

Is there an association between metabolic syndrome and drug resistance in patients with epilepsy?

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Abstract

Epilepsy is one of the most prevalent neurological disorders, affecting approximately 1% of the population, with one-third of patients developing drug-resistant epilepsy (DRE). In addition, metabolic syndrome (MetS), through inflammation and oxidative stress mechanisms, may influence epilepsy outcomes. The main objective of the current study is to determine the prevalence of MetS among patients with epilepsy (PWE) and evaluate its association with DRE. This cross-sectional study was conducted between March and October 2024 at a regional hospital in Tehran, involving 180 PWE aged 18 to 70 years. Participants were classified into well-controlled epilepsy and DRE groups based on the International League Against Epilepsy criteria. MetS was also diagnosed using the International Diabetes Federation guidelines. Data were analyzed using SPSS software, which illustrated that MetS was present in 33.8% of participants, with a significantly higher prevalence in well-controlled epilepsy patients (47.7%) compared with those with DRE (20%, $P < .001$), and it played a role in predicting response to treatment in PWE. Furthermore, body mass index, waist circumference, and blood pressure were significantly higher in the well-controlled group ($P = .012$ and $P = .007$, respectively). MetS was more prevalent in well-controlled epilepsy patients and was associated with a decreased risk of DRE. However, further research is needed to explore the relationship between MetS and DRE.

Abbreviations: ASM = antiseizure medication, BMI = body mass index, BP = blood pressure, DRE = drug-resistant epilepsy, FBS = fasting blood sugar, HDL = high-density lipoprotein, HDL-C = high-density lipoprotein cholesterol, IDF = International Diabetes Federation, ILAE = International League Against Epilepsy, MetS = metabolic syndrome, PWE = patients with epilepsy, T-chol = total cholesterol, TG = triglycerides, WC = waist circumference.

Keywords: drug-resistant epilepsy, epilepsy, metabolic syndrome, prevalence, risk factors

1. Introduction

Epilepsy is one of the most common brain diseases that, regardless of gender, age, and race, affects 5 to 10 individuals per 1000 yearly.^[1] Despite the availability of diverse therapeutic regimens for epilepsy management, one-third of patients exhibit inadequate responses to these interventions, failing to achieve sustained seizure remission.^[2] In such cases, the International League Against Epilepsy (ILAE) defined drug-resistant epilepsy (DRE) as the failure of adequate trials of 2 tolerated, appropriately chosen, and appropriately used antiseizure medications (ASMs), whether as monotherapies or in combination, to achieve sustained seizure freedom.^[3] DRE is associated with a heavy healthcare-related economic burden.^[4,5] Therefore, the

identification of risk factors that play a role in DRE assumes importance.^[3,5]

Metabolic syndrome (MetS), according to the International Diabetes Federation (IDF), is defined by the presence of 3 or more of the following parameters: insulin resistance, low degree of high-density lipoprotein cholesterol (HDL-C), elevated triglycerides (TG), central obesity, and hypertension.^[6] MetS should be distinguished from the metabolic etiology of epilepsy as defined by the ILAE classification, where seizures are a core symptom of a specific metabolic disorder.^[7] MetS contributes to the development of a proinflammatory and oxidative stress state within the body.^[8] On the other hand, Hayatdavoudi et al^[9] demonstrated that inflammation had a significant impact on the pathophysiology of epilepsy by disrupting the blood-brain barrier, which maintains a stable environment for cells of the

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central nervous system, and stimulating astrocytes involved in regulating ion channels and neuronal depolarization. It appears that these 2 conditions are linked through inflammation. As seizure control represents a significant challenge for epilepsy patients,^[10] it is essential to ascertain the determinants of seizure control.

Furthermore, several studies indicated that a significant association was observed between individuals with epilepsy who are obese and may have a higher risk of developing DRE.^[11,12] On the other hand, repeated seizures create an extraordinary metabolic burden,^[13] and this increase in energy expenditure may lead to weight loss.^[14] So, further research is needed to investigate this correlation between seizure and MetS. Therefore, the main aim of the present cross-sectional study is to estimate the prevalence of MetS among individuals who suffer from epilepsy and examine the probable association between MetS and response to ASM among them.

