RESEARCH PAPER

Atherosclerotic Changes Associated with Long-Term Use of Antiepileptic Drugs in Epileptic Children: A Case-Control Study

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ABSTRACT

Background: Epilepsy affects approximately 50 million individuals globally, and long-term antiepileptic drug (AED) therapy, while essential for seizure control, may adversely influence lipid metabolism and vascular integrity. Evidence regarding subclinical atherosclerotic changes among pediatric patients on chronic AED therapy remains limited, particularly in the Egyptian population.

Objective: To assess the association between extended AED use and early atherosclerotic changes determined by carotid intima–media thickness (CIMT), and to compare the vascular and metabolic effects of different AED classes in children with epilepsy.

Methods: This case–control study included 120 children (60 epileptic cases and 60 age- and sex-matched controls). Clinical evaluation, GASE scoring, fasting lipid profile, and bilateral carotid ultrasound for CIMT were performed.

Results: Children on AED therapy had significantly elevated TC, TG, LDL-C, and LDL/HDL ratios, and lower HDL-C ($p \leq 0.001$). CIMT was significantly increased bilaterally ($p \leq 0.001$). Sodium valproate and carbamazepine caused the most significant metabolic and vascular changes, while levetiracetam showed minimal effects.

Conclusions: Extended application of traditional AEDs is linked with dyslipidemia and increased CIMT, indicating early atherosclerosis. Levetiracetam demonstrated a safer metabolic profile. Cardiovascular monitoring is recommended in the management of pediatric epilepsy.

Keywords: Epilepsy; AEDs; Atherosclerosis; CIMT; Lipid profile; Children; Levetiracetam; Sodium valproate; Carbamazepine; Cardiovascular risk

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INTRODUCTION

Epilepsy is a highly prevalent chronic neurological disorder encompassing a spectrum of conditions characterized by recurrent, unprovoked seizures resulting from abnormal neuronal electrical activity, affecting an estimated 50 million people worldwide [1–3]. Although there are many antiepileptic drugs (AEDs) available and some patients respond satisfactorily to AEDs, the percentage of individuals not achieving seizure control remains ~30%, defined as drug-resistant epilepsy [4,5]. Compared to older AEDs, such as phenytoin, carbamazepine, and valproate, new-generation drugs like levetiracetam and oxcarbazepine have better tolerability and lower pharmacokinetic interactions [4,6].

Long-term AED therapy, although essential for seizure control, has been associated with several systemic side effects, including metabolic, endocrine, and cardiovascular disturbances [7–9]. Previous evidence suggests that prolonged application of enzyme-inducing AEDs, as carbamazepine and phenytoin, may adversely influence lipid metabolism, thyroid function, and oxidative stress, thereby accelerating the atherosclerotic process [10–12]. This potential atherogenic effect is supported by both adult and pediatric studies showing raised carotid intima-media thickness (CIMT) among patients on long-term AED monotherapy; CIMT is a validated, noninvasive indicator of early atherosclerosis and an established predictor of cardiovascular risk [13–15].

The underlying mechanisms linking epilepsy and atherosclerosis appear multifactorial. AEDs can alter lipid metabolism by increasing serum total cholesterol (TC), low-density lipoprotein (LDL) cholesterol, and triglycerides (TG) while reducing high-density lipoprotein (HDL) levels [16–18]. In addition, AED-induced hyperhomocysteinemia, mediated by impaired folate metabolism, may contribute to endothelial dysfunction,

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oxidative stress, and vascular inflammation. Elevated homocysteine has been shown to damage endothelial cells through the production of reactive oxygen species (ROS) and a decline in nitric oxide bioavailability, promoting vascular injury and atherogenesis [19–22]. Other metabolic abnormalities, such as hyperuricemia, may further potentiate oxidative stress and vascular remodeling, thereby compounding cardiovascular risk [23,24].

