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**Influence of sodium valproate treatment on body mass and insulin  
resistance parameters in children with epilepsy**

Утицај натријум-валпроата на телесну масу и параметре инсулинске  
резистенције код деце са епилепсијом

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## Influence of sodium valproate treatment on body mass and insulin resistance parameters in children with epilepsy

### Утицај натријум-валпроата на телесну масу и параметре инсулинске резистенције код деце са епилепсијом

#### SUMMARY

**Introduction/Objective** One of the main side-effects in patients undergoing valproic acid treatment is weight gain. Weight gain might be the reason for drug discontinuation, especially in adolescent girls, and it has to be considered also before introducing the drug. The main goal of our study is to investigate a possible influence of antiepileptic therapy with sodium valproate on weight and glucose homeostasis in pediatric patients with epilepsy.

**Methods** The investigation included a total of 49 healthy children with recently diagnosed epilepsy. We measured height, weight and serum 12-hour overnight fasting glucose and insulin level before initiation and after 6- and 12-month valproic acid treatment period. The BMI and HOMA indexes were calculated for each patient and correlated after the initiation of therapy and after 6 and 12 months of therapy.

**Results** We found that children significantly gained weight with statistical significance ( $p < 0.01$ ) even after 6 months of therapy with a significant glucose metabolism change and statistical difference in average serum glucose and insulin levels ( $p < 0.05$ ).

**Conclusion** Our results show that a 12-month treatment with valproic acid in children with epilepsy has a great impact on weight gain and glucose homeostasis and metabolism. We strongly recommend that all children with recently diagnosed epilepsy at the initiation of valproate therapy should be closely monitored on a 6-month basis. Consultation of nutritionist is advised especially in children with preexisting problem with body weight.

**Keywords:** valproic acid; child epilepsy; insulin; weight; HOMA

#### САЖЕТАК

**Увод/Циљ** Добитак у телесној маси је један од најчешћих нежељених ефеката примене терапије валпроатима код пацијената са епилепсијом. Повећање телесне масе је често главни разлог самовољног прекида терапије, нарочито у групи адолесценткиња.

Циљ рада је био да се испита утицај примене валпроата на телесну масу и гликорегулацију деце са епилепсијом.

**Метод** Истраживање је укључило укупно 49 здраве деце са новодијагностикованом епилепсијом. Мерена је телесна висина, телесна маса те узоркована гликемија и инсулин наште. Параметри су испитивани пре почетка антиепилептичне терапије валпроатима, а потом након 6 и 12 месеци терапије. *BMI* и *HOMA* индекси су израчунавани коришћењем математичке формуле за сваког пацијента на сваком мерењу понаособ.

**Резултати** Истраживање је показало да постоји статистички значајно повећање телесне масе већ након 6 месеци примене терапије валпроатима ( $p < 0,01$ ), те да постоји статистички значајно повећање просечних вредности гликемије и инсулина након 12 месеци терапије ( $p < 0,05$ ).

**Закључак** Наше истраживање је показало да 12-месечна примена валпроата код деце са новодијагностикованом епилепсијом има значајан утицај на повећање телесне масе и утиче на гликорегулацију и метаболизам глукозе. Препоручујемо да се деци са новодијагностикованом епилепсијом, која започну терапију валпроатима, редовно прате на 6-месечним контролама.

**Кључне речи:** валпроат; дечја епилепсија; инсулин; телесна маса; *HOMA*

## INTRODUCTION

Epilepsy is a disease characterized by an enduring predisposition to generate epileptic seizures and by the neurobiological, cognitive, psychological, and social consequences of this condition [1, 2]. The epilepsy syndrome cluster of features incorporates seizure types, electroencephalogram (EEG), and imaging features that tend to occur together [3]. Factors that contribute to an epilepsy syndrome include the age of onset, remission, triggers, diurnal

variation, intellectual and psychiatric dysfunction, EEG findings, imaging studies, family history, and genetics.

Children epilepsy prevalence is estimated to 0.5 – 4% of children population, depending on countries and world regions. The incidence of epilepsy differs by age and is highest in first year of life with a descending trend as the children get older. The data on annual incidence show discrepancies among world regions and vary from 33 – 82 / 100,000 in children [4, 5].

