotherapy than in the control group, regardless of weight changes; however, there was no statistically significant difference between the two groups. We are of the opinion that our study is not consistent with the literature because we did not consider VPA use and weight changes in the patient group. Moreover, BMI was within normal limits in our groups, and we think that this may also have an effect on our results. In our study, we found that there was a decrease in serum adiponectin levels as the duration of drug use and dose increased, but it was not statistically significant. Our different results from the literature may be due to our methodology. We think that the analysis of the correlation with serum drug level may make the results more effective. Furthermore, we are of the opinion that the analysis of the changes in drug dose and serum adiponectin may be more reliable in explaining the correlation between dose and adiponectin.

It has also been reported that CBZ treatment is associated with low weight gain [31] or is not associated with weight gain [32]. In addition, although a correlation between leptin [33], a protein product of adipocytes, and weight gain has been reported [34], no correlation between CBZ and leptin has been reported [32, 35]. There is no adult study investigating the correlation between adiponectin, an adipose-derived hormone, and CBZ treatment. In our study, there was no correlation between the use of CBZ and serum adiponectin. A decrease was found in adiponectin levels as CBZ drug dose and duration of use increased; however, it was not statistically significant. When CBZ is considered to cause low weight gain, the correlation between VPA and adiponectin can also be expected to be seen in CBZ treatment, in other words, adiponectin levels decrease with drug dose or duration of use. In our study, the serum adiponectin level of the CBZ group was lower than that of the control group, and adiponectin level decreased as drug dose and duration of use increased, but there was no statistically significant correlation.

In our study, the serum carnitine levels of the patients using VPA were found to be lower than that of the healthy control group, but this was not statistically significant. In the literature, no correlation has been found between VPA dose and duration of use and carnitine level [36, 37]. In our study, it was found that serum carnitine level decreased as VAP dose and duration of use increased, but this was not statistically significant, and there was no significant correlation between drug dose and duration of use, and carnitine level. Different results have been reported in the studies investigating the correlation between CBZ use and serum carnitine levels. Other than the study reporting decreased serum carnitine level [18], the exact opposite was also argued [38]. In our study, we found that the serum carnitine levels of the patients using CBZ were lower than that of the control group, but there was no statistically significant difference. Although serum carnitine levels decreased with CBZ dose and duration of use, no statistically significant correlation was found. Since more than 90% of carnitine is stored in tissues such as liver, muscle, brain, the measurement of carnitine level from an area where it is found less may have an effect on our determinations.

Plasma adiponectin levels are significantly lower in males than in females [39]. In our study, it was observed that there was no significant difference in serum adiponectin level between genders in patients receiving VPA treatment ($p=0.068$).

In conclusion

We found in our study that as the dose and duration of CBZ and VPA decreased in epilepsy patients receiving CBZ and VPA monotherapy, it reduced serum carnitine and adiponectin levels, but it did not cause a statistically significant change and there was no significant correlation between

these parameters. There is a need for more extensive studies with larger number of patient populations to investigate the effect of these drugs on serum levels of adiponectin and carnitine with an antioxidant effect, which have a role in metabolic functions. In patients treated with long-term antiepileptic drugs, the addition of antioxidant agents may be beneficial.

Compliance with ethical standards

Conflict of interest We declare that we have no financial and personal relationships with other people or organizations that can inappropriately influence our work. We declare that we have no conflict of interest.

Ethical approval The approval for the study was obtained from the Atatürk university local ethics committee (1/10/12.03.2012).

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