THE PREDICTORS OF EARLY ATHEROSCLEROSIS IN YOUNG ADULT EPILEPTIC PATIENTS

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ABSTRACT

Background: Patients with epilepsy develope a wide range of medical and neurologic disorders, compared with the general population. The association between epilepsy and atherosclerosis is not clearly defined. Several studies claims that epileptic patients may have the risk to develop atherosclerosis.

Methods: This study included 40 adult epileptic and 40 control subjects. For all, Common carotid artery intima media thickness (CA-IMT), fasting lipid profile, serum uric acid (SUA), C -reactive protein (CRP) and glutathione peroxidase (GPX), were assessed.

Results: Total cholesterol (TC) ,low density lipoproteins (LDL), Total Triglycerides (TG) ,CRP, GPX were significantly higher in patients compared to control. CA- IMT was significantly higher in epileptic patients treated with antiepileptic drugs (AEDS) compared to control group. The longer the duration of AEDs the thicker was the CA-IMT.

Conclusions: Our results heightened atherosclerotic risk in patients with epilepsy on AEDS.

Key words: Lipid profile, CA-IMT, AEDS

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INTRODUCTION

Epilepsy is one of the most common serious neurological disorders which affect about 50 million people worldwide each year. [1] Antiepileptic drugs (AEDs) may differentially influence atherosclerotic risk in patients with epilepsy through alteration of vascular markers. In addition chronic exposure of AEDs may alter the oxidative/antioxidative balance that results in oxidative stress which further damages endothelial cells and contributes to the atherosclerotic process. [3] So, epilepsy and carotid atherosclerosis appear to share many risk factors. These shared risk factors include, weight gain and obesity, insulin resistance (IR), lipid abnormalities, high levels of inflammatory and oxidative stresses and increased CA–IMT. [2] ,[4],[5]. CA-IMT as assessed by ultrasound is considered to be a surrogate measure of atherogenesis and has been strongly correlated with risk of both stroke and myocardial infarction [6].

AIM OF WORK

This study aimed to evaluate the CA-IMT in adult epileptic patients on antiepileptic drugs (AEDs) and its relation to oxidative stress and vascular risk biomarkers.

PATIENTS AND METHODS

This study included 40 adult patients with primary epilepsy and 40 age and sex matched healthy control. The patients were selected from outpatient clinic of neurology department of Zagazig University Hospital (from April 2014 to May 2015). All patients were selected as receiving AEDs (carbamazepine and/or sodium valproate) as mono or polytherapy for at least 2 years. Patients aged from 18-45 years of both sexes having two or more unprovoked seizures were included in the study. Exclusion criteria included Patients with symptomatic epilepsy, Patients taking other regular medication beside AEDs; thiazide diuretics, and contraceptive pills; Subjects with any risk for atherosclerosis including: diabetes mellitus, smoking hypertension, hypothyroidism. Patients with history of vascular disease; cerebrovascular stroke, myocardial infarction, Patients with diseases that may affect serum uric acid level ;history of gout or acute renal failure and patients with conditions that could influence the level of oxidative stress such as malignancies and drug abuse and patients using supplemental antioxidant.

All patients underwent assessment and classification of epilepsy according to the International League against Epilepsy (1989)[7] . Fasting (at least 10 hours) venous blood samples (2 mL) of patients and control subjects were withdrawn sera were separated. They were kept frozen for the assay of serum levels of TC, TG, HDL-c, LDL-c, GPX, CRP and SUA. Autoanalyser by colometric method applied for triglycerides and cholesterol measurements. AutoZyme high-density lipoprotein (HDL) cholesterol regent used for HDL determination while LDL calculated by Freidwald formula: LDL = TC - (HDL × 0.2 Triglycerides). Glutathion peroxidase was determined spectrophotometrically according to the method described **Hefeman et al.** [8] A radiology specialist performed B mode ultrasound examinations with using high resolution 7.5 MHz transducers (iU22 Philips ultrasound) on subjects in the supine position. Images of wall thickness of common carotid artery IMT were recorded at both right and left common carotid arteries to assess the extent of atherosclerosis. Both the left and right common carotid arteries (CCAs) were scanned, The IMT, the interface between the lumen, intima ,media and adventitia, was measured using a computer software program. For each subject the mean IMT was calculated as the average of all mean IMT measurements.

