Research Article / Araştırma Makalesi

Evaluation of Serum Lipid Levels in Patients Using Carbamazepine

Karbamazepin Kullanan Hastalarda Serum Lipid Düzeylerinin Değerlendirilmesi

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Abstract: Epilepsy is a neurological disease that requires long-term drug therapy. Carbamazepine (CBZ) is a drug that is effective in partial seizures, including complex partial seizures, and tonic-clonic seizures. It was aimed to evaluate the effect on serum lipid profile in patients who used CBZ. Medical biochemistry laboratory data between January and December 2021 were analyzed retrospectively. Patients (n=59) who used monotherapy and at least 2 years of CBZ were included in the study. Patients under 18 years of age were not included. In the control group, 34 healthy people with normal blood parameters, who applied to outpatient clinics for different reasons at the same age, and did not have a disease that would affect the lipid profile, were selected. The mean age of the patients was 36 ±8 years. LDL-cholesterol levels were found to be higher in patients treated with carbamazepine compared to the control group ($p<0.05$). There was no significant difference in serum triglyceride (TG), and HDL-cholesterol levels in the patient and control groups ($p>0.05$). There was no gender difference in the effect of carbamazepine on LDL-cholesterol ($p>0.05$). High serum LDL-cholesterol levels cause atherosclerosis and coronary artery disease. The lipid profile of carbamazepine, which is used regularly at the therapeutic level, changes. Due to the association of high LDL-cholesterol levels with atherosclerosis, it is important to monitor lipid levels in patients using CBZ, especially considering the long duration of use of this pharmacotherapy.
Keywords: Carbamazepine, cholesterol/blood, lipid/blood, LDL-cholesterol, HDL-cholesterol

Özet: Epilepsi, uzun süreli ilaç tedavisi gerektiren nörolojik bir hastalıktır. Karbamazepin (CBZ), kompleks parsiyel nöbetler dahil parsiyel nöbetlerde ve tonik-klonik nöbetlerde etkili olan bir ilaçtır. Bu çalışmada, karbamazepin kullanan hastalarda serum lipid profili üzerine etkisinin değerlendirilmesi amaçlandı. Ocak-Aralık 2021 tarihleri arasındaki tıbbi biyokimya laboratuvar verileri geriye dönük olarak analiz edildi. Çalışmaya monoterapi ve en az 2 yıl CBZ kullanan hastalar (n=59) dahil edildi. 18 yaş altı hastalar dışlandı. Kontrol grubu olarak kan parametreleri normal, farklı nedenlerle polikliniklere başvuran, aynı yaşta, lipid profilini etkileyecek bir hastalığı olmayan 34 sağlıklı kişi seçildi. Hastaların yaş ortalaması 36±8 idi. Karbamazepin ile tedavi edilen hastalarda kontrol grubuna göre LDL-kolesterol düzeyleri daha yüksek bulundu ($p<0,05$). Hasta ve kontrol grupları arasında trigliserit (TG) ve HDL-kolesterol düzeyleri arasında anlamlı fark yoktu ($p>0,05$). Karbamazepinin LDL-kolesterol üzerindeki etkisinde cinsiyet farkı yoktu ($p>0.05$). Yüksek serum LDL-kolesterol seviyeleri kesinlikle ateroskleroz ve koroner arter hastalığına neden olmaktadır. Terapötik düzeyde düzenli olarak kullanılan karbamazepinin lipid profili değişmektedir. Yüksek LDL-kolesterol düzeylerinin ateroskleroz ile ilişkisi nedeniyle, özellikle bu farmakoterapinin uzun süreli kullanımı göz önüne alındığında, CBZ kullanan hastalarda lipid düzeylerinin izlenmesi önemlidir.
Anahtar Kelimeler: Karbamazepin, kolesterol/kan, lipid/kan, LDL-kolesterol, HDL-kolesterol.

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1. Introduction

Epilepsy is a common serious neurological disorder characterized by recurrent seizures that can occur at any age, race, and social class. Epilepsy begins after birth and affects the entire age range, and has many causes, with many different seizure types and identifiable syndromes. Different studies have been conducted on the prevalence of epilepsy in our country, and it can be said to be approximately 7-10 per thousand (1, 2).

