

Effects of carbamazepine on serum leptin, insulin levels and oxidative stress in epileptic patients

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ABSTRACT

Objectives: To assess the effect of carbamazepine (CBZ) monotherapy in male adult epileptic patients on serum leptin, insulin levels, body mass index and oxidative stress represented by serum malondialdehyde (MDA) in comparison to healthy controls.

Patients and methods: To achieve the aims of the current study, a case-control study design was adopted. A total of 38 male adult patients with primary generalized epilepsy, on continuous CBZ monotherapy, for at least six months before participation in the study, were collected over the period from Sept. 2010 to Jan. 2011. Forty apparently healthy male volunteers without previous history of epilepsy were recruited as controls. Fasting blood samples were taken and sera were separated and used to measure serum levels of leptin and insulin, and MDA. Body mass index (BMI) was calculated as weight in kilograms divided by the squared height in meters.

Results: The results of this study revealed that there was insignificant difference in BMI, serum leptin and insulin between male epileptic adult patients and their matched control subjects. The results also revealed that male epileptic adult patients had a significantly higher ($p < 0.001$) serum MDA compared to their matched control subjects.

Conclusion: Carbamazepine is a relatively low risky antiepileptic drug (AED) in terms of obesity, while it can cause oxidative stress as reflected by an elevated serum MDA in comparison to controls.

Keywords: Epileptic patients, carbamazepine, BMI, leptin, insulin, malondialdehyde

الخلاصة

الأهداف: لتقييم تأثير الكاربامازيبين كعلاج أحادي في مرضى الصرع من البالغين الذكور على مستوى اللبتين والأنسولين في مصل الدم وجهد الأوكسدة ممثلاً بالمالونديليهايد ومؤشر كتلة الجسم بالمقارنة مع مجموعة ضبط.

المرضى وطرق العمل: للوصول الى أهداف هذه الدراسة، تم تحديد تصميم معين لهذه الدراسة. شملت الدراسة 38 من الذكور البالغين المصابين بالصرع الابتدائي الشامل على علاج أحادي مستمر بالكاربامازيبين لفترة لا تقل عن 6 أشهر. تم انتقاء الحالات وفق ضوابط خاصة للفترة من سبتمبر 2010 الى كانون الثاني 2011. شملت الدراسة أيضا 40 من الذكور الأصحاء بلا تاريخ سابق للصرع كمجموعة ضبط. سحبت عينات دم في حالة الصيام صباحا وتم استخدام المصل المستحصلة لقياس مستوى اللبتين والأنسولين ومستوى المالونديليهايد. تم حساب مؤشر كتلة الجسم باستخدام معادلة وزن الجسم بالكيلوغرام مقسما على مربع الطول بالأمتار.

النتائج: أظهرت النتائج تأثيراً غير معنوي لعقار الكاربامازيبين على مؤشر كتلة الجسم ومستوى اللبتين والأنسولين في مصل الدم لمرضى الصرع من الذكور بالمقارنة مع مجموعة الضبط. أظهرت النتائج أيضا ان زيادة معنوية في مستوى

المالونديليهايد عند مرضى الصرع من الذكور المثبتين على الكاربامزابين كعلاج أحادي مستمر بالمقارنة مع مجموعة الضبط.

الاستنتاج: من الممكن الاستنتاج ان الكاربامزابين كعقار مضاد للصرع هو نوعا ما قليل المخاطر فيما يتعلق بزيادة الوزن وحالة المتلازمة الأيضية ولكن ممكن ان يسبب زيادة في جهد الأكسدة (متمثلاً بزيادة مستوى المالونديليهايد في مصّل الدم بالمقارنة مع مجموعة الضبط).

مفتاح الدلالة: مرضى الصرع, الكاربامزابين, دلالة كتلة الجسم, اللبتين, الأنسولين, المالونديليهايد.

Many types of endocrine and metabolic dysfunctions are associated with epilepsy and its medications that may impair individual's overall function.^(1,2) Epilepsy and its medications are associated with weight changes in which weight gain is the most common and distressing problem.⁽³⁾ Weight gain is a difficult problem at any age, particularly in adolescence, a period of increased awareness to body weight and image.⁽⁴⁾ Weight gain not only affects body image and self-confidence with adverse psychological effects leading to non-compliance to medications,⁽⁵⁾ but also associated with pathologic consequences related to obesity as dyslipidemia, hypertension, diabetes mellitus and atherosclerosis with its related vascular complications.⁽⁶⁾ Epilepsy and antiepileptic drugs(AEDs) may alter weight homeostasis regulating process including the two main homeostatic hormones, leptin and insulin. Increased blood levels of leptin and insulin due to leptin and insulin resistances are observed in patients with epilepsy.^(7,8)