RESULTS

Table 1 showed the demographic and clinical characteristics of patients and controls.. The mean systolic and diastolic blood pressure, BMI and fasting blood glucose of patients showed no significant difference compared with control subjects. Most of patients 75% (n=30) had primary generalized; while 25% (*n* = 10) had focal epilepsies. About 42.5% of patients were on polytherapy while 57.5% were on monotherapy with 43.4% on carbamazepine (CBZ) and 65.6% on valproate (VPA).

Table (1): Demographic and clinical characteristics of epileptic patients and controls

Demographic data	patients (n = 40)	Controls (n =40)
Age (years)	33.14 ± 6.84	30.7 ± 8.86
Male/female	18/22	21/19
Age at onset of disease (years)	14.03 ± 5.43	-
Duration of disease (years)	17 ± 9.25	-
Systolic blood pressure (mmHg)	130.2 ± 6.49	127.88 ± 10.97
Diastolic blood pressure (mmHg)	78.23 ± 6.48	82 ± 8.53
Body mass index (kg/m2)	26.93±3.34	23.96±3.22
Type of epilepsy (number (%)		
Generalized	30 (75%)	-
partial	10 (25%)	
AED (s) utilized (number (%)		
Monotherapy	23 (57.5%)	
CBZ	10 (43.4%)	-
VPA	13 (56.6%)	
Polytherapy	17 (42.5)	
Drug dose (mg)		
CBZ (range, mean S.D	900± 253.86	-
VPA (range, mean S.D.)	1003.8 ± 276.48	

Data are expressed as mean±S.D. and number (%).AED(s): antiepileptic drugs, CBZ: carbamazepine, VPA: valproic acid.

In our patients the levels of measured biomarkers versus control were TC [220.42±58.21 versus 140.00±35.09], TG [166.93±78.85 versus 93.49±35], LDL-c [141.31±43.88 versus 92.85±17.87], CRP [11.77±12.96 versus 3.82±0.63], GPX

[64.31±12.17 versus 74.87±9.5], with a significant difference between the two groups. Although uric acid levels were within the range of normal as healthy controls but VPA-treated patients (mono- and polytherapy) showed significant elevation in uric acid levels. Lower levels of HDL were detected in our patients despite the AED(s) Compared to control group, thickened CA-IMT significantly, the right CA-IMT (p<0.001), left CA -IMT (p<0.001) and the mean CA- IMT (p<0.001) especially in patients treated with carbamazepine (CBZ) [mono- and poly-therapy] than those treated with VPA. As regard to studied correlations; the present study revealed a significant positive correlation between the duration of anticonvulsant therapy and each of the total cholesterol (r =0.63, p< 0.001), serum triglyceride (r =0.52, p =0.001) LDL levels (r =0.44, p =0.005) and CRP (0.41, p=0.009). The duration of AED therapy was also, positively correlated with right CA-IMT (r =0.69, p <0.001), left CA-IMT (r=0.63, p<0.001), Mean CA-IMT (r=0.67, p<0.001). **Table (2)**

Table (2): Vascular risk factors and biomarkers of oxidative stress in the two studied groups

Variable	Control (n=40)	Cases (n=40)	Test	P
	Mean ± SD	Mean ± SD		
FBS (mg/dl)	93.8 ± 6.73	87.3 ± 14.65	T 1.73	0.32 NS
Total cholesterol:	139 ± 36.09	220.42 ± 58.63	**T 7.48**	**<0.001****
HDL-c:	46.28 13.25	47.7 ± 7.17	MW 164	0.55 NS
LDL-c:	92.85 ± 17.78	141.31 ± 48.52	**MW 56**	**<0.001****
Triglyceride:	92.5 ± 35.65	166.93 ± 80.4	**MW 37**	**<0.001****
CRP:	3.82 ± 0.63	11.77 ± 12.96	**MW 39**	**<0.001****
Uric acid:	4.61 ± 0.99	5.08 ± 2.27	MW 114	0.06 NS

FBS: fasting blood sugar, HDL:high density lipoprotein, LDL :low density lipoprotein, CRP: C - reactive protein, GPX: glutathion peroxidase, MW: Mann Whitney test, BMI: Body mass index, carotid artery intima-media thickness (CA-IMT)

