

Evaluation of risk factors for metabolic syndrome in epileptic patients in Palembang, Indonesia: a hospital-based and case-control study

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ABSTRACT

Aim To examine the association between metabolic syndrome and risk factors in epileptic patients at Dr. Mohammad Hoesin General Hospital in Palembang, Indonesia.

Methods A hospital-based comparative case control research was conducted from July to September 2023. A total of 102 patients in the epilepsy group and 102 in the control group participated in this study. We conducted the data collection approach in three stages: a questionnaire, anthropometric measures and biochemical analysis.

Results Epilepsy patients were more likely to develop metabolic syndrome than the controls. The epilepsy group exhibited higher triglycerides, fasting blood sugar, and lower high density lipoprotein (HDL) values than the control group. The epilepsy group exhibited sedentary behaviour, while the control group had moderate to intense physical activity ($p < 0.05$). Epilepsy patients who take polytherapy, or several antiepileptic drugs, were 8.43 times more likely to develop metabolic syndrome (OR=8.43; 95%CI=1.45-32.12). Epilepsy patients with body mass index (BMI) >25 had 1.57 times the risk of metabolic syndrome (OR=1.57; 95%CI=1.16-2.34). Epilepsy patients with total cholesterol levels >200 mg/dL have a 5.81-fold higher risk of metabolic syndrome (OR=5.81; 95%CI=1.23-23.32).

Conclusion Our study found that more than a quarter of epilepsy patients have metabolic syndrome. The main risk factors for metabolic syndrome in epilepsy patients were a sedentary lifestyle, several antiepileptic medications, overweight, and increased total cholesterol levels.

Keywords: anticonvulsants, blood glucose, cholesterol, sedentary behaviour, triglycerides

INTRODUCTION

Epilepsy is a prevalent neurological disorder worldwide (1,2). From data provided by the World Health Organization (WHO), the global prevalence of epilepsy is around 50 million individuals (2). Epilepsy is a neurological condition defined by the occurrence of repeated seizures (3). Seizures are instances of atypical electrical activity in the brain that can lead to alterations in awareness, movement, sensation, thoughts, or behaviour (4).

Risk factors for non-communicable diseases (NCDs), such as metabolic syndrome (MetS), are often observed within the epilepsy community (5). This condition leads to increased illness and death among patients with epilepsy (PWE) (6,7). Atherosclerosis-promoting factors such as obesity and significant changes in metabolic components may contribute to this gradual onset (7,8). Metabolic syndrome (MetS) is a condition char-

acterized by an imbalance in calory intake, linked to sedentary lifestyles and eating patterns (9). It increases the risk of chronic illnesses like heart disease, stroke, diabetes, and epilepsy, with recurrent seizures being a 2.5-fold risk (10). Obesity, a key component of metabolic syndrome, can cause brain inflammation, disrupting function and increasing the risk of seizures due to elevated levels of proinflammatory cytokines. Brain inflammation can lead to cell destruction, cognitive impairment, chemical imbalance, and increased seizure risk due to disruption of nerve impulses and decreased brain function (11,12). Hypertension, marked by elevated blood pressure, can damage blood vessels in the brain, reducing blood supply and increasing the likelihood of seizures (13). This injury can lead to a decrease in the delivery of oxygen and nutrients to the brain, which can impact cognitive performance. Cerebral blood vessel thrombosis can lead to cerebral infarction, whereas brain haemorrhage can also elevate the likelihood of seizures. Elevated levels of cholesterol and triglycerides in dyslipidaemia can cause plaque buildup on blood vessel walls. This can impede the flow of blood to the brain and raise the likelihood of experiencing seizures (14).

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MetS is not only a contributing factor for illness and death in people with epilepsy, but the prolonged use of antiepileptic medicines, such as carbamazepine and phenytoin, also leads to metabolic profile problems that trigger the onset of MetS (15). There has been no research conducted in Indonesia to analyse the correlation between metabolic syndrome and risk variables in patients with epilepsy.

The aim of this study was to examine the association between metabolic syndrome and risk factors in epilepsy patients by comparing the data before and after anti-seizure medication (ASM).