Carbamazepine is a drug that is effective in partial seizures, including complex partial seizures, and tonic-clonic seizures. After absorption from the gastrointestinal tract, it is metabolized in the liver by the cytochrome P-450 enzyme system. Antiepileptic drugs are important in preventing seizures. Depending on the type of epileptic seizure, the duration of treatment may last four to five years, sometimes for a lifetime. The side effects of the use of antiepileptic drugs vary. In addition to its early side effects, behavioral, memory, hormonal, and hematological side effects can be observed in long-term use. Although it is thought that deaths from cardiovascular diseases are more common in epileptic patients compared to the general population and that this situation is not directly related to the use of antiepileptic drugs, the cause is still unknown (3, 4).

Atherosclerosis is the most common cause of death in developed countries; it causes serious mortality and morbidity by causing diseases such as cerebrovascular disease, coronary heart disease, and peripheral artery occlusion (5). The World Health Organization has reported that atherosclerosis will be the first cause of mortality worldwide shortly. Although clinical signs of atherosclerosis are not typically seen until the sixth decade of life, many risk factors for coronary artery disease and stroke facilitate the development of atherosclerosis in the early stages of life (6). The relationship between serum lipid and lipoprotein concentrations and atherosclerosis is known. It has been shown that drugs used for a long time can affect serum lipid surfaces in different ways (7).

2. Materials and Methods

2.1. Study design

All the methods in the study were approved by the Non-Interventional Clinical Research Ethical Committee of Eskişehir Osmangazi University (Date: 15/02/2022 #14). The study was carried out by the statement of the Helsinki Declaration.

Patients over the age of 18 years who were admitted to the neurology outpatient clinic with a diagnosis of epilepsy between January and December 2021 were included in the study. Laboratory data of the patients were retrospectively analyzed. Serum carbamazepine levels of 72 patients were measured between these dates. Patients (n=59) who were on monotherapy and CBZ for at least 2 years were included in the study. Patients with chronic diseases other than epilepsy, pregnant and lactating women, and patients who reported chronic alcohol consumption were excluded.

All these data were obtained from hospital automation records. The control group was composed of 34 healthy individuals who applied to the outpatient clinics for control or administrative reasons, did not have any disease that would affect their lipid profile, had normal blood parameters (blood serum glucose, liver function tests, and serum creatinine within normal limits) and were the same age as the patient group.

Serum carbamazepine was measured with the Chemiluminescence Microparticle Immunoassay (CMIA) method. The serum lipid panels (HDL-cholesterol, and triglyceride) of the patients and controls were studied using the colorimetric, Endpoint Reaction. LDL-cholesterol levels were determined by using the Friedewald Formula (LDL-cholesterol = (Total cholesterol - HDL-cholesterol) - TG/5) if the triglyceride level was below 400 mg/dL and by direct LDL-cholesterol measurement by using the colorimetric method if the triglyceride level was above 400 mg/dL. Architect C8200 Integrated System (Clinical Chemistry and Immunoassay Analyzer, Abbott Diagnostics, USA) device was used for all these analyses.

2.2. Statistical analysis

Kolmogorov-Smirnov and Shapiro-Wilk tests were used to determine the distribution. Parameters that showed normal distribution were expressed as mean ± standard deviation (SD), and those that did not were expressed as median (25-75 percentile). While evaluating the study data, the Independent Sample T test was used for two-group comparisons of normally distributed parameters, and the Mann-Whitney U test was used for two-group comparisons of non-normally distributed parameters. Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) 21. If $P<0.05$, the difference between the means was considered significant.

3. Results

A total of 59 patients, 24 males, and 35 females, were included in the study. The mean age of female patients was 36 years and 37 years for male patients. The epilepsy duration of the patients included in the study was a minimum of 2 years and a maximum of 23 years. The mean duration of CBZ use was 8.12 ± 4.8 years. CBZ blood levels ranged between 1.39 and 15.6 µg/ml. The duration of antiepileptic use and drug blood levels of the CBZ group are presented in Table 1.

The control group consisted of 17 females and 17 males. The mean age of the control group was 36 years. There was no significant difference between the groups in terms of gender and age ($p>0.05$).

HDL-cholesterol, triglyceride, and LDL-cholesterol levels of the patient and control groups were compared. The mean values of HDL-cholesterol, LDL-cholesterol, and TG in the patient and control groups are presented in Table 1. Mean ± SD, median, and percentile values are presented in Table 1.

Table 1. Demographic and clinical parameters of the epilepsy patient and control groups.