Table (3): Intima-media thickness of epileptic patients and healthy controls

Variable	Control (n=40)	Cases (n=40)	MW	P
	Mean ± SD	Mean ± SD		
Rt:	0.69 ± 0.14	0.95 ± 0.35	**136**	**<0.001****
Lt:	0.65 ± 0.18	1.02 ± 0.41	**122**	**<0.001****
Mean:	0.67 ± 0.12	0.99 ± 0.37	**150**	**<0.001****

Data are expressed as mean±S.D, MW: Mann Whitney test

Table (4): Correlation between CIMT and vascular risk factors of the epileptic group:

Variable	Rt CA-IMT (n=40)		Lt CA-CIMT (n=40)		Mean CA-IMT (n=40)	
	r	P	r	P	r	P
Age	**0.77**	**<0.001****	**0.79**	**<0.001****	**0.80**	**<0.001****
BMI	**0.30**	**0.05***	**0.32**	**0.04***	**0.33**	**0.04***
Age of Onset	0.02	0.89	0.11	0.51	0.06	0.69
Duration of epilepsy	**0.70**	**<0.001****	**0.68**	**<0.001****	**0.71**	**<0.001****
Duration of therapy	**0.69**	**<0.001****	**0.63**	**<0.001****	**0.67**	**<0.001****
Frequency of seizers	**0.84**	**<0.001****	**0.77**	**<0.001****	**0.83**	**<0.001****
Total Cholesterol	**0.71**	**<0.001****	**0.75**	**<0.001****	**0.75**	**<0.001****
HDL	-0.16	0.31	-0.26	0.11	-0.22	0.17
LDL	**0.63**	**<0.001****	**0.66**	**<0.001****	**0.66**	**<0.001****
Triglyceride	**0.68**	**<0.001****	**0.78**	**<0.001****	**0.75**	**<0.001****
CRP	**0.38**	**0.02***	**0.37**	**0.02***	**0.40**	**0.01***
GPX	0.19	0.21	0.24	0.15	0.07	0.65
Uric acid	**0.35**	**0.03***	**0.38**	**0.02***	**0.38**	**0.02***

Data are expressed as mean±S.D. and number (%).HDL:high density lipoprotein, LDL :low density lipoprotein, hs-CRP: high sensitivity C -reactive protein, GPX: glutathion peroxidase, CA-IMT carotid artery intima-media thickness, r:correlation coefficient

Table (5): Effect of AEDS on vascular risk factors in the cases group:

Variable	CBZ (n=10)	VPA (n=13)	Poly therapy (n=17)	Test	P
	Mean ± SD	Mean ± SD	Mean ± SD		
Total cholesterol:	a 225.62 ± 59.22	a 174.22 ± 46.51	a 253.7 ± 43.87	**F** **9.58**	**<0.001***
HDL:	a 41.78 ± 13.93	a 42.78 ± 8.68	a 50.42 ± 15.16	F 1.50	0.24 N.S
LDL:	a,c 145.94 ± 48.72	b 112.56 ± 42.91	c 160.56 ± 44.11	**K** **8.28**	**0.02***
Triglyceride:	a, c 155.08 ± 68.87	b 126.41 ± 56.04	c 203.61 ± 88.89	**K** **6.85**	**0.04***
CRP:	a 12.65 ± 17.58	b 7.47 ± 7.18	a 13.81 ± 11.73	**K** **5.45**	**0.04***
GPX:	a 57.38 ± 15.35	a 63.53 ± 10.53	a 68.97 ± 9.57	F 3.23	0.06 NS
Uric acid:	a 5.23 ± 2.37	b 6.99 ± 2.06	a 6.21 ± 2.46	**K** **5.61**	**0.04***
Rt CA-IMT:	a 1.02 ± 0.39	b 0.74 ± 0.23	a,c 1.06 ± 0.34	**K** **11.96**	**0.003***
Lt CA-IMT:	a 1.15 ± 0.52	b 0.83 ± 0.36	a,c 1.09 ± 0.34	**K** **8.24**	**0.02***
Mean CA-IMT:	a 1.09 ± 0.45	b 0.78 ± 0.28	a,c 1.08 ± 0.33	**K** **10.77**	**0.005****