Recent studies have emphasized that the vascular effects of AEDs differ depending on their enzyme-inducing or non-enzyme-inducing properties. Enzyme-inducing antiepileptic drugs (e.g., phenytoin, carbamazepine) increase hepatic cytochrome P450 activity, resulting in alterations in lipid metabolism and inflammatory pathways. At the same time, non-enzyme-inducing drugs (e.g., valproate, levetiracetam) exhibit a more neutral or sometimes protective metabolic profile [25,26].

Despite numerous investigations that have assessed the relationship between AED use and cardiovascular probable determinants, data in the pediatric and young adult Egyptian population remain scarce. Most available evidence comes from Western and Asian populations, where dietary and genetic factors differ [27–30]. Understanding these associations in young epileptic patients is clinically crucial since early vascular changes may be reversible if detected and managed promptly.

Therefore, our study aims to evaluate the impact of prolonged AED therapy on early markers of atherosclerosis, particularly CIMT, in patients with epilepsy. This study also seeks to compare the effects of different AED classes on metabolic and vascular parameters, thereby clarifying their potential contribution to cardiovascular risk in this vulnerable cohort.

2. PATIENTS AND METHODS

2.1 Study Design and Setting

This case-control study was executed at the Neurology Outpatient Clinic, Faculty of Medicine, Al-Azhar University – Assiut Hospitals, between June 2024 and January 2025. The study aimed to assess atherosclerotic changes linked with the extended application of AEDs in children with epilepsy. The research protocol was reviewed and authorized by the Medical Research Ethics Committee of Al-Azhar University (Approval No. [to be inserted]). A documented consent was obtained from the parents or legal guardians of all participants before their inclusion in the study.

2.2 Study Population

A total of 120 children were recruited and randomly placed into two equal groups. Group A (participants) included sixty children identified with idiopathic epilepsy who had been receiving regular AED therapy for at least one year. Group B (controls) consisted of 60 asymptomatic children matched for age and sex. The patients were recruited randomly from those attending systematic follow-up visits at the Neurology Outpatient Clinic.

2.3 Eligibility Criteria

Children between 2 and 18 years with idiopathic epilepsy, on continuous AED therapy for a minimum duration of one year, consuming a regular diet, and maintaining stable levels of physical activity with appropriate growth and development for age, were included. All included patients demonstrated good compliance with treatment and regular follow-up.

Exclusion criteria were the administration of drugs with known effects on lipid metabolism (e.g., corticosteroids, thiazides, anticoagulants), the presence of hepatic, renal, or cardiac diseases, or secondary epilepsy due to trauma, infection, tumor, or structural brain malformations. Patients with metabolic disorders affecting lipid metabolism, such as obesity (BMI > 95th percentile for age and sex), primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC), or type I hyperlipoproteinemia, were excluded. Children with vascular diseases that could affect vascular elasticity or IMT (e.g., hypertension) were also excluded.

2.4 Clinical and Neurological Assessment

All participants underwent a detailed medical record and physical examination. History taking recording participants' demographics, age at seizure onset, seizure characteristics, family record of epilepsy, treatment outcomes, episodes of status epilepticus, and ongoing AED therapy (drug type, dose, and duration).

General examination assessed vital signs and excluded systemic diseases, with particular attention to signs of pallor, cyanosis, jaundice, or lymphadenopathy. Anthropometric measures (weight, height, and BMI) were recorded for all participants. Each patient underwent a complete neurological examination to confirm the diagnosis and assess disease status.

2.5 Assessment of Epilepsy Severity

The Global Assessment of the Severity of Epilepsy (GASE) Scale was used to evaluate epilepsy severity in the patient group [31]. The GASE is a validated, clinician-rated, single-item, 7-point Likert instrument intended to quantify the global impact of epilepsy in children. It considers seizure frequency and intensity, occurrence of falls or injuries, postictal manifestations, number and dosage of AEDs, drug-related adverse effects, and interference with daily activities. Additional indicators, including the incidence of convulsive status epilepticus and nocturnal seizures, were also recorded.

