

## Brief Report

# The Investigation of Insulin Resistance in Two Groups of Epileptic Patients Treated with Sodium Valproate and Carbamazepine

### Abstract

**Background:** Valproic acid (VPA) is a widely used broad-spectrum antiepileptic drug for therapy of generalized and focal epilepsies. Cross-sectional studies have suggested that valproate treatment may be associated with hyperinsulinemia. We decided to investigate hyperinsulinemia as a health-threatening side effect of VPA in Iranian epileptic patients. **Materials and Methods:** Body mass index (BMI), lipid profile, fasting serum insulin, fasting blood glucose (FBS), and homeostatic model assessment-insulin resistance (HOMA-IR) were measured in 30 VPA-treated epileptic patients and 30 controls (CBZ-treated). The Chi-square test, *t*-test, and Pearson correlation test were used. **Results:** BMI was higher in VPA group than in control group ( $25.7 \pm 3.5 > 21.7 \pm 4.1$ ) ( $0.000 < 0.05$ ). Prevalence of obesity was 16.6% in VPA group that was almost the same and even lower than general Iranian population. Serum triglyceride (TG) ( $150 \pm 77.2$ ) was higher than CBZ group ( $114 \pm 35.2$ ) ( $P = 0.023 < 0.05$ ). However, serum high-density lipoprotein level was lower in VPA group than controls ( $45.2 \pm 11.7 < 54.4 \pm 13.9$ ) ( $P = 0.008 < 0.05$ ). Serum insulin, FBS, HOMA-IR, cholesterol, and low-density lipoprotein did not demonstrate statistically significant differences between the two groups ( $P > 0.05$ ). **Conclusion:** Despite the majority of previous studies that are against VPA and according to our study, VPA could be prescribed safely and it may not cause IR and its complications.

**Keywords:** Body mass index, carbamazepine, epilepsy, homeostatic model assessment insulin resistance, insulin resistance, lipid profile, sodium valproate

### Introduction

Valproic acid (VPA) is a widely used broad-spectrum antiepileptic drug (AED) for therapy of generalized and focal epilepsies.<sup>[1-3]</sup> A significant weight gain in the course of treatment of epilepsy with VPA was described in several clinical studies.<sup>[4-8]</sup> Although several studies have analyzed this side effect of VPA treatment, the cause remained unknown.<sup>[9]</sup> Several mechanisms have been postulated, including increased appetite and food intake,<sup>[10-12]</sup> increased thirst and energy-rich beverages,<sup>[10,11]</sup> a direct effect of VPA, or a metabolite on the hypothalamus,<sup>[12]</sup> decreased capacity for luxury or facultative thermogenesis (minor temperature changes in hypothalamus can be an explanation for increased appetite),<sup>[10,11,13]</sup> and impaired metabolism of fatty acid.<sup>[10]</sup> Weight gain due to VPA treatment is usually observed during the first 3 months of therapy,<sup>[14-18]</sup> reaching its maximum amount after 6 months.<sup>[11-13,19]</sup> Rather than cosmetic

adverse effects, obesity and its associated insulin resistance (IR) are leading cause of premature death. It is estimated that approximately 300,000 death per year happened due to obesity-related morbidity.<sup>[20]</sup> Obesity has also become one of the most important health problems all around the world and it is no longer the sole problem of the developed countries, as its prevalence is increasing all over the globe including South-East Asia, Middle East, and Iran.<sup>[21,22]</sup> Psychosocial consequences are substantial as well,<sup>[23]</sup> including a decline in health-related quality of life.<sup>[24,25]</sup> The overweight and obesity may soon become as much health-threatening as cigarette smoking. Obesity is known as the gateway disease that can lead to the metabolic syndrome and type 2 diabetes with increasing risk of cardiovascular and stroke diseases, hypertension, obstructive sleep apnea syndrome, obesity hypoventilation syndrome, gallbladder disease, and certain types of cancer. It should be considered

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that epilepsy is, after headache, the second most common neurological disorder.<sup>[26]</sup> In addition, because epileptic patients have to use AED for a long time and often lifelong, these complications, especially cardiovascular and cerebrovascular, are inevitable. On the other hand, weight gain can cause noncompliance or discontinuation of anticonvulsants. We chose carbamazepine (CBZ) for comparison due to its lower side effect on insulin, lipid levels, and weight gain.<sup>[27,4]</sup> As different studies reported controversial results and also there was not any definite survey in our population, we decided to investigate the IR in two groups of epileptic patients treated with sodium valproate (VPA) and CBZ. By determining the association between VPA and hyperinsulinemia, we could decrease related mortalities and morbidities by modifying this side effect.