Leptin controls weight homeostasis through two main neuropeptidergic systems that both project into the arcuate nucleus, neuropeptide Y(NPY) and pro-opiomelanocortin (POMC) expressing neurons.^(9,10) These neurons exert two opposite functions. NPY expressing neurons are anabolic, upon stimulation, food intake and metabolic efficiency are increased while energy expenditure is decreased. In contrast, the counterpart POMC expressing neurons are catabolic, upon stimulation, food intake and metabolic efficiency are decreased while energy expenditure is increased.⁽¹¹⁾

It has been reported that increased generation of free radicals or decreased

activity of antioxidant defense systems can cause some forms of seizures and in addition can increase the risk of seizure recurrence.^(12,13) Many AEDs are metabolized to generate reactive metabolites with the capability of covalent binding to macromolecules as proteins or other vital biomolecules and hence eliciting systemic toxicity.^(13,14) Lipid peroxidation caused by increased generation of free radicals or decreased activity of antioxidant defense systems have been suggested to be critically involved in seizure control.⁽¹²⁾ The aims of this study are to assess the effect of CBZ monotherapy in male epileptic patients on BMI, serum leptin, insulin and MDA levels (as a representative of oxidative stress), in comparison with healthy controls.

Patients and methods

A. Epileptic patients

This study included 38 male adult patients with primary generalized epilepsy, on continuous carbamazepine (CBZ) (Tegretol) [Novartis, Switzerland] monotherapy, for at least six months before participation in the study. These patients were referred from the private clinic of a consultant neurologist over the period from Sept. 2010 to Jan. 2011. Patients with the following criteria were excluded from this study:

1. Patients with secondary epilepsy.
2. Patients with other neurological, medical, or psychiatric disorders.
3. Patients with rapidly progressive disorders that could alter their weight.
4. Patients with family history of body weight disorders.
5. Patients treated with other AEDs beside CBZ.

6. Patients treated with CBZ for less than six months.

Approval to conduct this study was obtained from the ethical committee of the Local Health Authority in Mosul City and from the College of Medicine-University of Mosul. Blood samples were taken from them and assay of serum leptin, MDA and insulin levels were done.

B. Control subjects

Forty apparently healthy male volunteers without previous history of epilepsy were recruited as controls with age matching to the patients group. The control group was judged free of any illness by history and clinical examination. They were included in the study to compare the normal values for serum leptin, insulin and MDA levels.

C. Specimen collection and analysis

Samples from the control (friends and relatives) and the patients were collected and assay of serum levels of leptin, insulin, MDA and TAS were done as in the patients group. Serum leptin was measured by enzyme linked immunosorbent assay (ELISA) technique, using the IBL leptin ELISA Kit (Germany), which is an immunoassay for the quantitative in vitro diagnostic measurement of leptin in serum and plasma. Serum insulin was also measured by ELISA kit (DRG-Germany). Serum MDA levels were measured using TBA assay method.⁽¹⁵⁾ Body mass index (BMI) was calculated using the following equation:

$$\text{BMI} = \text{Weight (Kg)} / \text{Height (m}^2\text{)}^{(16)}$$

Statistical analysis

The data obtained in the current study were analyzed using Statistical Package for Social Sciences (SPSS) (version 16). Standard statistical methods were used to determine the mean and standard deviation. Unpaired t-test was used to compare the results of different biochemical parameters of epileptic adult patients with their matched controls.

Results

Table (1) and (2) demonstrated the demographic characteristics of the male epileptic adult patients and their matched control subjects respectively.

Table (3) demonstrated the comparison of BMI, serum levels of leptin, insulin and MDA between male epileptic adult patients receiving continuous CBZ monotherapy and their matched control subjects.

The results of this study revealed that there was insignificant difference in BMI, serum leptin and insulin between male epileptic adult patients receiving continuous CBZ monotherapy and their matched control subjects. The results also revealed that male epileptic adult patients on continuous CBZ monotherapy had a significantly higher ($p < 0.001$) serum MDA compared to their matched control subjects.

Table (1): The characteristics of the male epileptic adult patients.

Parameters	Mean± SD Number=38
Patients age (years)	29.54±5.36
Body mass index (BMI) (kg/m ²)	24.59±2.92
Duration of illness (years)	3.25± 2.05
Duration of using CBZ (months)	25.09± 20.08
Dose of CBZ (mg/day)	590.90±144.44

Table (2): The characteristics of the control adult subjects.