The detection and classification of epilepsy were established in accordance with the International League Against Epilepsy (ILAE) 2017 classification, which defines focal, generalized, combined generalized and focal, and those with unknown onset [32].

2.6 Laboratory Investigations

Venous blood samples (5 mL) were collected from each participant under strict aseptic conditions. The samples were allowed to clot at room temperature for 30 minutes and subsequently centrifuged at 3000 rpm for 15 minutes. The resulting serum was aliquoted and kept at −80°C until further analysis.

Routine investigations included complete blood count, erythrocyte sedimentation rate, C-reactive protein, hepatic and renal function tests, and coagulation profile (PT, PTT, INR). The serum lipid profile was determined using enzymatic colorimetric methods. The parameters measured

were TC, TG, HDL, and LDL. LDL was calculated according to the Friedewald formula [33].

2.7 Radiological and Neurophysiological Assessment

Electroencephalography (EEG) was performed for seizure characterization and classification. Bilateral CIMT was assessed using high-resolution B-mode ultrasonography (GE volsun logic P7 Italy with linear transducer). All examinations were performed by a single experienced sonographer blinded to participant group assignment, ensuring measurement consistency and eliminating inter-observer variability.

Participants were positioned supine with neck extension and head rotation (45 degrees contralateral to the examined side). The common carotid artery was identified in longitudinal view, and CIMT was measured at a standardized location 1 cm proximal to the carotid bulb bifurcation. CIMT was defined as the distance between the lumen-intima interface and the media-adventitia interface on the far wall. Three measurements were obtained from each side, and the mean value was calculated for analysis. All measurements were performed according to the Mannheim CIMT and Plaque Consensus recommendations. (Figure 1).

CIMT was evaluated using high-resolution real-time B-mode ultrasonography. Both the right (RT) and left (LT) common carotid arteries were examined over a 1 cm segment proximal to the bifurcation. CIMT was known as the interval between the anterior boundary of the lumen echo and the anterior boundary of the media–adventitia echo. A CIMT greater than 0.9 mm was considered thickened. Measurements were performed according to standardized protocols by a radiologist who was blinded to the participants' clinical data, and the mean of both sides was used for analysis.

