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Original Article

# Metabolic Syndrome and Insulin Resistance in Sodium Valproate or Carbamazepine Monotherapy: A Case-control Study

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## ABSTRACT

**Background:** Medications can increase the incidence rate of metabolic syndrome (MetS) and insulin resistance (IR). This study aimed to evaluate the effects of Carbamazepine (CBZ) or Valproate (VPA) as monotherapy on the development of MetS and IR in adult Iranian epileptic patients.

**Methods:** In this observational analytic case-control study, 80 epileptic patients were treated with VPA (40 patients) or CBZ (40 patients) monotherapies for more than 6 months, and 45 age- and sex-matched controls were included.

**Results:** Subjects with MetS or with IR had higher age, weight, waist, FBS, cholesterol, systolic and diastolic pressure, TG, LDL, insulin, BMI, and lower HDL. In MetS and IR, the frequency of VPA or CBZ use was significantly higher than the control group. The multiple regression analysis showed that in VPA-treated epileptic patients, the risk of MetS was increased 19 times higher than controls (OR= 19.20; 95% CI= 2.62-140.23, P=0. 004) and risk of IR was increased 15 and 9 times more than controls (OR=14.83; 95% CI=3.03-72.56, P=0.001) and (OR=9.13; 95% CI=2.55-32.65, P= 0.001), respectively. An increase in the waist, DBP, and insulin level were also shown as important factors in the risk of MetS. In patients under CBZ therapy, the risk of MetS reduced by 17% less than controls and the risk of IR increased 7 times more than controls.

**Conclusion:** Treatment with VPA may increase the likelihood of developing MetS and IR more than the CBZ therapy in epileptic patients in Iran.

**Keywords:** Cholesterol, CBZ therapy, VPA-treated patients

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## Introduction

Epilepsy is one of the most prevalent neurological illnesses, especially in young children and old age people of both males and females of all races. Among the antiepileptic drugs (AEDs), Valproate (VPA) and Carbamazepine (CBZ) are more frequently used for both epileptic and non-epileptic purposes such as bipolar syndrome and migraine prophylaxis (1, 2). Many patients may need a long-term treatment, therefore, understanding the safety of the drugs is important for patients and neurologists. One of the recognized and public side effects of long-term treatment with VPA or CBZ is obesity, which occurs in many patients and is related to important metabolic and endocrine disease (3, 4). Obesity in association with dyslipidemia, hypertension, and IR has an essential role in promoting the development of metabolic diseases and long-term vascular complications (5). In 1988, Reaven described metabolic syndrome (MetS) as a group of metabolic risk factors such as obesity, dyslipidemia, hyperglycemia, and hypertension (6). MetS is a major public health concern and its prevalence is about 24.7-28.8% in the adult population (7). Insulin resistance (IR), adiposity of visceral, dysfunction of endothelium, and atherogenic dyslipidemia can be considered as the central and prominent features of MetS. These impairments are interrelated and can share principal mediators and pathophysiological mechanisms (7). Several studies have reported that there is an increased risk of MetS after the prolonged taking of AEDs, mainly VPA (8). In a study conducted by Kim and Lee (2007), the metabolic and hormonal disturbances in women on AED monotherapy were investigated and it was found that the VPA monotherapy could induce MetS in women more frequently than CBZ, lamotrigine, or topiramate (9). Their findings showed that VPA can more significantly affect the development of MetS than the other. In another study on epileptic patients who were treated with VPA or CBZ, the risk of MetS was similar (2). Previous studies demonstrated that CBZ by activation of the hepatic cytochrome P450 enzyme can be involved extensively in the synthesis and metabolism of cholesterol (10). In patients with CBZ monotherapy, increases in total cholesterol, TG, HDL-C, and low-density lipoprotein cholesterol were reported (11, 12).

Among the above-mentioned criteria, IR and associated factors have an essential role in the development of metabolic dysfunction (13). Previous studies reported controversial results about the risk of IR in epileptic patients treated by VPA or CBZ. Najafi *et al.* (2017) suggested that VPA may not cause IR and could be prescribed safely (14); on the other hand, some clinical studies pronounced a significant IR in epileptic patients treated with VPA (15).

As different studies reported controversial results about the risk of MetS and IR in epileptic patients treated with VPA or CBZ and the paucity of evidence on MetS and IR in the Iranian patients with epilepsy, the present study was conducted to investigate the risk of MetS and IR in two groups of epileptic patients treated with VPA or CBZ and compare them with normal control.

## Methods

### Subjects

This study was performed in a Neurology Clinic in Shiraz between May 2018 to March 2019.