PATIENTS AND METHODS

Patients and study design

Single-centre comparative case control research was conducted at Dr. Mohammad Hoesin General Hospital in Palembang, Indonesia, involving 1423 individuals diagnosed with epilepsy. The study was conducted from July to September 2023. The case group consisted of adult epilepsy patients, while the control group consisted of adult patients seeking medical care at the outpatient clinic (except severe diseases, mental illness and pregnant women). The study excluded patients with severe diseases (ischemic heart disease, stroke, lower respiratory tract infections, chronic obstructive pulmonary disease, cancer, tuberculosis, and cirrhosis), pregnant women, and mental issues. The sample size was established using Epi Info version 7 (16). The prevalence of elevated blood pressure, a component of MetS, was 27.4%, while the prevalence of epilepsy was estimated to be 50%. A minimum sample size of 186 was required, with additional 10% added to ensure the final sample size of 204. The sample procedure included successive sampling to ensure age and gender matching between the case and control groups.

The association between metabolic syndrome and risk factors in epilepsy patients was determined comparing the data before and after anti-seizure medication (ASM). The behavioural risk factors evaluated in epilepsy patients before and after antiepileptic medication were physical activity levels, fruit and vegetable consumption, alcohol intake, and smoking habits. The components of metabolic syndrome assessed included obesity, high density lipoprotein cholesterol (HDL-c), triglycerides (TG), blood pressure (BP), fasting blood sugar (FBS), metabolic syndrome (MetS) status, low density lipoprotein (LDL-c), and total cholesterol levels.

This study received ethical approval from the Ethical Committee of the Faculty of Medicine, Universitas Sriwijaya (Ref. No. 209/FKUNSRI/III/2023, approval date May 31, 2023).

Methods

The study involved three stages of data collection: questionnaire administration, anthropometric measurements and biochemical analysis. Participants in both groups completed a structured questionnaire that gathered information on socio-demographic characteristics (age, gender, education, occupation), lifestyle factors (physical activity, dietary habits, smoking, alcohol consumption), and epilepsy-specific details (type of epilepsy, duration, anti-epileptic drug use) through self-reporting or with the assistance of family members and healthcare professionals. The questionnaire was developed

based on a comprehensive literature review and expert consultation to ensure content validity. It was also pilot-tested on a small group of individuals with epilepsy to assess its clarity, comprehensibility, and internal consistency (Cronbach's alpha =0.92). Trained research personnel conducted anthropometric measurements after they chose the patients in the neurology polyclinic. These included height (measured using a stadiometer with participants standing barefoot and upright against a flat surface), weight (measured using a calibrated digital scale with participants wearing light clothing and no shoes), waist circumference (measured at the midpoint between the lower rib margin and the iliac crest using a non-stretchable measuring tape), and blood pressure (measured using a validated digital blood pressure monitor after participants had rested for at least 5 minutes in a seated position (Omron, Jakarta, Indonesia)).

Venous blood samples (5 mL) were collected from participants after an overnight fast of at least 8 hours. The samples were centrifuged, and the serum was analyzed using a Dimension EXL 200 System chemical analyzer (Siemens, Jakarta, Indonesia) to assess the following parameters; fasting blood glucose, triglycerides, high-density lipoprotein cholesterol (HDL-c), total cholesterol, low-density lipoprotein cholesterol (LDL-c) calculated using the Friedewald formula (17).

Metabolic syndrome was diagnosed using the National Cholesterol Education Program Adult Treatment Panel III criteria (18), which include three indicators: waist circumference (WC) >102 cm for male and 88 cm for females, systolic blood pressure \geq 130 mmHg or a diastolic blood pressure \geq 85 mmHg, triglyceride level \geq 150 mg/dL, HDL-c <40 mg/dL for males and <50 mg/dL for females, and fasting blood glucose level \geq 110 mg/dL. Alcohol consumption status was defined as those who had consumed alcohol on more than one occasion each week in the previous year, while smoking status refers to those who had smoked within the previous year. Fasting was characterized by the absence of calorie consumption within an 8-hour period. Vigorous physical activity was defined as activities that induce an elevated breathing rate and a robust heart rate for at least 30 minutes for a minimum of three days a week. Moderate physical activity was defined as activities that resulted in a moderate elevation in breathing frequency and heart rate for at least 30 minutes for at least three days per week. Low-level physical activity was defined as activities that do not match the standards for vigorous and moderate physical exercise. Low consumption of fruits and vegetables was defined as consuming less than five servings (equivalent to 400 grams) of fruits and vegetables daily. When it comes to raw green leafy vegetables, one serving was equivalent to one cup. For cooked veggies, one serving was equal to half a cup. As for fruits like apples, bananas, and oranges, one serving was considered to be one medium-sized fruit. For cooked or canned fruit or juice, one serving was equal to half a cup. Drug-responsive epilepsy was defined as epilepsy where the patient receiving the current anti-seizure medication (ASM) regimen had been seizure-free for a minimum of three times the longest pre-intervention interseizure interval or 12 months, whichever was longer, drug-resistant epilepsy was defined as epilepsy where seizures persisted and seizure freedom was unlikely to be achieved with further manipulation of ASM, and undefined was whether the epilepsy was drug resistant, drug responsive or neither (19,20).