The medical approach and treatment of childhood epilepsy differs from epilepsy in adulthood due to different etiology, seizure semiology, existence of specific epileptic syndromes of childhood, comorbidities, child development. Childhood epilepsies that are pharmaco-resistant have a great impact on psychomotor development, cognition, and are a great burden for the family of the child. [6]

The aim of epilepsy treatment is to achieve a total or optimal seizure control and establish a good quality of life for patients with epilepsy [7].

A longtime treatment with antiepileptic drugs in childhood has a great risk of side effects that can cause damage to the child's development and health and can be a burden to health in adulthood. The experience and close monitoring of patients with a long-time antiepileptic treatment is of great importance in the pediatric epilepsy practice.

One of the most widely used antiepileptic drug in children and adults is Valproic acid / sodium valproate (VPA). Valproate has multiple mechanisms of action, including GABA potentiation, blocking of T-type calcium channels, and blocking of sodium channels. One of the most observed side effects in clinical practice of VPA treatment is weight gain. [8, 9]. The incidence of this side effect differs among authors in published data, from 10 to 70% in child population [10, 11].

Transient weight gain can lead to a chronic medical problem – obesity. Childhood obesity is a well defined independent risk factor for increased morbidity for the cardiovascular disease in adulthood [12]. It is also often related to metabolic and lipid disorders, hypertension, arterogenesis and diabetes. Metabolic syndrome is nowadays a well defined entity which has a high risk of cardiovascular morbidity and diabetes mellitus type 2 [13]. It is defined and diagnosed in case of visceral / central obesity, lipid metabolism

disorder (elevated LDL cholesterol, triglycerides, lower HDL cholesterol), glucose intolerance and hypertension [14].

Therefore, it is of great importance to recognize and identify children with an increased risk of metabolic syndrome, with its impact for comorbidities that are associated with it in adulthood. One of the parameters for metabolic syndrome is insulin resistance, which is a strong prediction factor for the development of diabetes mellitus type 2 [15].

One of the suggested mathematical models in insulin resistance evaluation is the HOMA index, developed by Matthews et al. [16]. The HOMA index is calculated according to the formula: Glycemia (mmol/l) X serum Insulin level (mcU/ml) / 22.5. The International Diabetes Federation (IDF) defined a criteria for recognizing groups of patients with a high risk of developing metabolic syndrome in childhood [17].

The aim of the study was to investigate the influence of VPA as monotherapy in children with recently diagnosed epilepsy to body weight and insulin resistance parameters, its impact on glycoregulation and on insulin resistance development in childhood. The parameters were obtained after 6 and 12 months of VPA therapy in otherwise healthy children with recently diagnosed epilepsy.

## METHODS

The investigation included a total of 49 healthy children with recently diagnosed epilepsy. After the diagnosis of epilepsy was made (2 unprovoked events confirmed as seizures and epileptiform EEG changes), a monotherapy with VPA was initiated.

Anthropometric parameters were analyzed – body height and weight and body mass index (BMI) were calculated using the formula  $BMI = \frac{BM}{BH^2}$ . All patients were classified for puberty stage using the Tanner method. Pubic and axillary hair was examined, and so was breast development in girls, and genitals and testicle volume in boys. All children were classified according to the Tanner stages 1–4. Prepubertal children had Tanner stage 1 (pubic hair and testicle volume for boys and pubic hair and breast development for girls). The pubertal group included children with any of the sex characteristics of Tanner stage 2. Every child had a blood sample collected at 08:00 am, before the meal, after a 12-hour overnight

fasting, and before the morning dose of VPA. Blood samples of glucose, insulin and valproic acid level were taken. Using the mathematical model, the HOMA index (insulin resistance index) was calculated for each patient. The valproic acid serum level was used in statistical analysis to establish the variability among patients and to evaluate a correlation between the valproic acid serum level and other investigated parameters.

Sampling was made at the initiation of therapy, after 6 months and 12 months of continuous therapy with sodium valproate. Samples were collected at 08:00 am, after a 12-hour night fasting and before the morning dose of valproate was taken.

The exclusion criteria were: obese children (BMI more than 25 kg/m<sup>2</sup> before the initiation of therapy), children with diagnosed chromosomal anomalies, children with a chronic inflammatory autoimmune disease, children with congenital or chronic heart, lungs, liver and kidney diseases, which can influence glucose and lipid metabolism. Children with chronic neurological conditions (cerebral palsy, congenital neurological disease) and children with any finding other than normal on brain CT or MRI were also excluded.

Data were collected and analyzed using computer program IBM SPSS 20.0 and presented on tables and graphs.