Before data collection, this research was approved by the Medical Research Ethics Committee and Institutional Review Board of Shiraz University of Medical Sciences (Ethical code: ir.sums.med.rec.1397.s34) and all methods were performed following the relevant guidelines and regulations. The written informed consent was obtained from the patients for publication of data. A total of 170 epileptic patients who had taken VPA or CBZ for more than 6 months were identified. Finally, 80 patients taking VPA (n=40) or CBZ (n=40) who met the inclusion criteria and 45 control subjects participated in this study. The exclusion criteria were as follows: (1) patients aged ≤ 18 or > 55 years, (2) polytherapy with other antiepileptic drugs, (3) severe physical and/or mental disability, (4) current pregnancy or lactation, (5) malignancy, (6) monotherapy with CBZ and VPA for less than 6 months. Patients with diabetes or thyroid diseases were not excluded. Patients who had normal social activities were included in this study despite mental deficits or minor physical activity. 45 healthy subjects with matched age and sex were randomly selected as controls.

### Collection of Anthropometric and Laboratory Data

After taking the written informed consent from each participant, the patient was examined by a neurologist and their clinico-medical

history of epilepsy including the type of epilepsy, a dose of CBZ and VPA, and the duration of treatment was recorded in a data-collection form. Also, the history of other related concomitant medical conditions such as thyroid dysfunction, diabetes, hypertension, known endocrinopathies, vascular diseases, lipid metabolism disorders, and a change in body weight after taking AEDs, and malignancy were recorded. Then, the demographic data (age, gender), blood pressure (mm/Hg), and anthropometric parameters of height (cm), weight (kg), and waist circumference (cm) were obtained and recorded from all the participants. Arterial blood pressure was measured using a sphygmomanometer, with an appropriate cuff size suitable for each patient after approximately 15 min of inactivity and rest while seated.

Anthropometric data were measured after 10 h of overnight fasting without shoes and with light clothes. Using a calibrated weighing scale, measurements were conducted. In a standing position, the mid-level between the lateral rib margin and the iliac crest was taken as waist circumference. Body mass index (BMI), which is a person's weight in kilograms divided by height in meters squared ($kg/m^2$), was calculated. The value above 25 $kg/m^2$ was considered as high BMI. Laboratory tests, including LDL-C, HDL-C, TG, total cholesterol (C), serum insulin level, FBS, and high sensitivity C-reactive protein (hsCRP) were evaluated. All the samples were taken from the patients in the morning (between 8 am and 11 am). The levels of FBS, fasting serum insulin, and CRP were measured using hexokinase, electrochemical luminescence, and enzyme-linked immunosorbent assay (ELISA) methods, respectively. High-density lipoprotein cholesterol, LDL-C, total cholesterol, and TG concentrations were measured using an enzymatic colorimetric assay.

**Definition of MetS Based on IDF Criteria**

According to the International Diabetes Federation (IDF) criteria (16), the MetS was diagnosed by: Waist circumference ≥94 cm in men and ≥80 in women plus two of the following factors: Reduced HDL-C <40 mg/dL (1.03 mmol/L) in males, and <50 mg/dL (1.29 mmol/l) in females, TG levels ≥150 mg/dL (1.7 mmol/L) or specific treatment for these lipid abnormalities, systolic BP ≥130 or diastolic BP ≥85 mm Hg antihypertensive medication use, raised FBS ≥100 mg/dL (5.6 mmol/L), or previously diagnosed type 2 diabetes if above 5.6 mmol/L or 100 mg/dL.

**Definition of MetS Based on NCEP Criteria**

According to the National Cholesterol Education Program Adult Treatment Panel (NCEP ATP III) criteria (17), the MetS was diagnosed by the presence of at least 3 of the followings: Waist circumference >102 cm in men and >88 cm in women, blood pressure >130/85 mm Hg or treatment for diagnosed hypertension, FBS concentration ≥100 mg/dl or previously diagnosed diabetes, TG concentration ≥150 mg/d, and HDL-C concentration <40 mg/dL in men and <50 mg/dL in women or drug treatment for these lipid abnormalities.

**Definition of IR**

The quantitative insulin sensitivity check index (QUICKI), homeostatic model assessment (HOMA-IR), and McAuley indexes were used to evaluate IR in this study (18, 19). The following equation was used for calculation of homeostatic model assessment HOMA-IR= [fasting serum glucose (mmol/L) × fasting serum insulin (lU/mL)]/22.5]. An increase in HOMA-IR matched the increased IR. The following equations were used for the evaluation of the QUICKI and McAuley indexes. QUICKI =1/{log [fasting serum insulin (IU/mL)]+ log [fasting serum glucose (mg/dL)]}. McAuley=exp {2.63-0.28 ln [fasting serum insulin (IU/mL)]-0.31 ln [serum TG (mmol/L)]}. The increased values of QUICKI and the McAuley indexes corresponded to the decreased IR.