Table 1. Sociodemographic, behavioural risk factors, and baseline data of patients before anti-seizure medication (ASM)

Variables	Category	Control group	Epilepsy group	p
Age (Mean ±SD)	N/A	35.54 ± 12.61	35.59 ± 12.62	1.000
No (%) of patients				
Gender	Male	56 (54.9)	56 (54.9)	1.000
	Female	46 (45.1)	46 (45.1)	
Occupation	Civil servant/employees	40 (39.2)	30 (29.4)	0.022
	Students	40 (39.2)	35 (34.3)	
	Unemployed/housewives	22 (21.6)	37 (36.3)	
Education	Primary school	25 (24.5)	43 (42.2)	0.032
	High school	54 (52.9)	49 (48.0)	
	College/university	23 (24.6)	10 (9.8)	
Physical activity level	Vigorous	36 (35.3)	24 (23.5)	0.024
	Moderate	44 (43.1)	40 (39.2)	
Fruits and vegetables intake/day	Low	22 (21.6)	38 (37.3)	0.016
	<5 servings	50 (49)	62 (60.8)	
Alcohol consumption	≥ 5 servings	52 (51)	40 (39.2)	0.065
	Drinker	24 (23.5)	10 (9.8)	
Smoking	Non-drinker	78 (76.5)	92 (90.2)	0.063
	Smoker	25 (24.5)	11 (10.8)	
	Non-smoker	77 (75.5)	91 (89.2)	
(Mean ±SD)				
Epilepsy duration (years)	-	N/A	5.5 ± 3.5	-
ASM duration (years)	-	N/A	4.2 ± 2.8	-
Central obesity (NCEP-ATPIII)	Yes	11 (10.8)	13 (12.7)	0.111
	No	91 (89.2)	89 (87.3)	
HDL-c Level	Low	26 (25.5)	30 (29.4)	0.102
	Normal	76 (74.5)	72 (70.6)	
TG Level	Increased	20 (19.6)	24 (23.5)	0.096
	Normal	82 (80.4)	78 (76.5)	
BP level	Elevated	20 (19.6)	22 (21.6)	0.211
	Normal	82 (80.4)	80 (78.4)	
FBS (NCEP-ATPIII)	Increased	5 (4.9)	7 (6.9)	0.115
	Normal	97 (95.1%)	95 (93.1%)	
MetS (NCEP-ATPIII)	Yes	15 (14.7%)	18 (17.6%)	0.088
	No	87 (85.3%)	84 (82.4%)	
LDL-c level	Increased	20 (19.6%)	20 (19.6%)	1.000
	Normal	82 (80.4%)	82 (80.4%)	
Total cholesterol level	Increased	22 (21.6%)	22 (21.6%)	1.000
	Normal	80 (78.4%)	80 (78.4%)	

ASM: anti-seizure medications; BP: blood pressure; FBS: fasting blood sugar; HDL-c: high density lipoprotein cholesterol; LDL-c: low density lipoprotein cholesterol; MetS: metabolic syndrome; N/A: not applicable; NCEP-ATPIII: National Cholesterol Education Program Adult Treatment Panel III; TG: triglycerides.

Statistical analysis

Categorical variables were examined using frequencies and percentages, while continuous variables were represented by mean and standard deviation. The χ^2 test was utilized to compare categorical data and independent t-tests were used to examine continuous variables. The relationship between MetS and risk factors was examined using bivariate and multivariate binary logistic regression models. For the final analysis, the multivariate binary logistic regression model included variables with a $p < 0.25$ in the bivariate logistic regression. The predictive capacity of independent factors for outcomes (MetS) was interpreted using the adjusted odds ratio (AOR) at 95% confidence interval (CI). The adjusted odds ratio was used to interpret the predictive capacity of independent factors for outcomes.

RESULTS

A total of 102 patients in the epilepsy group and 102 patients in the control group participated in this study. Table 1 shows that the control group had similar age and gender distributions, while the epilepsy group had a higher percentage of unem-

ployed individuals ($p < 0.05$), and only elementary and secondary education ($p < 0.05$). The epilepsy group exhibited sedentary behaviour, while the control group had moderate to intense physical activity ($p < 0.05$). The epilepsy group had low fruit and vegetable consumption patterns, while the control group had more favourable habits ($p < 0.05$). No disparities were found in smoking behaviours or alcohol intake between the two groups.