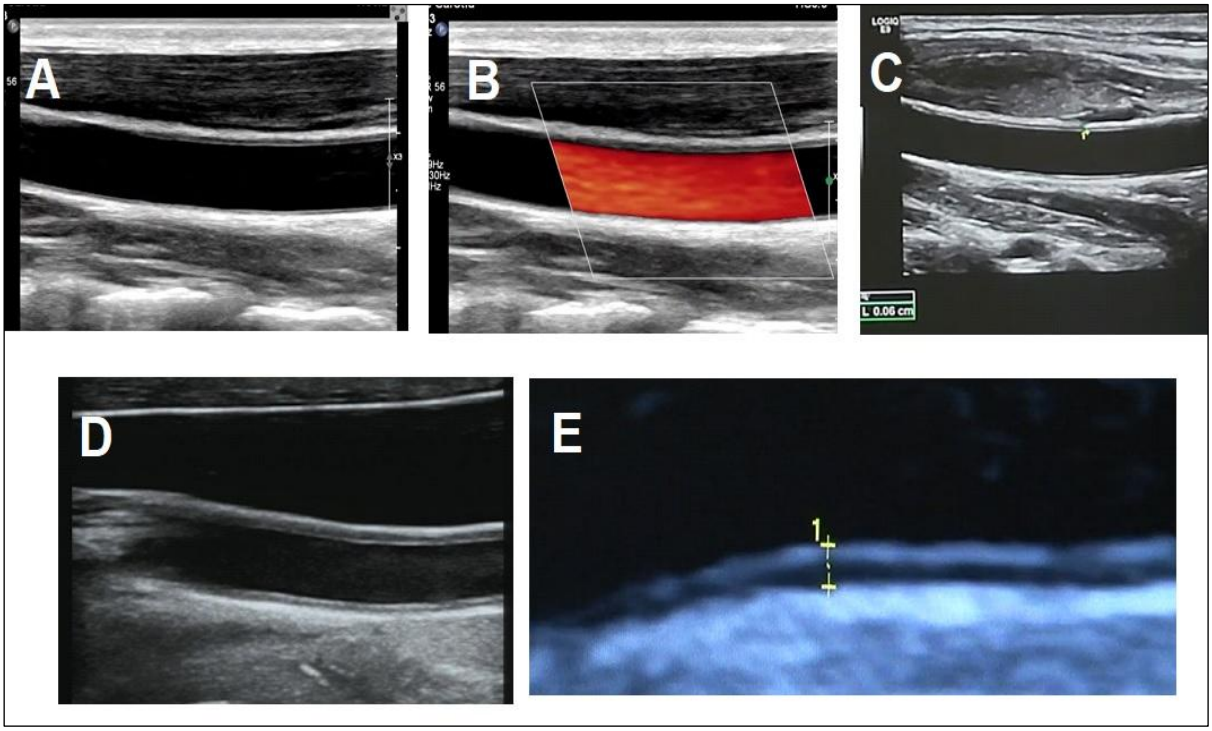

Figure 1: Multiple sagittal scans of two children; the three images above include B mode scan of the common carotid artery CCA (A), and a color Doppler examination of the CCA (B) and an average IMT measurement of approximately 0.6 mm. (C) The lower photos depict a slight increase in IMT on the sagittal scan of the common carotid artery (D), with a zoomed image illustrating the measurement method, which reaches 0.9 mm (E).

2.8 Bias Control

To minimize bias, random recruitment was implemented, and all evaluations were conducted by trained investigators who were blinded to the participants' medical status. Laboratory and radiological assessments were conducted according to standardized procedures to ensure intergroup comparability.

2.9 Sample Size Determination

It was determined assuming a power of 80%, a confidence level of 95%, and an expected difference in mean CIMT or lipid profile between cases and controls as supported by earlier published studies. The total sample size was set at 120 participants to accommodate potential data loss and ensure sufficient statistical power.

2.10 Statistical Analysis

Data were analyzed via SPSS version 26.0 (IBM, Armonk, NY, USA). Quantitative variables were shown as mean ± standard deviation (SD), while categorical variables were expressed as frequencies and percentages. The independent t-test was used for comparing continuous parametric data, and the Mann-Whitney U-test was used for non-parametric data. The chi-square test was applied to relate categorical

variables. A *p*-value <0.05 was considered statistically significant.

2.11 Ethical Considerations

All procedures were conducted in accordance with institutional and international ethical principles. A documented consent was obtained from the parents or legal guardians of all participants before their inclusion in the study. Participants' privacy and data confidentiality were fully protected, and all children continued to receive their standard medical care without any modification due to study participation.

3. RESULTS

3.1 Participant Characteristics (table 1):

A total of 120 children were recruited in the study, comprising 60 epileptic patients (case group) and 60 healthy age- and sex-matched controls. No statistically significant difference was observed among groups regarding age (median 8 vs. 9 years, p = 0.92) or gender distribution (male: 46.7% vs. 38.3%, p = 0.35). However, the case group showed a significantly higher body mass index (BMI) than the control group (mean 14.55 vs. 13.35 kg/m², *p* = 0.01).

Table 1: Demographic characteristics of the studied groups

Variable	Case group (n=60)	Control group (n=60)	p-value
Age (years), median (range)	8 (2–18)	9 (2–18)	0.92
Gender, male (%)	28 (46.7%)	23 (38.3%)	0.35
BMI (kg/m²), mean ± SD	14.55 ± 4.2	13.35 ± 3.6	0.01

3.2 Clinical Features of Epilepsy

Among the epileptic children, focal epilepsy was the most frequent type (48.3%), followed by generalized convulsive seizures (33.3%), myoclonic epilepsy (13.3%), and absence seizures (5%). Regarding the Global Assessment of Severity of Epilepsy (GASE) scale, 35% were classified as "a little severe," 30% as "somewhat severe," 18.3% as "moderate severe," and 16.7% as "quite severe."