**Sample Size**

According to Kim *et al.* (9), based on the comparison of means formula; with power of 80% and $\alpha = 0.05$, mean difference = 2.54, standard deviation (SD1) = 0.77, SD2 = 5.54, the sample size was determined as 38 for each group.

**Statistical Analysis**

The quantitative data were expressed as the mean and standard deviation. Demographic, anthropometric, and laboratory data were compared between patients who were on carbamazepine or valproate with controls by one-way ANOVA or Chi-square. The Chi-square and Mann-Whitney U tests were used for the univariate analysis on qualitative and

quantitative data, respectively. A logistic regression test was used to compare the anthropometric parameters, the laboratory data, and treatment (CBZ- or VPA-treated) to determine the risk of metabolic syndrome. Data were analyzed using statistical package for social sciences (SPSS Inc., Chicago, IL, USA) version 22. Statistically significant level was considered at $P < 0.05$.

## Results

A total of 170 patients with epilepsy diagnoses who had taken VPA or CBZ treatment were identified. The final study sample comprised 80 epileptic patients (54 men, 26 women) who met the inclusion criteria and were under treatment with CBZ or VPA for more than 6 months and 45 control subjects. None of the patients showed low serum levels of VPA and CBZ.

### Comparison of Demographic, Anthropometric, and Laboratory Data

Three studied groups were similar on all variables except for age and HDL level. Moreover, a significant difference in HDL level between 3 groups was found. Patients with CBZ therapy showed a higher HDL level than the others (Table 1).

**Table 1.** Demographic, anthropometric, and laboratory data of patients treated with carbamazepine or valproate and controls

| Variables | VPA-Treated (n= 40) | CBZ-Treated (n = 40) | Control (n = 45) | P-value* |
|---|---|---|---|---|
| **Age (year)** | 30.52±9.03 | 38.05±10.48 | 33.06±9.98 | 0.003* |
| **Sex (Male)** | 27(67.5%) | 27(67.5%) | 28(62.2%) | 0.83 |
| **Weight (kg)** | 73.41±16.01 | 73.03±14.26 | 73.70±12.98 | 0.97 |
| **Height (cm)** | 169.20±9.29 | 167.10±10.25 | 168.62±9.20 | 0.59 |
| **Waist (cm)** | 88.32 ± 12.57 | 90.70 ± 12.01 | 87.91 ± 8.95 | 0.47 |
| **FBS (mg/dL)** | 96.27 ± 15.90 | 101.95 ± 17.90 | 98.08 ± 11.37 | 0.23 |
| **CHOL (mg/dL)** | 183.02 ± 44.82 | 190.27 ± 40.56 | 182.62 ± 30.86 | 0.60 |
| **SBP (mm/Hg)** | 115.62 ± 15.15 | 119.62 ± 16.26 | 117.91 ± 11.05 | 0.45 |
| **DBP (mm/Hg)** | 74.12 ± 10.67 | 78.62 ± 11.60 | 73.88 ± 7.75 | 0.06 |
| **TG (mg/dL)** | 137.77 ± 74.21 | 145.22 ± 76.45 | 129.11 ± 54.18 | 0.55 |
| **HDL-C (mg/dL)** | 46.12 ± 12.72 | 55.30 ± 14.82 | 50.55 ± 12.15 | 0.01* |
| **LDL-C (mg/dL)** | 99.57 ± 35.19 | 98.20 ± 32.80 | 98.97 ± 22.55 | 0.98 |
| **Insulin (µU/mL)** | 12.24 ± 4.05 | 11.88 ± 3.91 | 10.46 ± 3.68 | 0.084 |
| **CRP (mg/L)** | 2084.02 ± 2417.49 | 5623.20 ± 1865.22 | 2387.13 ± 2381.41 | 0.26 |
| **BMI (kg/m$^2$)** | 25.56 ± 4.82 | 26.06 ± 4.06 | 25.85 ± 3.77 | 0.87 |
| **Daily drug dose (mg/d)** | 987 ± 380 | 610± 420 | | |
| **Serum drug (µg/ml)** | 67.0 ± 32.7 | 6.8 ±3.2 | | |

FBS: Fast blood glucose; CHOL: Cholesterol; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; TG: Triglycerides; HDL: High-density lipoprotein LDL: Low-density lipoprotein; CRP: C-reactive protein; BMI: Body mass index. Data are presented as mean ±SD.

*Statistically significant at P< 0.05 (one-way ANOVA and Chi-square).

