

Frequency of metabolic syndrome and insulin resistance in epileptic patients treated with sodium valproate or carbamazepine monotherapy: A Case-Control Study

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Research Article

Keywords: Metabolic syndrome, Carbamazepine, Sodium valproate, Insulin resistance, Epileptic patients

Posted Date: January 4th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-131323/v1>

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Abstract

Background

Metabolic syndrome (MetS) represents a collection of metabolic risk factors such as obesity, dyslipidemia, hyperglycemia, and hypertension. Medications can increase the incidence rate of MetS and insulin resistance (IR).

Objective

This study aims to evaluate the effects of Carbamazepine (CBZ) or Valproate (VPA) as monotherapy on the development of MetS and IR in the 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. MetS was assessed based on International Diabetes Federation (IDF) and National Cholesterol Education Program (NCEP) criteria.

Results

In the multiple regression analysis, in VPA-treated patients the risk of MetS (by IDF criteria) was increased 19 times higher than controls (OR = 19.20; 95% CI = 2.62-140.23, P = 0.004) and risk of IR (by HOMA and QUICKI) 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. Increase in waist, DBP, and insulin level were also showed as important factors in risk of MetS. In CBZ therapy, the risk of MetS (by IDF) depressed by 17% less than controls and the risk of IR (by HOMA) increased 7 times more than controls.

Conclusion

Treatment with VPA can increase the likelihood of developing MetS and IR while, CBZ therapy could decrease the risk of MetS and increase risk of IR in the epileptic patients in Iran compared to the general population.

1. Introduction

Epilepsy is one of the most prevalent neurological illnesses, especially in young children and old age people of both males and females in 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 be need long duration of treatment therefore, understanding the safety of the drugs is important for patients and neurologist. One of the recognized and public side effects of a long-term treatment with VPA or CBZ is obesity, which occurs in many of patients and it is related to important metabolic and endocrine disease [3-5]. The obesity in association with dyslipidemia, hypertension, and IR has an essential role in promoting the development of metabolic diseases and long-term vascular complications[6, 7]. In 1988, Reaven described metabolic syndrome (MetS) refers to a group of metabolic risk factors such as obesity, dyslipidemia, hyperglycemia, and hypertension[8]. MetS is a major public health concern and its prevalence is about 24.7-28.8% in the adult population [9] [10]. 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[9, 11]. Several studies have reported that there is an increased risk of MetS after prolonged taking of AEDs, mainly VPA[12-15] [16]. In a study conducted by Kim and Lee, the authors investigated the metabolic and hormonal disturbances in women on AED monotherapy and their findings showed that the VPA monotherapy could induce MetS in women more frequently than CBZ, lamotrigine, or topiramate[17]. Their findings documented that the VPA can more significantly affect the development of MetS than the other.

Among the above mentioned criteria, IR and associated factors have an essential role in the development of metabolic dysfunction[18]. Previous studies reported controversial results about the risk of IR in epileptic patients treated by VPA or CBZ. Najafi et al. suggested VPA may not cause IR and could be prescribed safely[19] on the other hand, some clinical studies pronounced a significant IR in epileptic patients treated with VPA [20-22]

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 persons with epilepsy, we decided 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.

2. Methods

2.1. Subjects

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

A total of 170 epileptic patients who had taken VPA (n = 40) or CBZ (n = 40) for more than 6 months were identified. Finally, 80 patients who encountered the inclusion criteria and 45 control subjects participated in this study. The exclusion criteria were as follows: (1) patients ≤ 18 or > 55 years old (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.

2.2. Collection of anthropometric and laboratory data

After the written informed consent was taken from each participant the patient was examined by a neurologist and their clinico-medical history of epilepsy, including the type of epilepsy, dose of CBZ and VPA and, the duration of treatment was recorded in a data gathering form. In addition, 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. By using a calibrated weighing scale measurement 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 formula of kilograms divided by height in meters squared, was calculated (m^2). The value above $25 \text{ kg}/m^2$ 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.