HDL:high density lipoprotein, LDL :low density lipoprotein, CRP: C -reactive protein, GPX: glutathion peroxidase, ,carotid artery intima-media thickness (CA-IMT), F:ANOVA F test, K: Kruskal Wallis test. Groups with different letters are significantly different

DISCUSSION

As atherosclerosis is a potentially preventable disease, early understanding of its risk factors in young adults is important to prevent its development in later life. our study revealed alteration of various vascular risk factors including lipid profile, CRP, GPX and uric acid in young adult patients with epilepsy on traditional AEDs and their contribution to increased CA-IMT, a strong potential marker of early or subclinical atherosclerosis**.**

Dyslipidemia has long been known to be an important risk factor for atherosclerosis **[9].**We demonstrated that alteration of lipid profile is common among patients with epilepsy in agreement with others **[10, 11, 12].** The increased levels of TC, LDL-c and TG were significantly higher in our patients than control group. This investigation is in coincidence with **Tomoum et al.**[13] and **Kumar et al.** [14] and but is against **Erdemir et al. and Keenan et al.** [15],[16] who did not observe any differences regarding serum lipid profiles between epileptic and healthy children. This modification of lipid profile is particularly significant among CBZ and polytherapy group than VPA group. Similar results were reported by other studies [17, 18, 19, 20]. In this respect, it has been reported that chronic treatment with AEDs may compete with cholesterol in the utilization of hepatic microsomal enzymes P-450 system leading to reduction in the transformation of cholesterol to bile acids resulting in increase in serum cholesterol level [21] while **Hsieh et al.** [22] reported that enzyme-inducing AEDs like CBZ increase the activity of the hepatic cytochrome P450 system, which is involved in synthesis of serum cholesterol, though direct studies are needed, our findings are wholly consistent with this hypothesis. The increased LDL-c levels in patients on AEDs may be an indirect effect of decreased thyroid hormone level which is a common side effect of AEDS [23]

CRP levels were significantly higher in our patients in comparison to control. This result goes hand in hand with many studies [24, 25, 26, 27, 28] whose results support the association between inflammation and epilepsy. Whereas the CRP level was significantly increased in the CBZ treatment group in our study, VPA induced insignificant change in CRP level. This is in agreement with [19,29]. In addition **Yuen et al.** [30] reported reduction of CRP level in patients treated with VPA, in agreement with **Mintzer** [31] who also reported that patients who were switched from inducing to non-inducing agents had marked reductions in CRP. This suggests that CYP450 induction may be responsible for CRP level increase [32].

Regarding oxidative stress biomarkers, uric acid levels were found to be slightly higher in our cases with no significant difference between cases and control. This finding is in parallelism with **Menon et al.** [11] however our results were in disagreement with **Krause et al.** [33] who revealed significantly lower serum concentrations of uric acid in epileptic patients compared to a group of normal controls. Uric acid was significantly higher in patients with VPA monotherapy than both the CBZ group and polytherapy group. Similar findings were reported by **Tan et al.** [25] Elevation of uric acid level in VPA group can be attributed to its altered renal secretion by VPA [34]**.** As such, long-term therapy with VPA in patients with epilepsy may increase the levels of uric acid that may contribute to atherosclerotic risk through inducing endothelial dysfuction and altering nitric oxide secretion. **Krause et al.** [33] reported that in patients taking enzyme-inducing drugs, uric acid levels were found to be lower than in those under VPA treatment and postulated that acceleration of protein synthesis, due to enzyme-induction may lead to lowering uric acid level and reported the possible use of this finding in the treatment of hyperuricemia.

Glutathione peroxidase in our patients was significantly higher than those in the control group. This is in agreement with several studies [11, 35, 36, 37]**.** We suggest that GPX upregulation, in patients with epilepsy receiving AEDS, might be a consequence of induced GPX synthesis in the liver as a compensatory mechanism for decreased glutathione levels in the same group of patients. We also observed slightly higher GPX level in VPA group and poly-therapy

group than CBZ group although the difference was not significant. This is in agreement with others [35, 36, 38]. **Hamed et al.** [5] demonstrated marked reduction in GPX levels among the untreated patients and elevated to normal levels with AED medications. It even increased above normal limits with VPA therapy (mono- and poly-therapy) which is consistent with our results. Alterations in the antioxidant system induced by AED therapy can be explained by the metabolism of AED into reactive epoxide intermediates, which can induce structural and functional impairments [39]. Therefore, we suggest that the risk of atherosclerosis in CBZ group may be related to inflammatory mechanisms manifested by increased CRP and in the VPA group may be associated with oxidative mechanisms through affection of the antioxidant enzymes