### Comparison between Demographic, Anthropometric, and Laboratory Data Between Subjects with MetS and Without MetS Based on IDF and NCEP Criteria

In this study, subjects with MetS (by IDF and NCEP criteria) had higher age, weight, waist, FBS, cholesterol, systolic and diastolic pressure, TG, LDL, insulin, BMI and lower HDL compared to those without MetS. Moreover, CRP level showed a significant elevation in MetS group (by NCEP criteria). It was found that approximately 50% of the subjects with MetS (by IDF and NCEP criteria) were accompanied by IR (by McAuley). In MetS (by IDF criteria), the frequency of VPA or CBZ use was significantly higher than that in the control group (Table 2).

**Table 2.** The effect of demographic, anthropometric, and laboratory data on the development of metabolic syndrome based on the IDF and NCEP criteria

| Variables | IDF With MetS n=36 | Without MetS n=89 | P-value* | NCEP With MetS n=33 | Without MetS n=92 | P-value* |
|---|---|---|---|---|---|---|
| **Age (year)** | 38.86±9.45 | 31.82±9.90 | <0.001* | 39.66±9.28 | 31.76±9.81 | <0.001* |
| **Sex (Male)** | 21(58.3%) | 61(68.5%) | 0.27 | 19(57.6%) | 63(68.5%) | 0.25 |
| **Weight (kg)** | 81.70±12.66 | 70.03±13.59 | <0.001* | 78.25±14.26 | 71.65±13.98 | 0.022* |
| **Height (cm)** | 168.36±10.34 | 168.30±9.25 | 0.97 | 168.12±9.93 | 168.39±9.44 | 0.89 |
| **Waist.C (cm)** | 98.50±7.04 | 85.06±10.19 | <0.001* | 96.33±9.23 | 86.28±10.65 | <0.001* |
| **FBS (mg/dL)** | 105.19±16.98 | 96.13±13.70 | 0.002* | 107.72±17.96 | 95.52±12.74 | <0.001* |
| **CHOL (mg/dL)** | 199.02±50.54 | 179.60±31.42 | 0.037* | 197.63±42.32 | 180.73±36.57 | 0.031* |
| **SBP (mm/Hg)** | 122.91±17.54 | 115.62±12.08 | 0.027* | 123.87±17.82 | 115.52±12 | 0.016* |
| **DBP (mm/Hg)** | 81.38±12.51 | 73.08±8.03 | 0.001* | 80.90±12.46 | 73.53±8.53 | 0.003* |
| **TG (mg/dL)** | 190.08±68.49 | 115.58±55.49 | <0.001* | 190.96±62.43 | 117.69±59.51 | <0.001* |
| **HDL-C (mg/dL)** | 46.38±11.98 | 52.38±13.94 | 0.026* | 45.66±11.77 | 52.44±13.87 | 0.014* |
| **LDL-C (mg/dL)** | 107.91±35.17 | 95.28±27.24 | 0.033* | 107.78±33.62 | 95.73±28.32 | 0.048* |
| **Insulin (µU/mL)** | 14.31±4.13 | 10.34±3.21 | <0.001* | 14.60±3.91 | 10.37±3.29 | <0.001* |
| **CRP (mg/L)** | 6132.22±19654.70 | 2190.44±2259.77 | 0.23 | 6696.24±20473.26 | 2116.67±2214.02 | 0.035* |
| **BMI (kg/m$^2$)** | 28.80±3.50 | 24.62±3.85 | <0.001* | 27.66±4.25 | 25.17±4 | 0.003* |
| **HOMA** | 36 (39.1%) | 56(60.9%) | <0.001* | 33(35.9%) | 59(64.1%) | <0.001* |
| **QUICKI** | 32 (43.2%) | 42(56.8%) | <0.001* | 32(43.2%) | 42(56.8%) | <0.001* |
| **McAuley** | 34 (54.8%) | 28(45.2%) | 0.004* | 32(51.6%) | 30(48.4%) | 0.19 |
| **Drug type** | | | | | | |
| **Valproate** | 17 (42.5%) | 23 (57.5%) | | 11 (27.5%) | 29 (72.5%) | |
| **Carbamazepine** | 14 (35.0%) | 26 (65.0%) | | 14 (35.0%) | 26 (65.0%) | |
| **Control** | 5(11.1%) | 40 (88.9%) | | 8 (17.8%) | 37 (82.2%) | |

FBS: Fast blood glucose; CHOL: Cholesterol; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; TG: Triglycerides; HDL: High-density lipoprotein LDL: Low-density lipoprotein; CRP: C-reactive protein; BMI: Body mass index. Significant correlations were identified by Chi-square and Mann-Whitney U tests. Data are presented as mean ±SD.
*Statistically significant at P< 0.05.