2.3. Definition of MetS based on IDF criteria

According to the International diabetes federation (IDF) criteria[23, 24], the MetS was diagnosed by: waist circumference ≥ 94 cm in men and ≥ 80 in women plus two of the following factors: reduced HDL-C $< 40 \text{ mg}/dL$ ($1.03 \text{ mmol}/L$) in males, and $< 50 \text{ mg}/dL$ ($1.29 \text{ mmol}/L$) in females, TG levels $\geq 150 \text{ mg}/dL$ ($1.7 \text{ mmol}/L$) or specific treatment for these lipid abnormalities, systolic BP ≥ 130 or diastolic BP $\geq 85 \text{ mm Hg}$ antihypertensive medication use, raised FBS $\geq 100 \text{ mg}/dL$ ($5.6 \text{ mmol}/L$), or previously diagnosed type 2 diabetes if above $5.6 \text{ mmol}/L$ or $100 \text{ mg}/dL$.

2.4. Definition of MetS based on NCEP criteria

According to the National Cholesterol Education Program Adult Treatment Panel (NCEP ATP III) criteria [25]. 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 $> 130/85 \text{ mm Hg}$ or treatment for diagnosed hypertension, FBS concentration $\geq 100 \text{ mg}/dL$ or previously diagnosed diabetes, TG concentration $\geq 150 \text{ mg}/dL$, and HDL-C concentration $< 40 \text{ mg}/dL$ in men and $< 50 \text{ mg}/dL$ in women or drug treatment for these lipid abnormalities.

2.5. 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[26, 27]. The following equation was used for calculation of homeostatic model assessment $HOMA-IR = \frac{\text{fasting serum glucose (mmol/L)} \times \text{fasting serum insulin (IU/mL)}}{22.5}$. Increase in HOMA-IR matched to the increased IR. The following equations were used for evaluation of the QUICKI and McAuley indexes. $QUICKI = 1 / \{ \log [\text{fasting serum insulin (IU/mL)}] + \log [\text{fasting serum glucose (mg/dL)}] \}$. $McAuley = \exp \{ 2.63 - 0.28 \ln [\text{fasting serum insulin (IU/mL)}] - 0.31 \ln [\text{serum TG (mmol/L)}] \}$. The increased values QUICKI and the McAuley indexes corresponded to the decreased IR.

2.7. Sample size

According to Kim et al.[17], based on the comparison of means formula; with power 80% and $\alpha = 0.05$, $\text{diff} = 2.54$, $SD1 = 0.77$, $SD2 = 5.54$, the sample size was determined as 38.

2.8. Statistical analysis

The quantitative data was expressed as the mean and standard deviation. Demographic, anthropometric and laboratory data were compared between patients 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. 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. Statistical package for social sciences (SPSS Inc., Chicago, IL, USA) version 22 was used for data analysis. $P < 0.05$ was considered statistically significant.

3. 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 on the CBZ or VPA for more than 6 months and 45 control subjects. None of the patients showed low serum levels of VPA and CBZ.

3.1. Comparison of demographic, anthropometric and laboratory data

Three studied groups were similar on all variables except for age and HDL level.

Moreover, we found significant difference in HDL level between 3 groups. Patients with CBZ therapy showed a higher HDL level than the others (Table 1).

3.1.1 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 & diastolic pressure, TG, LDL, insulin, BMI and lower HDL compare to without MetS. Moreover, CRP level showed significant elevation in MetS group (by NCEP criteria). We found, approximately 50% of 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 the control group. (Table 2).

3.2. Significant risk factors for development of MetS based on IDF and NCEP criteria.

In VPA-treated group the risk of MetS (by IDF criteria), significantly increase 19 times more than the control group (OR=19.20 95% CL2.62-140.23, P=0.004) and in CBZ-treated group was 17 percent less than control group (P=0.84) moreover, in epileptic patients for each unit increase in Waist risk of MetS (by IDF definition) significantly increased by 44% (OR=1.44 95% CL1.20-1.73, P<0.001). The results also showed 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% CL1.01-1.10, P=0.012, OR=1.02 95% CL1.006-1.03, P=0.006, OR=1.39 95% CL1.13-1.72, 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% CL1.10-1.39, P<0.001, OR= 1.04 95% CL1.008-1.07, P=0.021, OR=1.011 95% CL 1.001-1.02, P=0.026, OR=1.22 95% CL1.04-1.42, P=0.012). We found significant depression by 8% in risk of MetS based on NCEP criteria for each unit increase in HDL level (OR=0.92 95% CL0.87-0.98, P=0.021) (Table 3).