The statistical analysis used the arithmetic mean, the standard deviation for data description used test: the parameter data and testing difference used the T-test and FISHER ANOVA, a Chi-square test. For non-parameter data: the Mann-Whitney, the Wilcoxon, and the Freidman and Kruskal-Wallis tests were used. The correlation was investigated using the Pearson and Spearman correlation.

This investigation was approved by the Universty Children's Ethic Committee – number 017 13/77 on April 9, 2019.

## RESULTS

A total of 49 children were investigated. The average age at the time of the VPA therapy initiation was 9 years and 9 months. The patients were grouped according to their age and presence of sex characteristics (puberty). Statistical analysis of all groups showed no statistical difference between the investigated groups. The distribution of serum concentration

of VPA after 6 and 12 months of therapy showed no statistical difference ( $p > 0.05$ ), which proved that all of the investigated children received the drug in a similar therapeutic range.

The average body mass at the initiation therapy was 40.88 kg. After 6 months and 12 months of therapy the average body mass increased to 43.53 kg and 47.20 kg respectively. Statistical analysis shows that there is a highly statistically proven difference between these three groups ( $p < 0.01$ ), which indicates that the children gained weight significantly. This is more obvious when BMI is calculated for each investigated patient (Figure 1). A significant increase in BMI is seen after 6 and 12 months of therapy, respectively ( $p < 0.01$ ).

The average patient serum glucose level before the initiation of the therapy was 4.66 mmol/l. A significant increase after 6 and 12 months of continuous valproic acid therapy was observed, with the average fasting glucose level of 4.94 mmol/l and 4.97 mmol/L respectively. This difference showed a statistically significant difference between these three groups of parameters ( $p < 0.05$ ).

The average serum insulin level at the initiation of therapy was 5.69 mcU/ml. After 6 and 12 months of continuous anti-epileptic drug (AED), the average serum insulin levels were 8.68 mcU/ml and 13.10 mcU/ml, respectively. There was a statistically significant difference between these three groups of parameters ( $p < 0.05$ ) (Figure 2).

The calculated average HOMA value at the initiation of therapy was 1.18. After 6 and 12 months of continuous VPA therapy, the average HOMA values were 2.01 and 2.98 respectively (Figure 3). Analysis shows that there is a statistically significant difference between these three groups of parameters ( $p < 0.05$ ).

A correlation of weight change after 12 months of AED therapy between three age groups of patients showed that older children gain weight more than children at a younger age (Figure 4).

When correlating the influence of weight change in correlation to age, a statistically significant difference was shown between these three groups, with the highest statistical difference between the preschool (0-7 years) and the school group (older than 7 years) of children ( $p < 0.05$ ) (Table 1). The analysis of gender in relation to weight gain showed that there was no significant difference between boys and girls ( $p > 0.05$ ). Pubertal status analysis

also showed that there was no statistical difference in weight gain among pre-pubertal and pubertal children ( $p > 0.05$ ).

## DISCUSSION

Our investigation included a total of 49 children, with the average age of 9 years and 9 months. The investigated group of children was cohort in correlation to gender, age (preschool 0–7 years, elementary school 8–12 years, and adolescents 13–18 years) and the puberty status. All of the children received VPA in similar therapeutic doses, with no significant difference between the serum levels of valproic acid for each child. This is important to emphasize, since it excludes the possible bias of VPA doses to investigated side effects.

The investigated group of children was observed over a one-year period. The results show that the average weight has increased after 6 months for 2.5 kg, with a further average increase of 6 kg after a year of therapy ( $p < 0.01$ ). The calculated BMI for each patient has shown a statistically significant increase on average after 6 and 12 months of therapy ( $p < 0.01$ ). Our results are concordant with the results found in other authors investigations Sonmez FM et al. [18], Verotti et al [19], Egunsola O et al [20], Masuccio F et al. [21] and Ferrara P et al [22], which also found a significant increase in weight and BMI in VPA investigational group after 6 and 12 months of monotherapy . Publications investigating this effect of valproic acid therapy on subsequent weight gain show different findings for children and for adults. Bosnak et al [23], who investigated a group of 56 children, did not prove significance in calculated Z score for the period of 40 months. Sharpce C et al [10] found a significant increase in body mass in 24% of investigated children. Wirell et al [11] found that out of the group of children with significant weight gain 12 to 19% became obese, with weight more than 95<sup>th</sup> percentile for age. Among children, the publication data shows increased weight gain in group of female adolescents [21].. As for the Tanner stage, our results did not show a significant difference in weight gain in prepubertal and pubertal children, although an increased trend of weight gain has been observed in pubertal adolescents ( $p > 0.05$ ). Gender did not play a significant role in weight gain either, since both groups – boys and girls – gained weight at the same pace ( $p > 0.05$ ).