This study provides evidence of the high risk to develop atherosclerosis among patients with epilepsy. We demonstrated significant increase in the CA-IMT in epileptic patients in comparison to healthy control. This result is in agreement with **Mintzer** [31] as well as **Erdemir et al.** [14] and **Talaat et al**. [40] .On the other hand our results disagree with **Tomoum et al.** [12] **and Keenan et al.** [15] who found no difference between epileptic patients and control regarding CA-IMT . This disagreement can be attributed to differences in sample size and methodology. Furthermore, we found that patients treated with CBZ and polythearapy demonstrated more increase in CIMT than those treated with VPA this in concordance with **Hamed et al.** [5] However, according to **Belcastro et al.** [41] VPA can also cause insulin resistance with hyperinsulinemia which may also lead to atherosclerosis as insulin increases the activity of the enzymes involved in cholesterol synthesis .On the contrary **Mehrpour et al.** [42]documented that in Iranian they did not find any difference between the patients with epilepsy treated with either VPA or CBZ. Based on correlation analysis, our results revealed that age, BMI, systolic , diastolic blood pressure were significantly correlated with mean CA-IMT in agreement with others [25,43]. There is also a significant positive correlation between CA-IMT and duration of illness, duration of AEDS therapy and frequecy of seizures. We suggest that the duration of AED is one of the risk factors that accelerate the atherosclerotic process in agreement with others [19, 25, 44]. It is obvious that the results of this study may offer basis for discussion about the possible prevention of early atherosclerosis among patients with epilepsy.

CONCLUSION

Based on our results, we can conclude that epileptic patients on AEDs therapy have a potential risk of developing subclinical carotid artery atherosclerosis.

RECOMMENDATIONS

Regular checking of lipid profile and CA-IMT in epileptic patients with AEDs is needed. Further studies on epileptic patients with and without AEDs therapy are needed to prove the role of epilepsy. Future prospective studies on different AEDS are needed to evaluate the risk of different AEDS either in mono- or polytherapy.

Limitations

Though the small sample size was a limitation in our study, we were able to detect important significant relations and this makes our finding striking for their significance and attests to their robustness.

REFERENCES

1. **Hesdorffer D, Logroscino G, Benn E, Katri N, Cascino G, Hauser W.** Estimating risk for developing epilepsy: a population-based study in Rochester, Minnesota. Neurology 2011; 76(1):23-27.
2. **Hamed SA .**Atherosclerosis in epilepsy: its causes and implications. Epilepsy Behav 2014; 41:290-6.
3. **Katsiki k, Dimitri P. Mikhailidis a, Devaki R.** The effects of antiepileptic drugs on vascular risk factors: A narrative review Nair Seizure 2014; 23: (677–84).
4. **Aycicek A, Iscan A.**The effects of carbamazepine, valproic acid and phenobarbital on the oxidative and antioxidative balance in epileptic children. Eur Neurol 2007; 57:65–69.