## Significant Risk Factors for Development of MetS Based on the IDF and NCEP Criteria

In the VPA-treated group, the risk of MetS (by IDF criteria) significantly increased 19 times more than the control group (OR=19.20 95% CL: 2.62-140.23, P=0.004) and in the CBZ-treated group, was 17% less than control group (P=0.84); moreover, in epileptic patients, for each unit increase in waist, the risk of MetS (by IDF definition) significantly increased by 44% (OR=1.44 95% CL: 1.20-1.73, P<0.001). The results also showed that for each unit increase in FBS, TG, and diastolic pressure, the risk of MetS (by IDF definition) significantly increased by 5%, 2%, and 39%, respectively, (OR=1.05 95% CL: 1.01-1.10, P=0.012; OR=1.02 95% CL: 1.006-1.03, P=0.006; OR=1.39 95% CL: 1.13-1.72, P=0.002). In epileptic patients, for each unit increase in waist, FBS, TG, and insulin level, the risk of MetS (by NCEP criteria) significantly increased by 24%, 4%, 1%, and 22%, respectively, (OR=1.24 95% CL: 1.10-1.39, P<0.001; OR=1.04 95% CL: 1.008-1.07, P=0.021; OR=1.011 95% CL: 1.001-1.02, P=0.026; OR=1.22 95% CL: 1.04-1.42, P=0.012). A significant depression by 8% was found in the risk of MetS based on the NCEP criteria for each unit increase in HDL level (OR=0.92 95% CL: 0.87-0.98, P=0.021) (Table 3).

**Table 3.** Multivariate regression analysis for the development of metabolic syndrome based on the IDF and NCEP criteria

| Index | Variables | Crude OR | Adjusted OR 95%(CI) | P-value |
|---|---|---|---|---|
| | Control | - | 1 | |
| | Valproate | 5.91 | 19.20(2.62-140.23) | 0.004* |
| | Carbamazepine | 4.30 | 0.83 (0.12-5.36) | 0.84 |
| **IDF** | Waist (cm) | 1.19 | 1.44(1.20-1.73) | <0.001* |
| | FBS (mg/dL) | 1.04 | 1.05(1.01-1.10) | 0.012* |
| | TG (mg/dL) | 1.01 | 1.02(1.006-1.03) | 0.006* |
| | DBP (mm/Hg) | 1.09 | 1.39(1.13-1.72) | 0.002* |
| | Waist (cm) | 1.24 | 1.24 (1.10-1.39) | <0.001* |
| | FBS | 1.04 | 1.04 (1.008-1.07) | 0.021* |
| **NCEP** | TG | 1.01 | 1.01 (1.001-1.02) | 0.026* |
| | HDL | 0.92 | 0.92 (0.87-0.98) | 0.021* |
| | Insulin | 1.22 | 1.22 (1.04-1.42) | 0.012* |

FBS: Fast blood glucose; DBP: Diastolic blood pressure; TG: Triglycerides; HDL: High density lipoprotein.

**Comparison between Demographic, Anthropometric and Laboratory Data Between Subjects with IR and without IR Based on HOMA, QUICKI and McAuley Criteria**

Subjects with IR (by HOMA, QUICKI and McAuley criteria) had higher waist, FBS, DBP, TG, Insulin, and BMI (P<0.001). Moreover, in this study, people with IR (by QUICKI and McAuley criteria) showed a significant elevation in addition to the above-mentioned variables such as weight, Chol, SBP, and LDL level. It was found that in IR (by HOMA and QUICKI criteria), the frequency of VPA or CBZ use was significantly higher than that in the control group (Table 4).

**Table 4.** The effect of demographic, anthropometric, and laboratory data on the development of insulin resistance based on HOMA, QUICKI, and McAuley criteria