The exact mechanism of the effect of valproic acid on weight gain is still not clearly defined. Sidhu H.S. et al [24] found that group of patients treated with valproate had significant increase in HOMA and decrease in adiponectin levels and proposed that valproate induced hypoadiponectinemia which correlates with insulin resistance. Kanemura H. et al [25] investigated the effect of valproic acid on the serum insulin and glucose level and their correlation, and he concluded that one of the possible effect was through disturbed glycoregulation. Our results show that after 12 month of therapy with valproic acid a significant disruption in glycoregulation appeared and that the average serum glucose level (mmol/l) after 12 months was higher and showed a statistical significance as compared to the average glucose level at the initiation of therapy ( $p < 0.05$ ). The average serum insulin level after 12 months of VPA treatment was higher and showed a statistical significance ( $p < 0.05$ ) as compared to the average serum insulin level before valproic acid was initiated.

A well-defined cut-off HOMA values for an increased risk of developing metabolic syndrome in childhood is still not defined. Kurtoglu et al. [26] investigated the HOMA index in obese children and found that the cut-off values for the HOMA index were above 2.67 for prepubertal boys and 2.22 for prepubertal girls, with a higher risk of development of insulin resistance. Their results showed that pubertal boys and girls had a higher cut-off HOMA value for insulin resistance of 5.22 and 3.82, respectively. Our investigation showed that the average HOMA index for our patients had increased after 12 months of VPA therapy, with a high statistical significance ( $p < 0.01$ ) ranging from 1.18 to 2.98, respectively.

Although our research showed that VPA had a significant impact to glycoregulation and glucose homeostasis, none of the children developed clinical insulin resistance with the HOMA index above the cut-off values. This concurs with the results by Belcastro V et al. [9], Kanemura H et al. [25], Masuccio F et al [21] who also did not find statistical significance in VPA monotherapy group regarding insulin resistance parameters at the initiation of VPA therapy and after one year period. The research by Martin CK et al. [27] showed an increase in body weight in investigated patients, with lower values of serum glycemia after 12 months as compared to the control group of patients without VPA therapy, which contradicts our results. They concluded that this was probably due to an effect of VPA to increase appetite. Rakittin A et al. [28] concluded that metabolic changes during VPA treatment were primarily due to a direct primary effect of VPA, with lowering of the glucose level and thus increasing the appetite. They concluded that this effect was not the consequence of increased body



weight during VPA treatment. Our results showing significant increase in glucose level after a 12 month of VPA therapy might be due to a initial stage of insulin resistance development.

Another possible explanation of a significant increase of serum insulin and glucose as well as the HOMA index after VPA therapy could be the direct influence of VPA on the GABA receptors in pancreas beta – cells [29]. Impaired glycoregulation could be the cause of weight increase and metabolic disturbances during VPA therapy.

Research by Huan Zhang et al. [30] suggests a possible influence of VPA on weight gain by upregulation of hypothalamic fat mass and obesity-associated gene (FTO) expression, causing a hypothalamic dysfunction, resulting with enhanced appetite which contributes to weight gain.