2. Methods and materials

2.1. Study design and participants

The present cross-sectional study included adult patients (18–70 years) with a confirmed diagnosis of epilepsy according to the criteria of the ILA. Participants were recruited from both outpatient and inpatient neurology services at a regional hospital in Tehran between March 2024 and October 2024. All patients were under regular neurologic follow-up for at least 1 year and were receiving ASMs, with adherence to treatment confirmed by neurologist assessment. Both focal and generalized epilepsies were included.

DRE was defined according to ILAE criteria as the failure of adequate trials of 2 tolerated, appropriately chosen, and appropriately used ASMs (whether as monotherapy or in combination) to achieve sustained seizure freedom.^[3] Based on these criteria and neurologist assessment, participants were classified into either the DRE or well-controlled epilepsy group.

Sample size was estimated based on the reported prevalence of obesity in epilepsy,^[15] yielding an effect size (Cohen's $h \approx 0.55$). With a significance level of $\alpha = 0.05$ and 80% statistical power, a minimum of 140 participants (70 per group) was required to detect differences in MetS prevalence between groups. A total of 180 patients (80 females and 100 males) were ultimately enrolled, exceeding the required sample size and ensuring adequate statistical power.

Exclusion criteria were postmenopausal or pregnant women (due to metabolic alterations); individuals with endocrine disorders other than diabetes mellitus; active malignancy; current use of systemic corticosteroids; use of medications affecting body weight or metabolism; and documented nonadherence to ASM therapy.

2.2. Data gathering

Demographic and seizure-related parameters of included subjects, such as age, sex, education level, past medical history, past drug history of ASM, seizure attack-free days, duration of each seizure attack, seizure attack frequency in the past month, and the Seizure Severity Questionnaire, were gathered.

In addition, anthropometric measurements including weight (with a precision of 0.1 kg) in light clothing using a Seca scale, height (with a precision of 0.5 cm) using a wall-mounted stadiometer, and waist circumference (WC to the nearest 0.5 cm) using a measuring tape at the level of midway between the lower costal margin and the iliac crest were obtained by a trained assessor. Body mass index (BMI) was calculated by dividing weight in kilograms by height in meters squared. Blood pressure (BP) was measured using a sphygmomanometer. Serum triglyceride (TG), HDL-C, total cholesterol (T-chol), low-density lipoprotein

cholesterol (LDL-C), and fasting blood sugar (FBS) levels were measured from blood samples collected from participants after a 12 to 14 hour fasting. Or FBS were collected from participants after a 12 to 14 hour for the measurement of serum TG, HDL-C, LDL-C, T-chol, and FBS levels fast.

2.3. Metabolic syndrome: definition

MetS was diagnosed according to the harmonized definition proposed in the 2009 Joint Interim Statement developed in collaboration with the International Diabetes Federation.^[6] Based on this definition, participants with at least 3 or more of the following abnormalities were classified as having MetS: FBS ≥ 100 mg/dL or previously diagnosed diabetes; HDL-C < 40 mg/dL in men and < 50 mg/dL in women, or drug treatment for low HDL-C; TG ≥ 150 mg/dL or drug treatment for elevated TG; BP $\geq 130/85$ mm Hg or antihypertensive treatment; and abdominal obesity defined as waist circumference ≥ 94 cm for men and ≥ 80 cm for women.

2.4. Statistical analysis

All data were entered into Microsoft Excel and then analyzed using SPSS Statistics for Windows (Version 23.0; IBM Corp.). Qualitative variables were presented as frequency and percent, and quantitative variables as mean $\pm$ standard deviation. Differences between groups were assessed using the chi-square test for categorical variables. Continuous variables were first tested for normality using the Shapiro–Wilk test; normally distributed variables were analyzed with the independent-samples t test, and non-normally distributed variables with the Mann–Whitney U test. Clinically relevant variables, including age, gender, onset, and MetS, were considered for inclusion in the multivariable logistic regression model. Variables causing multicollinearity or unstable estimates were excluded to maintain model stability. Logistic regression analysis was then performed to identify factors predicting the development of DRE. Results were considered statistically significant at a two-tailed P value $< .05$.

2.5. Ethics approval

It should be mentioned that this current study has been registered with the registration number 70826 in the office of the Institute of Board Review of *Tehran University of Medical Sciences, Tehran, Iran*, and approved by the Ethics Committee of Research under the number: IR.TUMS.IKHC.REC.1403.083. In addition, informed consent was obtained from each participant before their involvement in the study.