Table 2: Clinical characteristics of the case group

Variable	Case group (n=60)
Type of epilepsy	
Generalized tonic-clonic	20 (33.3%)
Focal	29 (48.3%)
Myoclonic	8 (13.3%)
Absence	3 (5%)
GASE scale	
A little severe	21 (35%)
Somewhat severe	18 (30%)
Moderate severe	11 (18.3%)
Quite severe	10 (16.7%)

3.3 AED Use

Levetiracetam was the most frequently prescribed AED (40%), followed by sodium valproate (30%) and carbamazepine (30%). The mean duration of AED therapy was 3.5 ± 1.5 years.

3.4 Lipid Profile and CIMT (figure 2) (table 2)

Children receiving AEDs demonstrated significant alterations in lipid profile parameters compared with controls. Median TC, TG, LDL-c, and LDL/HDL ratio were all significantly elevated in the case group ($p \leq 0.001$), whereas HDL-c was significantly reduced ($p \leq 0.001$).

Both RT and LT common CCA IMT values were significantly elevated in the case group relative to the controls ($p \leq 0.001$).

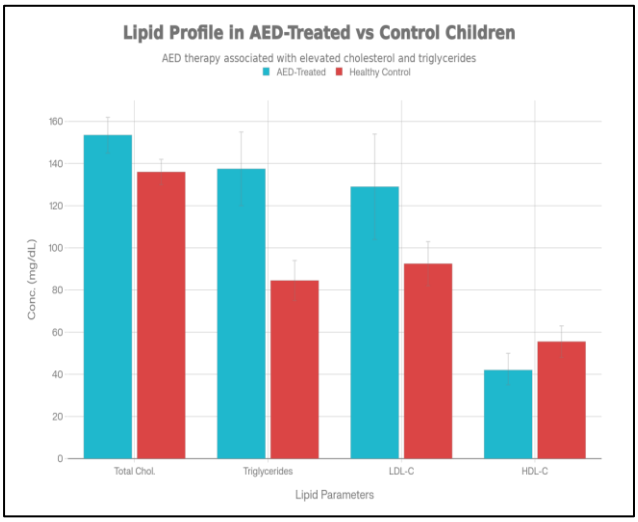

Figure 2: Lipid Profile Comparison - Bar chart showing abnormal lipid parameters in AED-treated vs. control children (↑TC, ↑TG, ↑LDL, ↓HDL)

3.5 Association Between Epilepsy Characteristics, AEDs, and Severity (table 3)

There was no statistically significant association between the GASE scale and the type of epilepsy (p = 0.175). Likewise, no significant relationship was found between GASE severity and the type or duration of AED use (p = 0.471 and p = 0.927, as listed). However, a significant association was identified between the type of epilepsy and the choice of AED ($p \leq 0.001$), as sodium valproate and carbamazepine were primarily prescribed for generalized tonic-clonic and focal epilepsies, respectively. At the same time, levetiracetam was more commonly used for generalized and myoclonic epilepsies.

A statistically significant linkage was found between the type of epilepsy and the specific AED used ($p \leq 0.001$). In

contrast, no significant difference was found in the duration of therapy among epilepsy types (p = 0.56).

Table 3: Antiepileptic drug use in the case group

Variable	Case group (n=60)
Na valproate	18 (30%)
Carbamazepine	18 (30%)
Levetiracetam	24 (40%)
Duration (years), mean ± SD	3.5 ± 1.5

3.6 CIMT and Epilepsy Type (table 4):

No statistically significant association was found between the type of epilepsy and common carotid artery (CCA) IMT on either side (p = 0.35 and 0.11, as listed). Although participants with myoclonic seizures demonstrated slightly higher IMT values, the differences did not reach significance.