| Variables | HOMA Index Cut-off Value > 2 | | P-value* | QUICKI Index Cut-off Value > 0.339 | | P-value* | McAuley Index Cut-off Value < 6.31 | | P-value* |
|---|---|---|---|---|---|---|---|---|---|
| | With IR n=92 | Without IR n=33 | | With IR n=74 | Without IR n=51 | | With IR n=62 | Without IR n=63 | |
| **Age (year)** | 34.72±10.07 | 31.39±10.51 | 0.10 | 35.21±10.45 | 31.86±9.72 | 0.071 | 35.54±10.69 | 32.17±9.59 | 0.06 |
| **Sex (Male)N%** | 61(66.3%) | 21(63.6%) | 0.78 | 49(66.2%) | 33(64.7%) | 0.86 | 37(58.7%) | 45(72.6%) | 0.10 |
| **Weight (Kg)** | 74.73±14.06 | 69.65±14.51 | 0.08 | 75.91±14.17 | 69.74±13.82 | 0.017 | 77.70±13.01 | 69.15±14.33 | 0.001 |
| **Height (cm)** | 168.50±9.86 | 167.81±8.71 | 0.72 | 168.98±9.53 | 167.35±9.55 | 0.34 | 170.30±9.31 | 166.36±9.42 | 0.02 |
| **Waist.C (cm)** | 90.26±11.54 | 85.24±9.29 | 0.026 | 91.68±10.92 | 84.94±10.41 | 0.001 | 93.09±9.66 | 84.84±11.13 | <0.001 |
| **FBS (mg/dL)** | 102.11±16.06 | 89.33±6.32 | <0.001 | 104.09±14.39 | 90.98±6.41 | 0.001 | 104.30±17.29 | 93.26±10.38 | <0.001 |
| **CHOL (mg/dL)** | 189.03±40.36 | 174.51±31.92 | 0.06 | 191.94±41.87 | 175.41±31.53 | 0.018 | 197.40±43.09 | 173.19±29.60 | <0.001 |
| **SBP (mm/Hg)** | 118.72±14.52 | 114.93±13.04 | 0.18 | 120.85±14.39 | 113.19±12.71 | 0.003 | 120.29±15.31 | 115.20±12.61 | 0.04 |
| **DBP (mm/Hg)** | 76.57±10.55 | 72.42±8.58 | 0.045 | 77.97±10.78 | 71.86±8.12 | 0.001 | 78.14±11.24 | 72.85±8.36 | 0.004 |
| **TG (mg/dL)** | 151.91±70.87 | 95.57±36.75 | <0.001 | 161.39±69.74 | 101.70±47.90 | 0.001 | 186.46±61.95 | 88.39±26.25 | <0.001 |
| **HDL (mg/dL)** | 49.46±11.97 | 53.96±17.25 | 0.10 | 48.27±10.95 | 54.11±16.29 | 0.028 | 46.37±10.90 | 54.87±14.78 | <0.001 |
| **LDL-C (mg/dL)** | 100.82±29.72 | 93.60±31.14 | 0.23 | 104.12±30.02 | 91.37±28.97 | 0.020 | 106.75±30.81 | 91.20±27.59 | 0.004 |
| **Insulin (µU/mL)** | 12.81±3.71 | 7.78±1.16 | <0.001 | 13.72±3.57 | 8.24±1.17 | 0.001 | 14.06±3.87 | 8.95±1.70 | <0.001 |
| **CRP (mg/L)** | 3815.7±12467.1 | 1959.5±2096.70 | 0.39 | 4176.5±13839 | 2091.1±2259. | 0.28 | 4627.3±15082. | 2044.6±2139.2 | 0.18 |
| **BMI (kg/m$^2$)** | 26.27±4.21 | 24.58±3.94 | 0.04 | 26.53±4.29 | 24.80±3.86 | 0.022 | 26.78±3.93 | 24.89±4.26 | 0.01 |
| **IDF** | 36(100.0%) | 0 | <0.001 | 32(88.9%) | 4(11.1%) | <0.001 | 34(94.4%) | 2(5.6%) | <0.001 |
| **NCEP** | 33(100.0%) | 0 | <0.001 | 32(97.0%) | 1(3.0%) | <0.001 | 32(97.0%) | 1(3.0%) | <0.001 |
| **Drug type** | | | | | | | | | |
| **Valproate** | 32(80%) | 8(20%) | 0.034 | 28(70.0%) | 12(30.0%) | 0.038 | 21(52.5%) | 19(47.5%) | 0.24 |
| **Carbamazepine** | 33(82.50%) | 7(17.5%) | | 26(65.0%) | 14(35.0%) | | 23(57.5%) | 17(42.5%) | |
| **control** | 27(60%) | 18(40%) | | 20(44.4%) | 25(55.6%) | | 18(40.0%) | 27(60.0%) | |

FBS: Fast blood glucose; CHOL: Cholesterol; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; TG: Triglycerides; HDL: High-density lipoprotein LDL: Low-density lipoprotein; CRP: C-reactive protein; BMI: Body mass index. Significant differences were identified by Chi-square and Mann-Whitney U tests. Data are presented as mean ±SD.
Statistically significant at P< 0.05.