Parameters	Control	Patients	p-value
Age (year)	36	36 ± 8	>0.05*
Gender (n)			>0.05**
Female	17	35	
Male	17	24	
Duration of using carbamazepine (year)	none	8,12 ± 4,8	
Carbamazepine drug level (µg/ml)	none	6,05 ± 4,32	
LDL-cholesterol (mg/dL) (Percentile 25 – 75)	101 (101 ±26)	125 (125±42)	<0.05**
HDL-cholesterol (mg/dL) (Percentile 25 – 75)	53 (40 – 66)	54 (40 – 65)	>0.05*
TG (mg/dL) (Percentile 25 – 75)	119 (75 – 133)	143 (107 – 165)	>0.05*

*Values are mean ± SD, significance was defined as $P < 0.05$. *Independent Sample T test*
***Mann Whitney U*

4. Discussion

Epilepsy is a disease that often requires lifelong medication. Long-term use of medication is associated with serious potential side effects. It has been known for many years that dyslipidemia is an important risk factor for atherosclerosis. LDL-cholesterol plays an important role in the atherosclerotic process by increasing endothelial permeability, increasing the formation of foam cells, and increasing the retention of lipoproteins in blood vessels (8). In addition, one of the side effects caused by the use of antiepileptics is increased oxidative stress. The cell structure is damaged as a result of chemical reactions of high amounts of free radicals with cell membrane lipids, proteins, and nucleic acids.

As in many diseases, it can be said that atherosclerosis is caused by increased oxidative stress (9). In the literature, there are controversial results of CBZ use on serum lipids. Chuang et al. reported that long-term CBZ and other antiepileptic treatments altered vascular risk factors due to increased serum lipid levels (10).

In a study conducted by Deniz et al. in 2011, LDL-cholesterol levels were found to be significantly higher, whereas no difference was observed in HDL-cholesterol levels (11). In a study conducted by Tekgül et al. on newly diagnosed epilepsy patients, no significant change was found in the lipid profile of patients receiving valproate, phenobarbital, and carbamazepine monotherapy before and 2 years after treatment in any group (12). On the contrary, El-Farahaty et al. observed an increase in LDL-cholesterol, and HDL-cholesterol levels in patients using CBZ, but found no significant change in TG (13). In another study published by Büyükgöl in 2020 LDL-cholesterol levels were found to be significantly lower in patients using CBZ compared to the control group (14).

Isojärvi et al. reported that serum HDL-cholesterol concentrations increased after 2 months of carbamazepine treatment, while serum LDL-cholesterol and triglyceride concentrations increased transiently in the first year of the drug. In the study, the increase in serum total cholesterol levels was associated with an increase in serum γ-glutamyltransferase concentrations (15). In a study conducted by Demircioğlu et al. in children, LDL-cholesterol, and HDL-cholesterol levels were found to be significantly higher in patients using CBZ (16).

In a study conducted by Mintzer et al. in 2020, an increase in LDL-cholesterol, and HDL-cholesterol levels and no change in triglyceride levels were observed. In addition, they stated that CBZ provided Class II evidence that it increased serum lipids (17). In a study conducted by Apak et al. in 2008, they reported an increase in HDL-cholesterol levels and a decrease in LDL-cholesterol levels (18).

In our study, we found that only LDL-cholesterol levels were higher in patients using CBZ compared with healthy individuals. No significant change was observed in the HDL-cholesterol and TG levels of the patients. This result is partially compatible with the literature. This may be due to the limited sample size and the retrospective design of the study. In addition, since the study was retrospective, the serum cholesterol levels of the patients at the beginning of drug treatment could not be measured. Since groups could not be formed with the current sample size, the relationship between CBZ use duration and serum lipid levels could not be studied. This is one of the limitations of the study.

All these findings suggest that long-term use of CBZ may be associated with an increase in serum LDL-cholesterol levels and may play a role in the development of atherosclerosis. Since antiepileptic treatments are long-term, the potential side effects of drugs used chronically in treatment should be taken into consideration. However, long-term and prospective studies on this subject will provide more definite results.

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Ethics

Ethics Committee Approval: The study was approved by Eskisehir Osmangazi University Noninterventional Clinical Research Ethical Committee (Decision no: 2022/14, Date: 15.02.2022).

Informed Consent: The authors declared that getting consent from the patients was unnecessary because the study was a retrospective data analysis.

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