## Materials and Methods

The study was carried out in the outpatient clinic, Department of Neurology, Alzahra University Hospital. Epilepsy type was classified according to the recommendations of the international league against epilepsy.<sup>[28]</sup> Sixty patients, who were between 18 and 50 years old, suffered from idiopathic generalized or focal epilepsy and received monotherapy treatment with VPA or CBZ were selected randomly. This study was done without health-controlled group. Patients who had other medical problems including renal failure, hepatic failure, endocrinopathy, symptomatic epileptic patient like tumor, trauma, infection, neurodegenerative disorders, and those who did not agree to participate in the study were excluded. Drug dosage was 400–2000 mg daily for VPA and 400–1200 mg daily for CBZ. Duration of therapy was at least 6 months, and as we have mentioned before, the maximum effect of VPA on weight gain is after the 6<sup>th</sup> month of treatment.<sup>[11-13,19]</sup> The protocol was approved by the Ethical Committee of our Institution, and an informed consent was obtained from all the patients after a full informative session. Patients' characteristics are explained in Table 1.

This study was a cross-sectional and descriptive one. At first, medical history of the patients was studied.

**Table 1: Characteristics of randomized subjects**

Demographic Characteristics	VPA group	CBZ group
Number of sexes (%)		
Female	23 (76.7)	18 (60)
Male	7 (22.3)	12 (40)
Age in years, mean (range)	33.76 (18-50)	33.43 (18-50)
Mean drug dosage (mg/day)	1013	673
Seizure type, <i>n</i> (%)		
Generalized onset	18 (60)	11 (36.67)
Partial onset	12 (40)	19 (63.33)
Prevalence of obesity	5 (16.6)	1 (3.3)
Prevalence of being overweight	12 (40)	7 (23.3)

VPA: Valproic acid, CBZ: Carbamazepine

Then they were clinically examined. The type of seizure, onset of seizure, kind of AED, and drug dosage, onset of treatment, and duration of treatment were registered. Body mass index (BMI) was measured ( $[\text{weight}/\text{height}^2]$   $[\text{kg}/\text{m}^2]$ ). According to the WHO and the National Heart, Lung, and Blood Institute, BMI results are classified as follows: Underweight:  $<18.5 \text{ kg}/\text{m}^2$ ; normal weight:  $18.5\text{--}24.9 \text{ kg}/\text{m}^2$ ; overweight:  $25\text{--}29.9 \text{ kg}/\text{m}^2$ ; Class I obesity  $30\text{--}34.9 \text{ kg}/\text{m}^2$ , Class II obesity  $35\text{--}39.9 \text{ kg}/\text{m}^2$ , and Class III obesity  $>40 \text{ kg}/\text{m}^2$ .<sup>[29,30]</sup>

After an overnight fast, blood samples were obtained at 8:00 AM in order to determine serum fasting insulin, fasting blood glucose (FBS), total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and triglyceride (TG).

Serum insulin and IR were measured with radioimmunoassay and homeostatic model assessment (HOMA) index, respectively.

HOMA is a method assessed to quantify IR and beta-cell function.  $\text{HOMA-IR} = \text{fasting serum insulin (mU/L)} \times \text{FBG (mol/l)} / 22.5$ .<sup>[31,32]</sup> Serum samples were analyzed in Hasht Behesht laboratory with radioimmunoassay method. The company that made glucose kit was Pars Azmun (Tehran, Iran) and the one that made insulin kit was radiocel (Tehran, Iran).

## Statistical analysis

Analysis was carried out using the statistical package of SPSS software (Version 16.0. Chicago, Inc) for personal computers. Chi-square test, *t*-test, and Pearson correlation test were used. *P* values less than 0.05 were considered significant.

## Results

A total of 60 subjects were randomized to treatment (30 VPA and 30 CBZ). There were 23 female and 7 male in VPA group, 18 female and 12 male in CBZ group [Table 1]. Chi-square test noted that difference in number of sexes was not statistically significant (*P*-value =  $0.15 > 0.05$ ). The main results are summarized in Table 2. BMI was higher in VPA-treated patients in comparison to CBZ group ( $25.7 \pm 3.5 > 21.7 \pm 4.1$ ). It was statistically significant due to *P* value of 0.000 ( $0.000 < 0.05$ ).

Serum TG levels were higher in VPA-treated patients than the other group ( $150 \pm 77.2 > 114 \pm 35.2$ , *P* =  $0.023 < 0.05$ ). VPA-treated patients had significantly lower serum HDL ( $45.2 \pm 11.7 < 54.4 \pm 13.9$ , *P* =  $0.008 < 0.05$ ).

There were no significant differences in serum LDL and total cholesterol between two groups (*P* =  $0.888 > 0.05$ , *P* =  $0.430 > 0.05$ ). There were also no statistically significant differences between the groups concerning fasting serum insulin, FBS, and HOMA-IR index (*P* =  $0.881 > 0.05$ ,  $0.999 > 0.05$ ,  $0.440 > 0.05$ ).