**Significant Risk Factors for Development of IR Based on HOMA, QUICKI, and McAuley Criteria**

Multiple logistic regression model showed that the IR risk (by HOMA criteria) in the VPA-treated and CBZ-treated groups significantly increased 15 and 7 times more than the control group, respectively (OR=14.83 95% CL: 3.03-72.56, P=0.001; OR=6.81 95% CL: 1.53-30.19, P=0.01). In epileptic patients, for each unit increase in FBS and TG, the risk of IR (by HOMA definition) significantly increased by 27% and 2% (OR=1.27 95% CL: 1.14-1.42, P<0.001; OR=1.02 95% CL: 1.004-1.03, P=0.014). The results also showed that the risk of IR significantly increased by 33% for each unit increase in BMI (OR=1.33 95% CL: 1.03-1.72, P=0.029). In the VPA-treated group, the IR risk (by QUICKI criteria) significantly increased 9 times and in the CBZ-treated group, it increased 2.37 times more than the control group, which was not significant (OR=9.13 95% CL: 2.55-32.65, P=0.001; OR= 2.37 95% CL: 0.63-7.83, P=0.2). In epileptic patients, for each unit increase in systolic pressure, FBS, and TG, the risk of IR (by QUICKI definition) significantly increased by 5%, 22%, and 1%, respectively (OR=1.05 95% CL: 1.01-1.10, P=0.017; OR=1.22 95% CL: 1.11-1.34, P<0.001; OR=1.01 95% CL: 1.003-1.02 P=0.047). For each unit increase in TG, the risk of IR significantly increased by 7% according to the McAuley definition (OR=1.08 95% CL: 1.04-1.11, P<0.001) (Table 5).

**Table 5.** Multivariate regression model for the development of insulin resistance based on HOMA, QUICKI, and McAuley criteria.

| Index | Variables | Crude OR | Adjusted OR(CI) | P-value |
|---|---|---|---|---|
| **HOMA** | Control | - | 1 | |
| | Valproate | 2.66 | 14.83 (3.03-72.56) | 0.001* |
| | Carbamazepine | 3.14 | 6.81 (1.53-30.19) | 0.011* |
| | FBS (mg/dL) | 1.21 | 1.27(1.14-1.42) | <0.001* |
| | TG (mg/dL) | 1.02 | 1.02(1.004-1.03) | 0.014* |
| | BMI | 1.10 | 1.33(1.03-1.72) | 0.029* |
| **QUICKI** | Control | - | 1 | |
| | Valproate | 2.91 | 9.13 (2.55-32.65) | 0.001* |
| | Carbamazepine | 2.32 | 2.37 (0.63-7.83) | 0.20 |
| | SBP mmHg | 1.04 | 1.05 (1.01-1.10) | 0.017* |
| | FBS (mg/dL) | 1.20 | 1.22(1.11-1.34) | <0.001* |
| | TG (mg/dL) | 1.02 | 1.01(1.003-1.02) | 0.047* |
| | Weight (Kg) | 1.04 | 0.66 (0.42-1.03) | 0.071 |
| | Height (cm) | 1.04 | 1.44 (0.97-2.14) | 0.70 |
| **McAuley** | FBS (mg/dL) | 1.10 | 1.05 (0.98-1.12) | 0.11 |
| | TG (mg/dL) | 1.07 | 1.08(1.04-1.11) | <0.001* |
| | BMI | 1.12 | 3.14(0.89-11.05) | 0.074 |

FBS: Fast blood glucose; SBP: Systolic blood pressure; TG: Triglycerides; BMI: Body mass index.

## Discussion

Several reports have shown the adverse effects of VPA including hyperinsulinemia weight gain (20), endocrine abnormalities, cognitive dysfunction (21), and fatty liver diseases (22, 23). Additionally, VPA has also been shown to induce oxidative stress and leads to a variety of toxicities (24); therefore, it has created a crisis for physicians and patients. This study aimed to determine the relationship between treatment with VPA or CBZ and MetS development and risk of IR in epileptic patients. The findings of this study showed that treatment with VPA may increase the risk of MetS based on the IDF criteria 19 times more than the control. There are several studies conducted on the significant effects of VPA on the development of MetS (25, 26).

Rakitin *et al.* (2014) reported that the risk of MetS did not increase in 118 epileptic patients who received VPA as monotherapy (1). The NCEP criteria were used for the evaluation of MetS risk in their study. In the present study, a significant increase was found in the risk of MetS based on the IDF index in patients treated with VPA, and the type of treatment did not show a significant correlation with MetS risk (by NCEP index).

Cabral *et al.* (2017) suggested that the incidence of MetS was significantly different based on each criterion used, the IDF criteria can present higher specificity and sensitivity for the evaluation and determination of the MetS (27).