Table 4: Lipid profile comparison among studied groups

Parameter (mg/dL), median (range)	Case group (n=60)	Control group (n=60)	p-value
TC	153.5 (60–267)	136 (98–196)	0.001
TG	137.5 (14–274)	84.5 (39–128)	≤0.001
HDL-c	42 (12–102)	55.5 (36–71)	≤0.001
LDL-c	129 (10–242)	92.5 (62–128)	≤0.001
LDL/HDL ratio	3.02 (0.23–12.17)	1.64 (0.99–2.56)	≤0.001

3.7 Lipid Profile and BMI Across Treatment Groups (table 5):

Lipid profile parameters differed significantly between the treatment and control groups ($p \leq 0.001$ for all). Median TC, TG, and LDL-c levels were highest in the sodium valproate group and lowest in the control group, while HDL-c levels showed the inverse pattern. Post-hoc comparisons revealed significantly elevated lipid levels in the valproate and carbamazepine groups compared with the levetiracetam and control groups. BMI did not differ significantly among the case subgroups or between cases and controls (p = 0.08).

Table 5: Comparison of CIMT among studied groups

Side	Case group (Mean ± SD)	Control group (Mean ± SD)	p-value
RTIMT	0.43 ± 0.03	0.37 ± 0.03	≤0.001
LTIMT	0.44 ± 0.02	0.37 ± 0.02	≤0.001

3.8 Comparison of CIMT by Type of Antiepileptic Therapy (table 6):

Further subgroup analysis was conducted to compare the effect of different AEDs on CIMT. Both sodium valproate and carbamazepine users demonstrated markedly higher RT and LTIMT values compared to levetiracetam-treated patients and healthy controls ($p \leq 0.001$). Nevertheless, no significant difference was documented between sodium valproate and carbamazepine groups (P_1=0.7 for RT IMT, P_1=0.44 for LTIMT). In contrast, the levetiracetam group exhibited IMT values comparable to controls on the RT side (P_6=0.45), yet a mild but significant difference was observed on the LT side ($P_6 \leq 0.001$). These data suggest that both sodium valproate and carbamazepine are linked with greater vascular wall thickening, whereas levetiracetam exerts a comparatively neutral vascular profile.

There was a statistically significant difference in both RT and LTCCA IMT among the different treatment groups and controls ($p \leq 0.001$). No significant difference was noted between the sodium valproate and carbamazepine groups, while both had significantly greater IMT compared to the levetiracetam and control groups.

Table 6: Comparison of CCA IMT among case subgroups according to treatment type and control group

	Na valproate (n=18)	Carbamazepine (n=18)	Levetiracetam (n=24)	Control (n=60)	p-value
RTIMT (Mean ± SD)	0.48 ± 0.03	0.49 ± 0.01	0.34 ± 0.03	0.33 ± 0.03	≤0.001

LTIMT (Mean ± SD)	0.48 ± 0.02	0.50 ± 0.02	0.36 ± 0.02	0.34 ± 0.02	≤0.001

3.9 Correlation between Age and CIMT (figure 3) (table 7):

A significant direct correlation was documented between age and CCA IMT on both sides. For the RTCCA, the correlation coefficient was r=0.65 (p=0.006), and for the LTCCA, r=0.72 (p=0.008). This refers to the fact that older children tend to have greater arterial wall thickness, suggesting an age-related increase in vascular remodeling among the study population.