3. Results

The mean age of the total 180 participants was 34.58 ± 11.50 years, and 44.4% were women. The individuals' average age at onset of epilepsy was 18.09 ± 12.75 years, with a median duration of epilepsy of 15.5 years. According to ILAE criteria, and a neurologist's assessment, 90 patients suffer from DRE, and the other half of participants were patients with well-controlled epilepsy. Statistically significant differences were observed in age ($P = .008$) and gender ($P = .036$) between the groups. Among the well-controlled epilepsy groups, 15 patients were on monotherapy with valproic acid, 6 were on carbamazepine, 33 were on levetiracetam, and the remaining individuals were on polytherapy with 2 or more ASMs.

Based on the IDF definition of MetS, 28 (15.5%) of the population studied had FBS ≥ 100 (6 of well-controlled epilepsy and 22 of DRE), 44 (24.4%) had TG ≥ 150 (26 of well-controlled epilepsy and 18 of DRE), 45 (25%) had BP $\geq 130/85$ (36 of well-controlled epilepsy and 9 of DRE), 42

(52.5%) of women had HDL-C <50, and 48 (48%) of men had HDL-C <40 (51 of well-controlled epilepsy and 39 of DRE). In addition, 49 (61.2%) of women had a waist circumference (WC) ≥ 80 and 57 (57%) of men had a WC ≥ 94 (64 of well-controlled epilepsy and 42 of DRE). Taken together, 61 (33.8%) of patients with epilepsy (PWE) reported having MetS. The mean BMI of the participants was 23.86 ± 4.25 kg/m². Among the PWE, 45 (25%) were classified as overweight (BMI 25–29.9 kg/m²) and 19 (10.5%) as obese ($30 \leq \text{BMI} < 35$ kg/m²).

Mean FBS was 88.68 ± 14.46 mg/dL, with a median (interquartile range) of total cholesterol 169.5 (143.25–188.75) mg/dL, TG 106 (74.25–152.5) mg/dL, LDL 97 (74–112) mg/dL, and HDL 44 (36–54) mg/dL. A comparison between the well-controlled epilepsy and DRE groups is shown in Table 1. The prevalence of MetS was significantly higher in patients with well-controlled epilepsy compared with the DRE group ($P < .001$). Also, a significant difference was observed between the well-controlled epilepsy and DRE groups in terms of weight, BMI, WC, and BP, with higher values found in the

well-controlled epilepsy group ($P = .008$, $P = .011$, $P < .001$, and $P < .001$, respectively).

Compared with the well-controlled group, individuals with DRE had an earlier age at seizure onset ($P < .001$) and reported higher seizure severity based on the Seizure Severity Questionnaire ($P < .001$). Also, the duration of attacks was longer in the DRE group compared with the other group ($P < .001$).

In addition, owing to multivariate analysis, it is common for the significance of predictive variables to change. Therefore, many studies include relevant and potentially predictive variables in their analysis.^[15] Using this criterion, logistic regression analysis revealed that the presence of MetS was associated with a decreased risk of DRE ($P = .001$, $R = 0.266$) (Table 2).

4. Discussion

The current cross-sectional study was carried out on the prevalence of MetS among PWE. Furthermore, we also evaluated how

Table 1

Comparative analysis of study variables between well-controlled epilepsy and drug-resistant epilepsy.