Parameters	Mean± SD Number=40
Subjects age (years)	30.05±5.95
BMI (kg/m ²)	23.33±1.91

Table (3): BMI and serum levels of leptin and malondialdehyde (MDA) in the male epileptic patients and their matched control subjects.

Parameters	Epileptic patients	Control subjects	P Value
BMI (kg/m ²) Mean ± SD	24.59±2.92	23.33±1.91	NS
Leptin (ng/ml) Mean ± SD	4.60±1.20	3.91±1.96	NS
MDA (µMol/L) Mean ± SD	1.88±0.19	0.95±0.22	<0.001
Insulin (mU/L)	8.37± 7.2	8.56± 7.00	NS

NS: statistically non-significant

Discussion

Epilepsy is a common chronic neurological problem. Its treatment is often for years or even lifelong.⁽¹⁷⁾ It should be noted that patients with epilepsy may manifest metabolic adverse effects throughout the course of their management with anti-epileptic drugs (AEDs), which on long-term may impair individual's overall function.⁽¹⁸⁾ Clinically significant weight gain has been reported with several AEDs including the conventional agents valproate (VPA), CBZ and the newer medications gabapentin and vigabatrin and may result in lack of compliance with or even discontinuation of therapy.⁽¹⁹⁾ Numerous studies reported weight gain with VPA in up to 50–70% of the patients.^(3,20,21) Its etiology is most likely multi-factorial and controversial. Weight gain appears to be less a problem with CBZ than with VPA. The proposed mechanism of CBZ-associated weight gain can arise from edema but has also been associated with increased appetite and food consumption in the absence of edema.⁽²²⁾ The CBZ-induced edema has been postulated to be caused by drug-induced alterations in the secretion of antidiuretic hormone (ADH), although studies only inconsistently show an effect of the drug on plasma ADH levels.⁽²³⁾

Our study revealed insignificant effect of CBZ on BMI which is consistent with the studies of Biton,⁽²⁴⁾ and Uludag *et al.*⁽²⁵⁾ but inconsistent with the studies of Richens *et al.*⁽²⁶⁾ and Hogan *et al.*⁽²⁷⁾ They reported that between 15% and 25% of patients treated with CBZ developed weight gain. The two common homeostatic hormones, insulin and leptin have been expected to form a common link to weight gain in epilepsy with the use of some AEDs.

Our study also revealed insignificant effect of CBZ on serum leptin level and insulin. Rauchenzauner *et al.*,⁽²⁸⁾ compared two patient groups that use VPA and non-VPA AEDs regarding serum leptin and insulin levels. They concluded that non-VPA AEDs, (lamotrigine and oxcarbazepin) were thought to have no effect on leptin and insulin levels. There are a few studies such as ours that evaluate effect of CBZ treatment directly on serum leptin and insulin levels. Our findings are consistent with

the results of Uludag *et al.* and Hamed *et al.*^(25,29)

Our study reported an elevated serum MDA level in epileptic male patients on CBZ therapy in comparison with healthy controls. Our findings are consistent with the results of the study conducted by Aycicek and Iscan.⁽³⁰⁾ They reported a markedly increased serum total peroxide levels in CBZ treated and untreated epileptic patients compared to healthy controls. Solowiej and Sobaniec⁽³¹⁾ on studying the effect of CBZ and VPA therapy on antioxidant enzyme activity and serum lipid peroxidation in young epileptic patients, concluded that MDA concentration was elevated in all epileptic patients, significantly both in VPA monotherapy and in polytherapy, while insignificantly in newly diagnosed epileptics and in CBZ monotherapy. In agreement with our findings the study conducted by Nemade *et al.*⁽³²⁾ They reported that epileptic patients on regular or irregular treatment (phenytoin and CBZ), have an increased serum MDA levels compared to healthy controls. On going with our findings, the two year prospective study conducted by Yuksel *et al.*,⁽³³⁾ they concluded from studying changes in the antioxidant system in epileptic children receiving antiepileptic drugs, that during CBZ therapy, lipid peroxidation levels increased when compared with the control group. On the other hand Liu *et al.*⁽³⁴⁾, reported no significant differences in lipid peroxidation in epileptic children on CBZ therapy compared with the controls.

In conclusion CBZ monotherapy can be regarded as a safe drug with regard to BMI, serum leptin and insulin levels, but it can cause oxidative stress as represented by elevated serum MDA levels.

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