Table 7: Correlation among age, RT, and LTCCA IMT

Variable	r	p-value
RT IMT	0.65	0.006
LT IMT	0.72	0.008

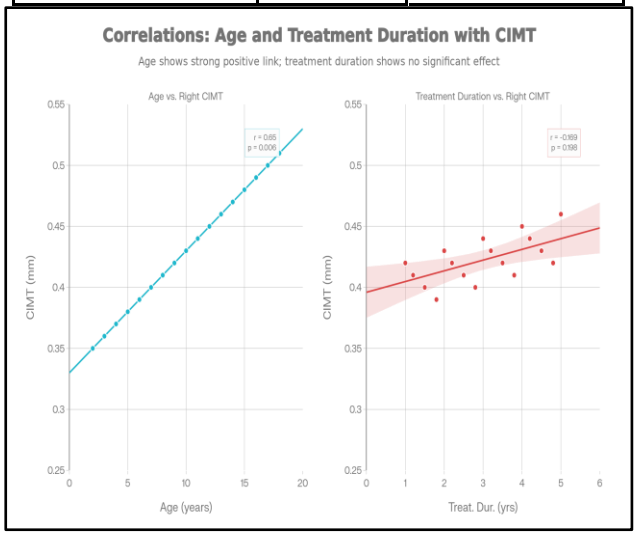

Figure 3: Age & Duration Correlations - Dual scatter plots: (Left) Age positively correlates with CIMT (r=0.65), (Right) Duration non-significantly correlates with CIMT (r=-0.169).

3.10 Correlation among Duration of Antiepileptic Therapy and Lipid Profile Parameters (table 8)

No significant correlation was found among the duration of AED therapy and any lipid parameter, including TC (r=−0.183, p=0.162), TG (r=−0.035, p=0.791), HDL-c (r=−0.126, p=0.337), LDL-c (r=0.055, p=0.678), and LDL/HDL ratio (r=0.139, p=0.288). This suggests that the lipid alterations observed are likely drug-specific rather than cumulative over time.

Table 8: Correlation among duration of AED use and lipid profile parameters

Parameter	r	p-value
TC	−0.183	0.162
TG	−0.035	0.791
HDL-c	−0.126	0.337
LDL-c	0.055	0.678
LDL/HDL ratio	0.139	0.288

3.11 Correlation among Duration of Antiepileptic Therapy and CIMT (Table 9)

Similarly, no statistically significant relationship was detected between the duration of AED exposure and carotid IMT. The correlation coefficients were r = -0.169 (p = 0.198) for RTIMT and r = -0.171 (p = 0.191) for LTIMT, indicating weak, non-significant inverse trends. These results suggest that vascular thickening may occur early during therapy and plateau over time rather than progressing linearly with treatment duration.

Table 9: Correlation among duration of AED use and CCA IMT

Parameter	r	p-value
RT IMT	−0.169	0.198
LT IMT	−0.171	0.191

4. DISCUSSION

4.1 Study Findings

This study investigated the effects of long-term AED use on lipid metabolism and CIMT among epileptic children compared with healthy controls. No significant differences were documented among groups concerning age or sex, but BMI was significantly elevated in the case group (p = 0.01). Children receiving AEDs showed significant lipid profile alterations, encompassing elevated TC, TG, LDL-C, and LDL/HDL ratio, with lower HDL-C levels relative to controls (p≤0.001). Furthermore, both RT and LT CCAIMT were significantly elevated in AED-treated patients (p ≤ 0.001), suggesting subclinical atherosclerotic changes. Among the AED subgroups, sodium valproate and carbamazepine were associated with the most significant lipid abnormalities and IMT thickening, while levetiracetam showed minimal effects. No significant correlation was documented between the duration of therapy and lipid profile or IMT values. However, IMT showed a positive correlation with age, indicating that older children exhibited more pronounced vascular changes.

4.2 Comparison with Previous Data

Our data are in consistent with those reported by Calik et al. and Karatoprak and Tosun, who documented no demographic differences among epileptic individuals and controls [34,35]. Regarding lipid alterations, similar results

were documented by Calik et al., Eltom et al., and Nasef et al., demonstrating elevated TC, LDL-C, and TG, alongside decreased HDL-C in individuals receiving sodium valproate or carbamazepine [36–38]. These lipid disturbances are believed to result from hepatic enzyme induction, oxidative stress, and mitochondrial dysfunction, which in turn influence lipid synthesis and metabolism [25,26].