## CONCLUSION

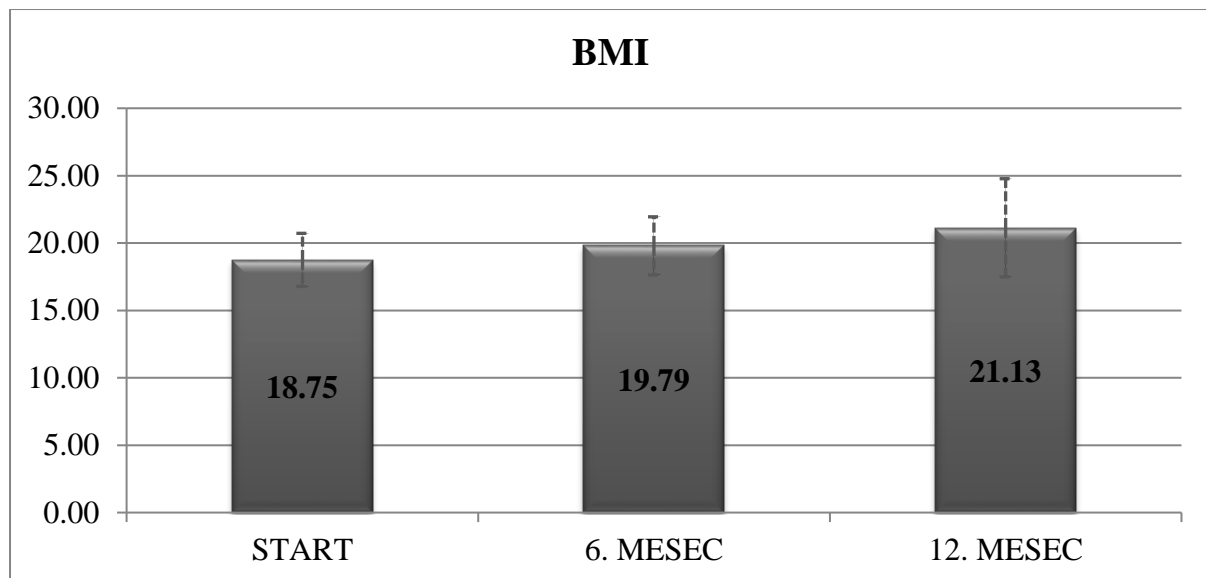
Our results have showed that a 12-month VPA treatment in children with epilepsy has a great impact on weight gain and glucose homeostasis and metabolism. Despite significant increase of weight gain and disturbed glucose homeostasis none of the children became obese nor did they develop clinical signs of insulin resistance. Our investigation showed that significant number of children increase weight during initial 12 months of VPA therapy and we strongly recommend that all children with recently diagnosed epilepsy should, at the initiation of VPA therapy, be closely monitored on a six-month basis. A close monitoring of weight, serum glucose and insulin should be conducted before and after 6 and 12-month VPA therapy. In case of a significant weigh gain and glucose metabolism disturbance, pediatric nutritionist and pediatric endocrinology consultation is suggested. Obese children starting VPA therapy should be closely monitored on a regular 6 months basis due to a fact that they are in great risk of developing father glycoregulation disturbance and progression or development of metabolic syndrome.