3.3. 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 significant elevation in addition to the variables mentioned above such as Weight, Chol, SBP, and LDL level. We found that, in IR (by HOMA and QUICKI criteria). the frequency of VPA or CBZ use was significantly higher than the control group (Table 4).

3.4. Significant risk factors for development of IR based on HOMA, QUICKI, and McAuley criteria

Multiple logistic regression model showed the IR risk (by HOMA criteria) in VPA-treated and CBZ-treated groups significantly increase 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, 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 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 VPA-treated group the IR risk (by QUICKI criteria) significantly increase 9 time and in CBZ-treated group non significantly increased 2.37 time more than the control group (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 our 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% (OR=1.05 95% CL1.01-1.10, 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).

4. Discussion

Several reports have shown the adverse effects of VPA (e.g., hyperinsulinemia weight gain[28, 29], endocrine abnormalities, cognitive dysfunction[30, 31] fatty liver diseases [32, 33]), additionally, VPA has also been showed to induce oxidative stress and leads to variety of toxicities[34, 35] therefore, has created a crisis for doctors and patients. The aim of this study was to determine whether treatment with VPA or CBZ is correlated with MetS development and risk of IR in epileptic patients. The findings of our study showed that, VPA treatment approximately increased the risk of MetS based on IDF criteria 19 times more than the control, There are several studies conducted on the significant effect of VPA on the development of MetS[2, 12, 13, 36]

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

Cabral et al. suggested ,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 [37].

Our results showed that CBZ therapy did not have any correlation with MetS risk (by IDF and NCEP criteria). There are, a few studies have discussed the MetS development in CBZ treated patients[2]. In current research the level of HDL-C in patients treated with CBZ showed significant elevation and this effect was especially marked in women who treated with CBZ. Interestingly, previous studies also reported similar results and described the gender effect of CBZ on HDL-C[2, 38]. The high concentrations of HDL, could potentially has a protective effect in this patient group [39]. We found in CBZ treated patients the risk of MetS (by IDF criteria) 17% less than control group and significant depression by 8% in risk of MetS (by NCEP criteria)for each unit increase in HDL. Moreover, in our patient's TG and cholesterol levels in CBZ group showed tendency to be more without statistical significance. Previous reports, has been described the lipid increasing effect of CBZ[40–42].

Our results showed, other than VPA use, increase in waist, FBS, TG, DBP, insulin level and decrease in HDL were important factors in risk of MetS in epileptic patients.

The current study found that, raised BMI was not a significant risk factor for MetS development however, waist circumference based on two indexes was presented as 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 study, this may be the main reason for these results.

There are contradictory results about the finding of lipid metabolism in VPA-treated patients. Some studies have reported no effect of VPA treatment on lipid metabolism[43, 44] and, whereas others have found increased TG[16, 42, 45], decrease in HDL level in VPA group[46].we found that, raised TG level acts as a main risk factor for MetS development based on two criteria and decrease in HDL was represented significantly for MetS risk based on NCEP index. The possible explanations for 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[16, 44]. We observed, significant elevated BP in patients with MetS compare to without MetS but after regression analysis increase in DBP represented significant correlation with MetS risk based on IDF index. However, previous study reported increased serum insulin levels can lead to increase BP elevated by sympathetic activity or impairing vasodilation induced by nitric oxide [47]in our 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, it is actually caused by insulin resistance.