The results of the present study showed that CBZ therapy did not have any correlation with MetS risk (by IDF and NCEP criteria). There are a few studies that have discussed the MetS development in CBZ-treated patients (2). In the present research, the level of HDL-C in patients treated with CBZ showed a significant elevation, and this effect was especially marked in women who were treated with CBZ. Interestingly, previous studies also reported similar results and described the gender effect of CBZ on HDL-C (2, 28). The high concentrations of HDL could potentially have a protective effect in this group (29). It was found that in the CBZ-treated patients, the risk of MetS (by IDF criteria) was 17% less than the control group, and also, a significant depression by 8% in the risk of MetS (by NCEP criteria) was reported for each unit increase in HDL. Moreover, the patient's TG and cholesterol levels in the CBZ group showed a tendency to be higher without statistical significance. Previous reports have described the lipid increasing effect of CBZ (11, 12, 30).

The results of this study showed that other than VPA use, an increase in the waist, FBS, TG, DBP, insulin level, and a decrease in HDL may act as important factors in the risk of MetS in epileptic patients.

The present study showed that high BMI was not a significant risk factor for MetS

development; however, waist circumference based on two indexes was presented as the main factor for MetS risk. The long-term VPA therapy may be discontinued in epileptic patients with severe weight gain due to side effects and they excluded from the study, this may be the main reason for these results.

There are contradictory results about lipid metabolism in VPA-treated patients. Some studies have reported no effect of VPA treatment on lipid metabolism (31, 32), whereas others have increased TG (11, 33, 34), decreased the HDL level in the VPA-treated group (35). It was found that raised TG level acts as the main risk factor for MetS development based on two criteria and a decrease in HDL was represented significantly for MetS risk based on NCEP index. The possible explanations for the variety of lipid levels in previous studies are that probably dyslipidemia indirectly occurs during the development of MetS, differences in the subject selection methods or, not paying attention to examining patients' fat profiles.

Elevated BP is an important side effect of prolonged VPA treatment (33). A significant elevated BP was observed in patients with MetS compared to those without MetS, but after regression analysis, an increase in DBP represented a significant correlation with MetS risk based on the IDF index. However, a study by Gallagher *et al.* (2010) showed that increased serum insulin levels can lead to an increase in BP level by sympathetic activity or impairing vasodilation induced by nitric oxide (36), in the present study, the increased proportion of high BP in VPA-treated patients with MetS, suggests that the tendency towards hypertension can be an indirect effect of VPA therapy, which is caused by insulin resistance.

Treatment with VPA increased the risk of IR based on HOMA and QUICKI criteria, approximately 15 and 9 times more than the control, respectively. On the other hand, CBZ therapy showed a significant correlation with IR risk based on HOMA index only. Most studies have used the HOMA index, and they have reported significantly increased values of IR in VPA-treated cases (1, 2, 25). However, Najafi *et al*. (14) studied the VPA-treated Iranian patients and reported that there were normal values of insulin and no evidence of IR was observed in the VPA-treated patients as case and CBZ-treated patients as controls, which is consistent with the results of a study conducted by Kwan *et al*. (37). Valproate does not stimulate insulin secretion directly, but it may interfere with liver metabolism (38). Insulin and C-peptide are secreted equally from the pancreatic islets, and by initial passage through the liver about half of the secreted insulin is removed (39). Other than taking the VPA or CBZ, an increase in FBS, TG, SBP, and BMI can be considered as important factors in the risk of IR in epileptic patients.

In the present study, the HsCRP of both participated cases and controls was measured to evaluate possible inflammatory effects of AEDs, but the findings showed that there was no significant difference in the levels of HsCRP between the VPA-treated group, the CBZ-treated group, and the controls. Although the result of this study was supported by Nisha *et al.* (40) in 2018, Chuang *et al.* (2012) showed an elevated concentration of HsCRP and oxidative stress following long-term AEDs treatment (41).

Using various indexes for evaluation of MetS and IR in epileptic patients is the strength of the present study which is more than those evaluated in other published studies. This study has some limitations, including limited sample size, lack of information on patients' MetS components before taking AEDs, and also, unmatched age of CBZ-treated and VPA-treated cases which was due to the nature of the study, in which CBZ usually should be prescribed for adult epileptics with partial epilepsy and VPA for younger subjects with generalized epilepsy.

Further studies with larger sample sizes are recommended to compare MetS before and after taking the AEDs.

## Conclusion

According to the results, taking sodium VPA may increase the likelihood of developing IR and MetS in adult epileptic patients while CBZ therapy may decrease the risk of MetS and increase IR risk.

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**Authors' contributions**
All authors contributed to the study's conception and design. Material preparation, data collection, and analysis was performed by Nasrin Jalali. The first draft of the manuscript was written by Mahnaz Bayat and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

**Conflict of interests**
The authors have no conflict of interests to declare

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