**Conflict of interest:** None declared.

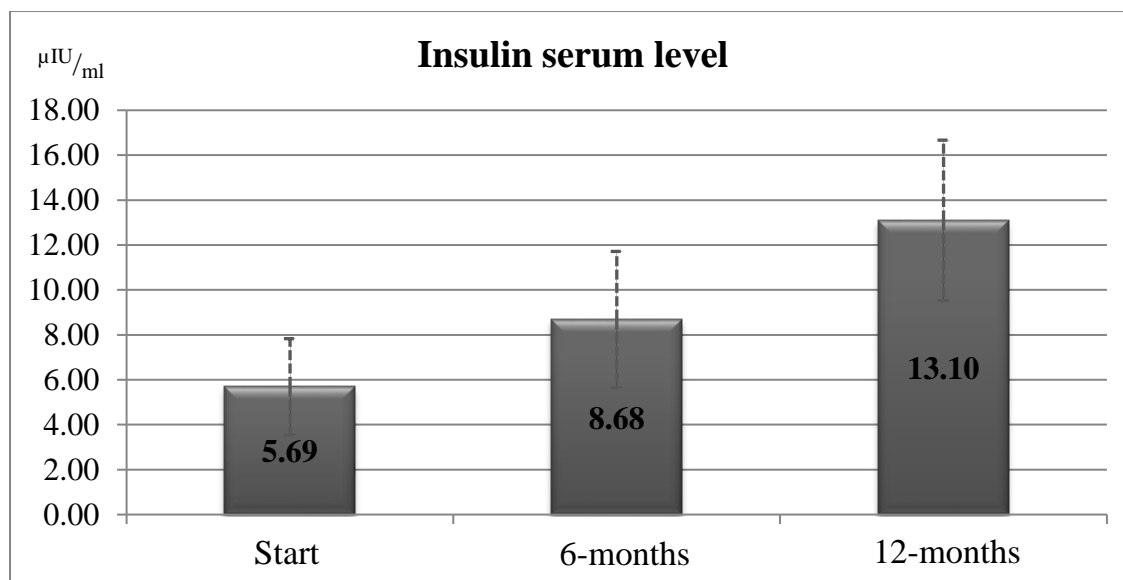
**REFERENCES**

1. Fisher RS, Cross JH, French JA, Higurashi N, Hirsch E, Janssen FE et al. Operational classification of seizure types by the International League Against Epilepsy: position paper of the ILAE Commission for Classification and Terminology. *Epilepsia* 2017;58(4):522–530. doi:10.1111/epi.13670.
2. Fisher RS, Acevedo C, Arzimanoglou A, Bogacz A, Cross JH, Elger CE, et al. ILAE official report: a practical clinical definition of epilepsy. *Epilepsia*. 2014 Apr;55(4):475-82. PubMed PMID: 24730690.
3. Scheffer IE, Berkovic S, Capovilla G, Connolly MB, French J, Guilhoto L et al. ILAE classification of the epilepsies: position paper of the ILAE Commission for Classification and Terminology. *Epilepsia* 2017;58(4):512–521. doi:10.1111/epi.13709.
4. Camfield P, Camfield C. Incidence, prevalence and aetiology of seizures and epilepsy in children. *Epileptic disorders: international epilepsy journal with videotape*. 2015 Jun;17(2):117-23. PubMed PMID: 25895502.
5. Aaberg KM, Gunnes N, Bakken IJ, Lund Søråas C, Berntsen A, Magnus P et al. Incidence and Prevalence of Childhood Epilepsy: A Nationwide Cohort Study. *Pediatrics*. 2017 May;139(5). doi: 10.1542/peds.2016-3908. Epub 2017 Apr 5.
6. Schraegle WA, Titus JB. The relationship of seizure focus with depression, anxiety, and health-related quality of life in children and adolescents with epilepsy. *Epilepsy Behav*. 2017 Mar;68:115-122. doi: 10.1016/j.yebeh.2016.12.009.
7. Blond BN, Detyniecki K, Hirsch LJ. Assessment of Treatment Side Effects and Quality of Life in People with Epilepsy. *Neurol Clin*. 2016 May;34(2):395-410, viii. doi: 10.1016/j.ncl.2015.11.002. Epub 2016 Mar 5. Review PMID:27086986.
8. Çiçek NP et al. The effects of valproate and topiramate use on serum insulin, leptin, neuropeptide Y and ghrelin levels in epileptic children. *Seizure*. 2018 May;58:90-95. doi: 10.1016/j.seizure.2018.03.013.
9. Belcastro V, D'Egidio C, Striano P, Verrotti A. Metabolic and endocrine effects of valproic acid chronic treatment. *Epilepsy Res* 2013;107(1-2):1–8. DOI: 10.1016/j.eplepsyres.2013.08.016.
10. Sharpe C, Wolfson T, Trauner DA. Weight gain in children treated with valproate. *Journal of child neurology*. 2009 Mar;24(3):338-41. PubMed PMID: 19258293.
11. Wirrell EC. Valproic acid-associated weight gain in older children and teens with epilepsy. *Pediatric neurology*. 2003 Feb;28(2):126-9. PubMed PMID: 12699863.
12. Reilly JJ, Kelly J. Long-term impact of overweight and obesity in childhood and adolescence on morbidity and premature mortality in adulthood: systematic review. *International journal of obesity*. 2011 Jul;35(7):891-8. PubMed PMID: 20975725.
13. Sherling DH, Perumareddi P, Hennekens CH. Metabolic Syndrome. *J Cardiovasc Pharmacol Ther*. 2017 Jul;22(4):365-367. doi: 10.1177/1074248416686187. Epub 2017 Jan 9.
14. Folić Nevena, Folić Marko, Marković Slavica, Anđelković Marija, Janković Slobodan. Risk factors for the development of metabolic syndrome in obese children and adolescents. *Srpski arhiv za celokupno lekarstvo* 2015 Volume 143, Issue 3-4, Pages: 146-152. <https://doi.org/10.2298/SARH1504146F>
15. Zaccardi F, Webb DR, Yates T, Davies MJ. Pathophysiology of type 1 and type 2 diabetes mellitus: a 90-year perspective. *Postgrad Med J*. 2016 Feb;92(1084):63-9. doi: 10.1136/postgradmedj-2015-133281. Epub 2015 Nov 30. Review. PMID:26621825.
16. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia*. 1985 Jul;28(7):412-9. PubMed PMID: 3899825.
17. Zimmet P, Alberti G, Kaufman F, Tajima N, Silink M, Arslanian S, et al. The metabolic syndrome in children and adolescents. *Lancet*. 2007 Jun 23;369(9579):2059-61. PubMed PMID: 17586288.
18. Sonmez FM, Zaman D, Aksoy A, Deger O, Aliyazicioglu R, Karaguzel G, et al. The effects of topiramate and valproate therapy on insulin, c-peptide, leptin, neuropeptide Y, adiponectin, visfatin, and resistin levels in children with epilepsy. *Seizure*. 2013 Dec;22(10):856-61. PubMed PMID: 23937963.
19. Verrotti A, Manco R, Agostinelli S, Coppola G, Chiarelli F. The metabolic syndrome in overweight epileptic patients treated with valproic acid. *Epilepsia*. 2010 Feb;51(2):268-73. PubMed PMID: 19682024.