VPA treatment 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 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, 36, 48]. However, Najafi et al[19] studied the VPA-treated Iranian patients and they reported that there were normal values of insulin and no evidence of IR in VPA-treated as case and CBZ -treated as controls and this finding has also been supported by a study conducted by Kwan et al[49]. Valproate does not stimulate insulin secretion directly, but it may interfere with the liver metabolism [50]. 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[51]. Other than taking the VPA or CBZ, increase in FBS, TG, SBP, and BMI were important factors in risk of IR in epileptic patients

In our study, the HsCRP of both participated cases and controls was measured to evaluate possible inflammatory effects of AEDs, but our 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 our result was supported by Nisha et al.[48] in 2018, but Chuang et al. showed that the elevated concentration of HsCRP and oxidative stress following long-term AEDs treatment [52].

Using the various indexes for evaluation of MetS and IR in epileptic patients is the strength of our study which is more than 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 study in which CBZ usually should be prescribed for adult epileptics with partial epilepsy and VPA for younger subjects with generalized epilepsy.

Further studies are warranted with larger sample size and comparison of MetS before and after taking the AEDs.

Conclusions

Taking sodium VPA can increase significantly the likelihood of developing of IR and MetS in the adult epileptic patients while, CBZ therapy could decrease the risk of MetS and increased IR risk.

Declarations

Ethics approval and consent to participate: Before data collection began this research has been approved by the medical research ethics committee and institutional review board of Shiraz University of Medical Sciences (approval number: ir.sums.med.rec. 1397.s34) and all methods were carried out in accordance with the relevant guidelines and regulations. The written informed consent was obtained from patients for publication of data.

Consent for publication: none

Availability of data and materials: The data supporting the findings of this study are available from the corresponding author on request.

Competing interests: The authors declare that they have no competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Funding: none

Authors' contributions: N.A has conceived and designed the concept and road map of the study, searched the literature collected the data, and drafted the manuscript. M.B, N.J, M.P, M.N and M.H. D helped design the study, searched the literature, reviewed the manuscript and helped with revision of the manuscript. M.B has critically reviewed the manuscript, designed the study, and helped in manuscript preparation. All authors have made substantive contribution and attest to approving the final manuscript.

Acknowledgments: The present article was extracted from the thesis written by Nasrin Jalali and was financially supported by Shiraz University of Medical Sciences (Grant No. ir.sums.med.rec. 1397.s34). The authors would like to thank Ms. Hosseini and Ms. Gholami from the Shiraz Neuroscience Research Center for their kind assistance.

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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/m2)	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 \pm SD. Statistically significant ($P < 0.05$). (One Way ONOVA and Chi-square)

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

IDF NCEP

Variables	With MetS N= 36	Without MetS N=89	P value*	With MetS N=33	Without MetS N=92	P value*
Age	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/m2)	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%)	<0.001*	32(51.6%)	30(48.4%)	<0.001*
Drug type			0.004*			0.19
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 (P< 0.05).

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

Index	Variables	Crude OR	Adjusted OR 95%(CI)	P
IDF	Control	-	1	
	Valproate	5.91	19.20(2.62-140.23)	0.004*
	Carbamazepine	4.30	0.83 (0.12-5.36)	0.84
	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*
NCEP	Waist (cm)	1.24	1.24 (1.10-1.39)	<0.001*
	FBS	1.04	1.04 (1.008-1.07)	0.021*
	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

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		P value*	QUICKI index		P value*	McAuley index		P valu
	Cut-off value > 2			Cut-off value > 0.339			Cut-off value < 6.31		
	With IR	Without IR		With IR	Without IR		With IR	Without IR	
	N=92	N=33		N=74	N=51		N=62	N=63	
Age	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	0.00
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	<0.0
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	<0.0
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	<0.0
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	0.00
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	<0.0
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	<0.0
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	0.00
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	<0.0
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/m2)	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%)	<0.0
NCEP	33(100.0%)	0	<0.001	32(97.0%)	1(3.0%)	<0.001	32(97.0%)	1(3.0%)	<0.0
Drug type			0.034			0.038			0.24
Valproate	32(80%)	8(20%)		28(70.0%)	12(30.0%)		21(52.5%)	19(47.5%)	
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 (P< 0.05).

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
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*
McAuley	Weight (Kg)	1.04	0.66 (0.42-1.03)	0.071
	Height (cm)	1.04	1.44 (0.97-2.14)	0.70
	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