Epilepsy group patients exhibited a higher likelihood of experiencing metabolic syndrome compared to those in the control group. Metabolic syndrome in the control group was detected in 15 (14.7%) patients, comparing to the control group, 27 (26.5%) ($p = 0.034$). The epilepsy group had significantly higher triglyceride level ($p = 0.432$), fasting blood sugar ($p = 0.005$), and lower HDL values ($p = 0.038$) compared to the control group (Table 2).

The lack of physical exercise in individuals with epilepsy was associated with a 4.87-fold increase in the chance of developing metabolic syndrome ($p = 0.039$). The use of many antiepileptic medicines (polytherapy) significantly raised the likelihood of developing metabolic syndrome in the patients with epilepsy, by a factor of 8.43 ($p = 0.014$). Epilepsy patients with a

Table 2. Risk factors for metabolic syndrome (MetS) and corresponding biochemical parameters of the two groups of patients

Variables	Category	No (%) of patients in the group		p
		Control	Epilepsy group	
Central obesity (NCEP-ATPIII)	Yes	11 (10.8)	16 (15.7)	0.286
	No	91 (89.2)	86 (84.3)	
HDL-c	Low	26 (25.5)	42 (41.2)	0.038
	Normal	76 (74.5)	60 (58.8)	
TG	Increased	20 (19.6)	35 (34.3)	0.040
	Normal	82 (80.4)	67 (65.7)	
LDL-c	Increased	20 (19.6)	18 (17.7)	0.612
	Normal	82 (80.4)	84 (82.3)	
Total cholesterol	Increased	22 (21.6)	20 (19.7)	0.432
	Normal	80 (78.4)	82 (80.3)	
BP	Elevated	20 (19.6)	18 (17.7)	0.612
	Normal	82 (80.4)	84 (82.3)	
FBS (NCEP-ATPIII)	Increased	5 (4.9)	17 (16.7)	0.005
	Normal	97 (95.1)	85 (83.3)	
MetS (NCEP-ATPIII)	Yes	15 (14.7)	27 (26.5)	0.034
	No	87 (85.3)	75 (73.5)	

NCEP-ATPIII, National Cholesterol Education Program Adult Treatment Panel III; HDL-c, high density lipoprotein cholesterol; LDL-c, low density lipoprotein cholesterol; MetS, metabolic syndrome; TG, triglycerides BP, blood pressure; FBS, fasting blood sugar.

Table 3. Multivariable binary logistic regression analysis of factors associated with metabolic syndrome (MetS) among the epileptic group.

Variables	Categories	MetS-NCEP-ATPIII		AOR (95% CI)	p
		Yes (n (%))	No (n (%))		
Number (%) of patients in the group					
Epilepsy subtype	Generalized onset	18 (66.7)	47 (62.7)	1	0.871
	Focal onset	2 (7.4)	14 (18.7)	0.2 (0.02-1.65)	
	Unknown onset	7 (25.9)	16 (18.6)	1.06(0.45-2.34)	
(Mean ±SD)					
Epilepsy duration	N/A	7.8±4.8	5.6±3.7	1.03(0.65-2.32)	0.765
Number (%) of patients in the group					
ASMs uses	Monotherapy	12 (44.4)	54 (72)	1	0.014*
	Polytherapy	13 (48.2)	11 (14.7)	8.43(1.45-32.12)	
	Not on ASMs	2 (7.4)	10 (13.3)	1.87(0.87-2.54)	
Drug responsiveness status	Drug responsive	19 (70.4)	42 (56)	1	0.432
	Drugs resistant	3 (11.1)	8 (10.7)	0.34(0.12-2.22)	
	Undefined	5 (18.5)	25 (33.3)	0.44(0.21-3.23)	
Level of physical activity	Adequate	12 (44.4)	52 (69.3)	1	0.039*
	Low	15 (55.6)	23 (31.7)	4.87(1.78-12.12)	
Fruit and vegetables intake	Adequate	7 (25.9)	38 (50.6)	1	0.096
	Low	20 (74.1)	37 (49.4)	3.73(0.76-9.54)	
Total cholesterol	<200	16 (59.3)	58 (77.3)	1	0.037*
	≥200	11 (40.7)	17 (22.7)	5.81(1.23-23.32)	
LDL-c	<130	14 (51.8)	59 (78.7)	1	0.765
	≥130	13 (48.2)	16 (21.3)	0.87(0.23-2.35)	
(Mean ±SD)					
BMI	N/A	25.8 ± 2.2	21.3 ± 2.1	1.57(1.16-2.34)	0.003*

*Statistically significant factors associated with MetS.