Variables	All participants (n = 180)	Well-controlled epilepsy (n = 90)	Drug-resistant epilepsy (n = 90)	P
Sex, N (%)				
Male	100 (55.6)	58 (64.4)	42 (46.7)	.036*†
Female	80 (44.4)	32 (35.5)	48 (53.3)	
Education, N (%)				
Illiterate	15 (8.3)	11 (12.2)	4 (4.4)	.084†
Undergraduate	78 (43.3)	36 (40)	42 (46.7)	
Diploma	60 (33.3)	33 (36.7)	27 (30)	
Academic degree	27 (15)	8 (8.8)	19 (21.1)	
Age (yr)	34.58 ± 11.50	36.83 ± 12.80	32.33 ± 9.59	.008*‡
Height (cm)	167.65 ± 7.92	168.43 ± 7.55	166.86 ± 8.24	.185‡
Weight (kg)	67.43 ± 14.54	70.33 ± 15.64	64.63 ± 12.80	.008*‡
BMI (kg/m ²)	23.86 ± 4.25	24.66 ± 4.76	23.06 ± 3.52	.011*‡
Overweight, N (%)	45 (25)	30 (33.3)	15 (16.7)	.015*†
Obese, N (%)	19 (10.5)	12 (13.3)	7 (7.7)	.213†
WC (cm)	87.15 ± 11.47	90.83 ± 11.59	83.46 ± 10.13	< .001*‡
SBP (mm Hg)	116.46 ± 12.97	119.83 ± 15.76	113.10 ± 8.20	< .001*‡
DBP (mm Hg)	77.1 ± 8.97	80.13 ± 8.68	74.06 ± 8.23	< .001*‡
BP $\geq 130/85$ (mm Hg), N (%)	46 (25.5)	37 (41.1)	9 (10)	< .001*‡
FBS (mg/dL)	88.68 ± 14.46	89.03 ± 12.04	88.33 ± 16.59	.747‡
TG (mg/dL)	106 (74.25–152.5)	88.5 (72–156)	109 (82–143)	.116§
HDL-C (mg/dL)	44 (36–54)	44 (36–48)	44 (36–58)	.138§
LDL-C (mg/dL)	97 (74–112)	93.5 (77–109)	104.5 (74–115)	.091§
T-chol (mg/dL)	169.5 (143.25–188.75)	159 (136–180)	172.5 (150–198)	.013*§
Metabolic syndrome, N (%)	61 (33.8)	43 (47.7)	18 (20)	< .001*†
Onset (age of diagnosis)	16.5 (9–25)	21 (16–31)	9 (3–19)	< .001*§
Duration of disease (yr)	15.5 (6.25–24.75)	8.5 (3–20)	21 (14–27)	< .001*§
Duration of attack (min)	1 (1–2)	1 (1–2)	2 (1–2.5)	.009*§
Frequency/mo	0.25 (0–7.75)	0	7.5 (3–13)	< .001*§
Free seizure day	90 (4–496.25)	452 (330–730)	4 (1–9)	< .001*§
SSQ total score	43.49 ± 18.50 (n = 153)	37.23 ± 17.72 (n = 63)	47.86 ± 17.64 (n = 90)	< .001‡
Drug, N (%)				
VPA	78 (44.1)	36 (40.0)	42 (48.3)	.292†
CBZ	69 (38.3)	18 (20.0)	51 (56.7)	< .001*†
LCM	45 (25.0)	15 (33.3)	30 (66.7)	.015*†
LEV	120 (66.7)	54 (45.0)	66 (55.0)	.082†
TPM	13 (7.2)	0	13 (14.4)	< .001*†
CLB	12 (6.7)	6 (6.7)	6 (6.7)	1.000†
LTG	43 (23.8)	6 (6.7)	37 (41.1)	< .001*†
PHB	9 (5.0)	0	9 (10.0)	.003*†

Values are given as mean $\pm$ standard deviation except for TG, T-chol, HDL-C, LDL-C, onset, duration, frequency/month, free seizure day given as median (Q1–Q3).

BMI = body mass index, DBP = diastolic blood pressure, FBG = fasting blood glucose, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, N = number, SBP = systolic blood pressure, SSQ = Seizure Severity Questionnaire, T-chol = total cholesterol, TG = triglyceride, WC = waist circumference.

†Pearson chi-square test.

‡Impaired sample t-test.

§Mann–Whitney U test.

* $P < .05$ was considered statistically significant.

Table 2**The multivariable logistic regression model in determining the role of metabolic syndrome in predicting drug-resistant epilepsy.**

Factor	Beta	P	OR	95% CI	
				Lower	Upper
Gender	0.198	.617	1.219	0.561	2.650
Age	0.042	.033*	1.043	1.004	1.084
Onset	−0.128	< .001*	0.880	0.842	0.920
Metabolic syndrome	−1.132	.001*	0.266	0.123	0.574

Hosmer–Lemeshow goodness of fit: Chi-square = 12.24, *P* = .141.**P* < .05 was considered statistically significant.

this prevalence differed between 2 subgroups of well-controlled epilepsy and DRE.

One-third of our study population was categorized as MetS, and a significant difference was shown in MetS prevalence between well-controlled epilepsy and DRE groups, with higher rates in the well-controlled group. According to logistic regression analysis, the presence of MetS, which was adjusted for sex, age, and onset of epilepsy, was associated with better control of epilepsy among individuals. However, this should be interpreted as a correlation rather than evidence of a causal relationship.