5. **Hamed SA, Hamed EA, Hamdy R, Nabeshima T.** Vascular risk factors and oxidative stress as independent predictors of asymptomatic atherosclerosis in adult patients with epilepsy. Epilepsy Res 2007; 74:183–92.
6. Lea L, Bryan P, Pathmaja P, Alicia B, Edward A . Carotid intima- media thickness for the practicing Lipidologist Journal of Clinical Lipidology 2010; 4: 24–35
7. **Commission on Classification and Terminology of International League against Epilepsy** Proposal for revised classification of epilepsies and epileptic syndromes. Epilepsia 1989 ; 30: 389-99.
8. **Hafeman DG, Sunde RA, Hockstka W .** Effect of dietary selenium on erythrocyte and liver glutathione peroxidase in the rat. J Nutr. 1974; 104:580–87.
9. **Kullo IJ, Ballantyne CM .**Conditional risk factors for atherosclerosis. Mayo Clin Proc 2005; 80:219–230.
10. **Mahmoudian, T, Iranpour R, Messri N.** Serum lipid levels during carbamzepine therapy in epileptic children. Epilepsy Behav. 2005; 6: 257—59.
11. **Hamed SA, Hamed, EA, Kandil, MR**. Serum thyroid hormone balance and lipid profile in patients with epilepsy.Epilepsy Res. 2005; 66, 173—83.
12. **Menon B, Ramalingam K, Kumar R.** Low plasma antioxidant status in patients with epilepsy and the role of antiepileptic drugs on oxidative stress. Ann Indian Acad Neurol 2014;25(17):398-404.
13. **Tomoum HY, Awadallah MM, Fouad DA, Ali AH.** Lipid Profile, Apolipoproteins A and B in Children with Epilepsy. J Child Neurol 2008; 23(11):1275- 81.
14. **Kumar RY, Harsh M, Asha M**. Effect of anticonvulsant drugs on lipid profile in epileptic patients. Ind J Pub Health Res Dev 2010; 1(1): 46.**50.**
15. **Erdemir A, Cullu N, Yiş U, Demircioğlu F, Kir M, Cakmakçi H.** Evaluation of serum lipids and carotid artery intima media thickness in epileptic children treated with valproic acid. Brain Dev 2009: 31(10):713-716.
16. **Keenan N, Sadlier L, Wiltshire K.** Vascular function and risk factors in children with epilepsy: Associations with sodium valproate and carbamazepine. Epilepsy Res. 2014; 108(6):1087-94.
17. **Eirís J, Novo-Rodríguez MI, Del Río M, Meseguer P, Del Río MC, Castro-Gago M.** The effects on lipid and apolipoprotein serum levels of long-term carbamazepine, valproic acid and phenobarbital therapy in children with epilepsy. Epilepsy Res. 2000; 41(1):1-7.
18. **Demircioglu S, Soylu A, Dirik E** .Carbamazepine and valproic acid: effects on the serum lipids and liver functions in children. Pediatr Neurol 2000; 23(2):142-6.
19. **Luef A , Rauchenzauner C, Waldmann T, ,Sandhofer W, Seppi K, Trinka E, et al.** Non-alcoholic fatty liver disease (NAFLD), insulin resistance and lipid profile in antiepileptic drug treatment Epilepsy Research 2009;86: 42—7.
20. **Chuang Y, Chuang H, Lin T, Chang C, Lu C, Chang W.** Effects of long-term antiepileptic drug monotherapy on vascular risk factors and atherosclerosis. Epilepsia 2012; 53:120–28.
21. **Isojirvi JI, Pakarinen AJ, Myllyla VV.** Serum lipid levels during carbamazepine medication: a prospective study. Arch Neurol 1993; 50:590-93.
22. **Hsieh C, Lai E, Yang Y, and Lin S.** Comparative stroke risk of antiepileptic drugs in patients with epilepsy Epilepsia 2013 ; 54(1):172–80.
23. **Hamed SA .** The effect of antiepileptic drugs on thyroid hormonal function: causes and implications. Expert Rev Clin Pharmacol 2015; 8(6):741-50.
24. **Ashfaq S, Abramson J ,Jones D,Rhodes S, Weintraub S, Hooper W et al.** The Relationship Between Plasma Levels of Oxidized and Reduced Thiols and Early Atherosclerosis in Healthy Adults . ACC 2007; 47(5):1005–11
25. **Tan T, Lu C, Chuang H, Lin T, Liou C, Chang W** Long-term antiepileptic drug therapy contributes to the acceleration of atherosclerosis. Epilepsia 2009; 50:1579–86
26. **Olesen JB, Abildstrom SZ, Erdal J**. Effects of epilepsy and selected antiepileptic drugs on risk of myocardial infarction, stroke, and death in patients with or without previous stroke: a nationwide cohort study Pharmacoepidemiol Drug Saf 2011; 20: 964-971
27. **Alapirttiy T , Waris M, Fallah M, , Riikka M, Kharazmi E, Peltola J.** C-reactive protein and seizures in focal epilepsy: A video electroencephalographic study. Epilepsia 2012; 53(5):790–96.
28. **Ishikawa N, Kobayashi Y, Fujii Y, Kobayashi M.** Increased interleukin-6 and high-sensitivity C-reactive protein levels in pediatric epilepsy patients with frequent, refractory generalized motor seizures. Seizure 2015; 25:136-40.