NCEP-ATPIII: National Cholesterol Education Program Adult Treatment Panel III; AOR, adjusted odds ratio; ASMs, anti-seizure medications; BMI, body mass index; CI, confidence interval; LDL-c, low density lipoprotein cholesterol; N/A: not applicable.

BMI above >25 had a 1.57 times higher chance of developing metabolic syndrome (p=0.003). Having total cholesterol level ≥200 mg/dL raises the risk of metabolic syndrome in epilepsy patients by a factor of 5.81 (p=0.037) (Table 3).

DISCUSSION

Our study findings indicate that 26.5% of epilepsy patients had metabolic syndrome, as determined by the NCEP-ATPIII criteria (18). The findings of this study are consistent with several studies that indicate a prevalence rate of around 25–30% for metabolic syndrome among individuals with epilepsy (5,21). The findings of this study indicate that insufficient physical

activity is a contributing factor that influences the occurrence of metabolic syndrome in individuals with epilepsy.

Sedentary behaviour might lead to an increase in body weight. The reason behind this fact is that engaging in physical exercise facilitates calorie expenditure and promotes the growth of muscular tissue. Engaging in physical exercise can also effectively lower LDL cholesterol levels and elevate HDL cholesterol levels (22). LDL cholesterol, also known as low-density lipoprotein cholesterol, is a kind of cholesterol that can elevate the likelihood of developing heart disease, including hypertension. HDL cholesterol, also known as high-density lipoprotein cholesterol, is a kind of cholesterol that has the ability to lower the likelihood of developing heart disease, including hyperten-

sion. Insufficient physical exercise can lead to elevated levels of LDL cholesterol and triglycerides (22). Our study found there was a significant difference in multivariate analysis of total cholesterol in the epilepsy group ($p < 0.05$). Previous studies have shown a significant difference in epilepsy patients, especially patients using monotherapy (23).

Inadequate physical exercise might lead to elevated blood glucose levels. This is due to the fact that engaging in physical exercise might enhance the body's responsiveness to insulin (22). Insulin is a hormone that facilitates the body's utilization of glucose as an energy source. A study found that low physical activity in epilepsy patients increases the risk of metabolic syndrome by 3-4 times compared to those with enough exercise, consistent with previous research (24).

Our study findings indicate that the utilization of polytherapy using antiepileptic medicines is associated with an increased risk of metabolic syndrome in individuals with epilepsy. The study demonstrated that the use of several antiepileptic medicines significantly increased the occurrence of metabolic syndrome by roughly 8.43-fold. Polytherapy, the use of antiepileptic drugs like phenytoin and carbamazepine, can increase the likelihood of metabolic syndrome in individuals with epilepsy (25). Phenytoin, commonly prescribed for various forms of epilepsy, can induce heightened hunger, salt and fluid retention, elevated blood pressure, and elevated LDL cholesterol and triglyceride levels, heightening susceptibility to heart disease and diabetes (26). Carbamazepine, on the other hand, can induce heightened hunger, salt and fluid retention, and elevated LDL cholesterol and triglyceride levels, increasing susceptibility to heart disease (27). However, there are several studies that yield conflicting findings. Prior studies have found no significant association between the specific type and dosage of antiepileptic medication and the occurrence of metabolic syndrome (8,9,28).

Our study has several limitations, including the single-centre study and the small number of patients. Conducting multi-centre research with a larger sample size will yield more accurate and comprehensive findings on the risk variables that impact metabolic syndrome in patients with epilepsy.

In conclusion, the findings of this study indicate that more than a quarter of patients with epilepsy have metabolic syndrome. The primary risk factors contributing to the increased likelihood of metabolic syndrome in patients with epilepsy include the sedentary lifestyle, concurrent use of multiple antiepileptic drugs, overweight, and increased total cholesterol level.

AUTHOR CONTRIBUTIONS

Conceptualization, S.H. and R.U.P.; methodology, Z.H.; software, F.O.; validation, S.H., R.U.P., and Z.H.; formal analysis, D.W.; investigation, F.O.; resources, S.H.; data curation, S.H.; writing—original draft preparation, S.H. and D.W.; writing—review and editing, S.H. and R.U.P.; visualization, Z.H. and D.W.; supervision, R.U.P.; project administration, S.H. All authors have read and agreed to the published version of the manuscript.

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TRANSPARENCY DECLARATION

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