Our findings are similar to the 32.6 percent of MetS prevalence in Söylemez et al research.^[16] Most studies examining the prevalence of MetS in seizure patients have not reported prevalence based on the response to ASMs, and the study populations were a mix of well-controlled and DRE patients.^[17–19] While Vooturi's study, which exclusively examined patients with well-controlled epilepsy, reported a 52.6% prevalence of MetS, the highest observed.^[20] Our findings corroborate these results, revealing a significantly higher prevalence of 47.7% in our well-controlled PWE compared with the 20% observed in those with refractory epilepsy.

Some studies have suggested a link between MetS and epilepsy.^[17,18,20] Potential factors include changes in inflammatory markers, adiponectin levels, and energy metabolism.^[21,22]

In epilepsy, disruptions in glucose and lipid metabolism can trigger inflammatory pathways, which in turn may increase neuronal excitability and contribute to disease progression.^[23] In line with this, clinical research has shown that adults with epilepsy—even those newly diagnosed and not yet on antiepileptic medication—tend to have higher BMI and obesity rates compared with healthy individuals. These metabolic changes are influenced by factors such as age, gender, epilepsy etiology, and inflammatory markers.^[24] Altogether, these findings provide a plausible biological explanation for the association we observed between MetS and treatment response in our study.

The association of MetS and response to ASMs has rarely been investigated. Although the prevalence of MetS varied between the two groups, a significant association was found between MetS and DRE, it important to note that this observational study should be viewed as hypothesis-generating, and further longitudinal research is required to confirm causal relationships. This discrepancy in prevalence may be attributed to the fact that certain ASMs—for instance, carbamazepine, topiramate, and lamotrigine, compared with others that can contribute to MetS,^[25] may not influence or may even reduce values of factors contributing to MetS and anthropometric indices such as BP, waist circumference, BMI, and insulin resistance.^[26–30] Potential mechanisms include reducing appetite and subsequent caloric intake, decreasing leptin levels while increasing adiponectin levels, enhancing insulin sensitivity, and influencing blood electrolyte concentrations.^[31–34] In our study population, those with DRE exhibited significantly higher consumption of these medications compared with the well-controlled group. The underlying mechanisms linking MetS to epilepsy and treatment response are complex and require further investigation.

Although our study did not stratify patients based on epilepsy type (focal vs generalized) or etiology, this represents an important area for future investigation. Detailed classification would require consistent access to neuroimaging and electroencephalography data, which were not uniformly available in our cohort. Future studies should aim to incorporate these clinical variables to better understand how epilepsy subtype and underlying etiology may influence the prevalence and impact of MetS.

The clinical implications of our findings are significant, as higher WC and high BP have a higher risk of developing cardiovascular diseases such as coronary heart disease or stroke.^[35–37] Therefore, PWE, especially those with well-controlled seizures, should be closely monitored for the development of MetS, particularly the 2 components of MetS definition criteria, WC and BP, which were significantly higher in participants with well-controlled epilepsy. Early diagnosis and management of MetS can help reduce the risk of cardiovascular complications and improve overall health outcomes.^[38]

While our study is the first to comprehensively examine the prevalence of MetS and its relationship to treatment response in PWE, it is not without limitations. The cross-sectional design hindered our ability to analyze how different ASMs affect MetS among participants with epilepsy. Nonetheless, future studies should employ a prospective cohort design with a larger sample size to further investigate this relationship. Moreover, exploring other relevant factors, such as physical activity, and including a healthy control group would enhance the robustness of the findings. In addition, certain clinically relevant variables, such as detailed ASM subtypes and seizure frequency, were not included in the multivariable analysis due to limited subgroup sizes and concerns regarding model instability and overadjustment. Future studies should also consider stratifying ASMs based on their enzyme-inducing properties to better understand their potential impact on lipid metabolism and the development of MetS in PWE. In addition, our study included both well-controlled and drug-resistant patients. However, all participants were recruited from a single tertiary referral center, which may overrepresent patients with more complex clinical profiles. Therefore, caution is needed when generalizing these findings to community-based or primary care populations.

5. Conclusion

In conclusion, our study results demonstrated that nearly one-third of individuals with epilepsy have MetS according to IDF 2009 criteria. The prevalence of MetS was significantly higher in well-controlled epilepsy patients (47.7%) compared with the DRE group (20%), and a role can be expected for MetS in predicting response to treatment in PWE. Further cohort-designed studies are needed to investigate the interaction between MetS and the development of DRE.

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