29. **Lopinto-Khoury C, Mintzer S. Antiepileptic drugs and markers of vascular risk** Curr Treat Options Neurol 2010;12:300–8.
30. **Yuen A, Bell G, Peacock J, Koepp M, Patsalos P, Sander J.** Effects of AEDs on biomarkers in people with epilepsy: CRP, HbA1c and eGFR. Epilepsy Res 2010 ;91(2-3):187-92.
31. **Mintzer S. (2010):** Metabolic consequences of antiepileptic drugs. Curr Opin Neurol; 23:164-9.
32. **Mintzer S, Skidmore CT, Abidin CJ, Morales MC,Chervoneva A, Capuzzi DM, et al.** Effects of antiepileptic drugs on lipids, homocysteine, and Creactive protein. Ann Neurol. 2009; 65:448–56.
33. **Krause K, Berlit P Schmidt-Gayk H , Schellenberg B.** Antiepileptic drugs reduce serum uric acid . Epilepsy Research 1987; 1(5):306-7.
34. **Yu ZF, Bruce-Keller AJ, Goodman Y.** Uric acid protects neurons against exctiotoxic and metabolic insults in cell culture, and against focal ischemic brain injury in vivo. J.Neurosci. Res 1998; 53(5): 613—25.
35. **Cengiz M, Yuksel A, Seven M.** The effects of carbamazepine and valproic acid on the erythrocyte glutathione, glutathione peroxidase, superoxide dismutase and serum lipid peroxidation in epileptic children. Pharmacol. Res 2000; 41:423—25.
36. **Ercegovac M , Jovic N , Simic T , Beslac-Bumbasirevic L , Sokic D , Djukic T , et al.** Byproducts of protein, lipid and DNA oxidative damage and antioxidant enzyme activities in seizure. Seizure 2010; 19 (4):205-10.
37. **Ercegovac M, Jovic N, Simic T, Bumbasirevic LB, Sokic D, Radojevic AR.** Antiepileptic drugs affect protein, lipid and DNA oxidative damage and antioxidant defense in patients with epilepsy. J Med Biochem 2013; 32:121-30.
38. **Kurekci AE , Alpay F , Tanindi S, Gokcay E , Ozcan O , Akın R , Isimer A, Sayal A.** Plasma trace element, plasma glutathione peroxidase, and superoxide dismutase levels in epileptic children receiving antiepileptic drug therapy. Epilepsia 1995; 36:600—04.
39. **Cárdenas-Rodríguez N, Coballase-Urrutia E, Pérez-Cruz C, Montesinos-Correa H, Rivera-Espinosa L, Sampieri A.** Relevance of the Glutathione System in Temporal Lobe Epilepsy: Evidence in Human and Experimental Models **.** Corporation Oxidative Medicine and Cellular Longevity 2014; 75: 1-12
40. **Talaat M, Kamel T, Rabah A, Ahmed S, El-Jaafary S, Abdelaziz G.** Epilepsy and antiepileptic drugs: risk factors for atherosclerosis**.** *International Journal of Neuroscience*; Informa Healthcare USA, Inc.ISSN: 0020-7454 print / 1543-5245.
41. **Belcastro V, D'Egidio C, Striano P, Verrotti A.** Metabolic and endocrine effects of valproic acid chronic treatment. Epilepsy Res 2013; 107:1-8.
42. **Mehrpour M • Shojaie M • Zamani B• Gharibzadeh S • Abbas M.** Atherogenic consequence of antiepileptic drugs: a study of intima-media thickness .Neurol Sci 2014; 35:253-57.
43. **Yang C, Sun Z, Li Y, Ai J, Sun Q and Tian Y.** The correlation between serum lipid profile with carotid intima-media thickness and plaque BMC Cardiovascular Disorders 2014; 14:181.
44. **Verotti A, Domizio S, Angelozzi B, Sabatino G, Morgese G, Chiarelli F.** Changes in serum lipids and lipoproteins in epileptic children treated with anticonvulsants. J Pediatr Child Health 1997; 33:242-5.