**Table 2: Means of measured variables**

Variable	Mean±SD		P	Normal range
	VPA group	CBZ group		
Insulin	10.04±4.33	9.87±4.43	0.881	7-25 µl/ml
FBS	82.37±8.51	82.36±7.66	0.999	65-110 mg/dl
HOMA-index	2.05±0.84	1.88±0.87	0.440	<2.5
BMI	25.68±3.51	21.72±4.06	0.000	20-25 kg/m <sup>2</sup>
Cholesterol	179.56±36.57	172.60±31.09	0.430	150-200 mg/dl
TG	150.70±77.15	114.43±35.19	0.023	50-150 mg/dl
HDL	45.17±11.73	54.36±13.93	0.008	29-80 mg/dl
LDL	103.10±29.30	102.03±28.95	0.888	>130 mg/dl

HDL: High-density lipoprotein, LDL: Low-density lipoprotein, BMI: Body mass index, FBS: Fasting blood glucose, HOMA: Homeostatic model assessment, TG: Triglyceride, SD: Standard deviation, VPA: Valproic acid, CBZ: Carbamazepine

Among VPA-treated patients, 40% (12 cases) had BMI between 25 and 29.9 (overweight) and 16.6% (5 cases) were obese (BMI > 30). However, the prevalence of being overweight and obesity in CBZ group was 23.3% and 3.3%, respectively.

## Discussion

Obesity and dyslipidemia with other known risk factors are the major problems of public health. Psychosocial consequences are substantial as well,<sup>[23]</sup> including decline in health-related quality of life.<sup>[24,25]</sup>

In this study, VPA treatment was shown to be associated with higher BMI, TG, and lower HDL than CBZ group. Despite the majority of previous studies that have mentioned obesity as a common complication of VPA,<sup>[4-8,11-19]</sup> we have found a few articles without this effect.<sup>[27,29]</sup> In our study, 16.6% (5 cases) of VPA-treated patients and 3.3% (one case) of CBZ-treated were obese. Forty percent (12 cases) of main groups and 23.3% (7 cases) of controls were overweight. In addition, we could not find any relationship between drug dosage and BMI ( $P < 0.05$ ). All our results did not show statistically significant difference in two sexes ( $P < 0.05$ ). There are several surveys that have studied the prevalence of obesity and being overweight in Iran. In Tehran, Lipid and Glucose Study (TLGS), 40% of the adult study population (lived in Tehran, Iran) were overweight (BMI, 25–29.9 kg/m<sup>2</sup>) and 23.1% of them were obese (BMI  $\geq$  30 kg/m<sup>2</sup>).<sup>[22]</sup> Moreover, in a recent survey of blood donors in Tehran, 47% of the studied Iranian adult population were overweight and 24% of them were obese.<sup>[34]</sup> Another study in Iran noted the prevalence of 62.2% for overweight women and 28% for obese ones.<sup>[35]</sup> There are several other investigations that correlated with these statistics, respectively.<sup>[34,35]</sup> An important finding is that the overall prevalence of obesity in an Iranian population is quite comparable to the United States<sup>[36]</sup> and higher than in the United Kingdom, France, the Netherlands, and Italy.<sup>[37-41]</sup> These results are consistent with similar reports from Iran,<sup>[22,42,43]</sup> as well as other

countries in the Middle East.<sup>[44-51]</sup> In one study in the Iranian population with 6246 participants, the mean TGs values were 190 and 162 mg/dl for males and females, respectively ( $P < 0.0001$ ). The mean HDL-cholesterol was 39 in males and 45 mg/dl in females ( $P < 0.0001$ ).<sup>[7]</sup> Hence, we must consider that although our results were statistically different in two groups, they were almost the same as the general population.

According to our results, we could mention that the prevalence of obesity and being overweight in VPA-treated patients is almost the same as the Iranian population and even lower for obesity, but in the control group (CBZ), it is less. It is controversial some studies showed that CBZ has no effects on the prevalence of metabolic syndrome in the epileptic patients.<sup>[52]</sup>

Due to this clue, something new might come to our mind that why these epileptic patients have even less BMI than the studied population? To find the answer, we must consider lots of factors, for example, neuropsychiatric, socioeconomic, genetic risks, and pregnancy,<sup>[53-57]</sup> which may interfere with our results. In addition, simultaneous study of other factors, for example, depression, nutrition in epileptic patients could help to find a true prevalence of this side effect. Statistically significant results for TG and HDL are related to BMI just the same as several previous studies.<sup>[8,16,33]</sup>

Different from the majority of previous surveys<sup>[6,9,16,27,33]</sup> and similar to a few of them<sup>[53-55]</sup> in our study not only FBS, serum insulin, and HOMA-IR did not show any statistically significant difference between two groups, but also all measurements were in normal range [Table 2]. Finally, IR did not happen in any of our patients. Our results could be in favor of VPA as an effective AED because as we mentioned hyperinsulinemia and IR are the major health problems for human beings. Reported IR might have other causes such as genetic rather than VPA side effect. In our study, we tried to find probable associations between different variables and we have found a direct relation between BMI and serum total cholesterol ( $r = 0.372$ ,  $P = 0.003$ ).

There was another statistically significant direct relation between HOMA-index and serum TG ( $r = 0.282$ ,  $P = 0.029$ ).

## Conclusion

Almost the same prevalence of obesity and being overweight in comparison to the Iranian population might be a key to find more important factors such as nutritional, depression, and genetic that cause changes in BMI of epileptic patients. Despite the majority of previous studies that are against VPA and according to our study and a few related articles VPA could be prescribed safely and it may not cause IR and its complications. Similar studies with larger number of subjects for acquiring better insight about

other causes of hyperinsulinemia and IR in this population are suggested.

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### Conflicts of interest

There are no conflicts of interest.

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