Conversely, some studies, such as those by Kishar et al. and Karatoprak and Tosun, reported non-significant differences in lipid levels, possibly due to shorter exposure durations, smaller sample sizes, or differences in dietary and genetic factors [39, 40]. The current study further confirmed that levetiracetam had a minimal effect on lipid metabolism, supporting previous observations that newer-generation AEDs are metabolically safer and non-enzyme-inducing.

In terms of vascular findings, our data showing increased IMT among sodium valproate and carbamazepine users agree with El-Farahaty et al., Chuang et al., and Nasef et al., who all demonstrated significant carotid thickening in patients using older AEDs [15,38,41]. These results reinforce the hypothesis that prolonged use of enzyme-inducing AEDs may accelerate vascular remodeling and endothelial dysfunction. Furthermore, the positive correlation between age and IMT in our study aligns with the data of Tan et al. and Chuang et al., supporting the natural age-related progression of arterial wall changes, which may be exacerbated by long-term AED therapy [15, 42].

4.3 LIMITATIONS

Several limitations of this study merit consideration. Being a case-control design, it identifies associations rather than establishing direct causal relationships between AED exposure and atherosclerotic changes. The relatively small sample size and recruitment from a single center may have limited the statistical power and generalizability of the findings. Additionally, potential confounding factors—such as dietary habits, physical activity, socioeconomic status, and family history of dyslipidemia—were not fully controlled, which may have affected lipid profiles and vascular outcomes. Furthermore, although CIMT is a well-validated marker of early atherosclerosis, it reflects only structural changes rather than functional endothelial alterations. Biochemical indicators of oxidative stress, inflammatory cytokines, and genetic susceptibility were not assessed, which could have provided further mechanistic insights into AED-induced vascular effects. Future multicenter investigations with larger sample sizes and adjustment for metabolic confounders are required to validate and expand upon these results.

4.4 INTERPRETATION

The results of this study indicate that sodium valproate and carbamazepine exert adverse effects on lipid metabolism and carotid wall thickness in epileptic children. In contrast, levetiracetam appears to have a neutral metabolic profile. These findings suggest that enzyme-inducing and hepatically metabolized AEDs may accelerate subclinical atherosclerosis, possibly through lipid dysregulation and oxidative stress mechanisms. Clinicians should therefore consider metabolic risk when prescribing long-term AEDs, especially in pediatric patients requiring chronic therapy. Regular monitoring of lipid profile and carotid IMT may help identify early vascular changes and allow timely intervention. The absence of significant correlation between treatment duration and IMT suggests that metabolic changes may occur early in therapy, highlighting the need for early surveillance.

4.5 CONCLUSION

In conclusion, chronic use of traditional AEDs, like sodium valproate and carbamazepine, in epileptic children is associated with significant alterations in lipid profile and increased CIMT, reflecting early atherosclerotic changes. Levetiracetam demonstrated a favorable metabolic and vascular profile, supporting its use as a safer alternative when clinically appropriate. These findings underscore the importance of cardiovascular risk assessment in the management of pediatric epilepsy. Future multicenter longitudinal studies with larger cohorts are recommended to confirm these associations, explore underlying mechanisms, and guide the selection of AEDs with minimal vascular and metabolic adverse effects.

DECLARATIONS

Ethics Approval and Consent to Participate

The study protocol was reviewed and authorized by the Medical Research Ethics Committee of the Faculty of Medicine, Al-Azhar University, Assiut, Egypt (Approval No. [MSC/AZHAR/NAP020-2024-357]). The study was conducted in accordance with the ethical principles of the Declaration of Helsinki (2013 revision). A documented consent was obtained from the parents or legal guardians of all participants before their inclusion in the study..

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