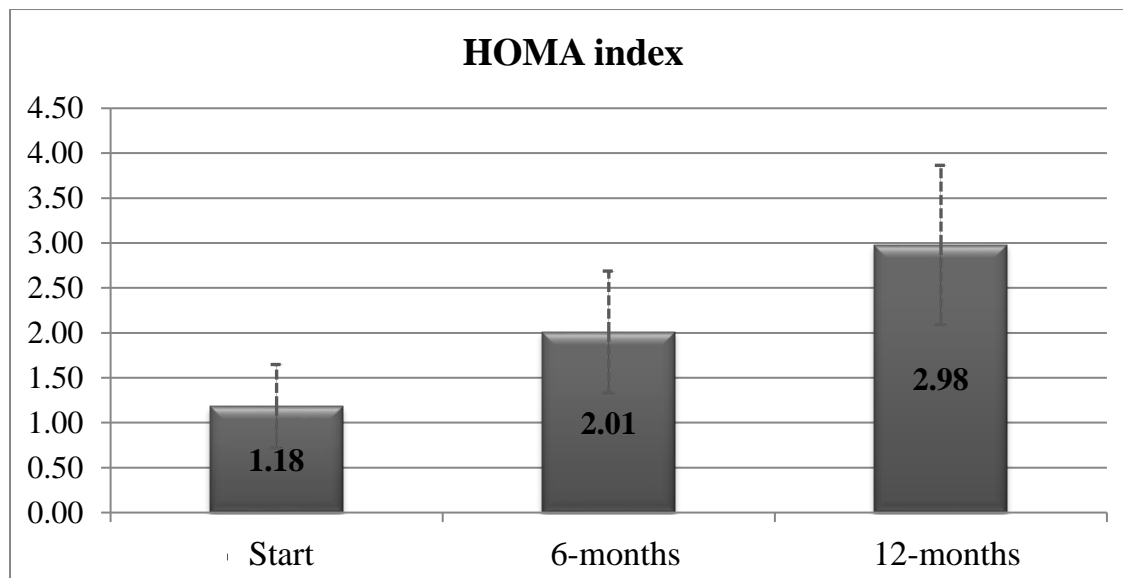
20. Egunsola O, Choonara I, Sammons HM, Whitehouse WP. Safety of antiepileptic drugs in children and young people: A prospective cohort study. *Seizure*. 2018 Mar;56:20-25. doi: 10.1016/j.seizure.2018.01.018. Epub 2018 Feb 2. PMID:29427834.
21. Masuccio F, Verrotti A, Chiavaroli V, de Giorgis T, Giannini C, Chiarelli F, et al. Weight gain and insulin resistance in children treated with valproate: the influence of time. *Journal of child neurology*. 2010 Aug;25(8):941-7. PubMed PMID: 20207607.
22. Ferrara P, Gatto A, Blasi V, DI Ruscio F, Battaglia D. The impact of valproic acid treatment on weight gain in pediatric patients with epilepsy. *Minerva Pediatr*. 2017 Jun 22. doi: 10.23736/S0026-4946.17.04938-6.
23. Bosnak M, Dikici B, Haspolat K, Dagli A, Dikici S. Do epileptic children treated with valproate have a risk of excessive weight gain? *Journal of child neurology*. 2003 Apr;18(4):306; author reply PubMed PMID: 12760438.
24. Sidhu HS, Srinivas R, Sadhotra A. Evaluate the effects of long-term valproic acid treatment on metabolic profiles in newly diagnosed or untreated female epileptic patients: A prospective study. *Seizure*. 2017 May;48:15-21. doi: 10.1016/j.seizure.2017.03.007.
25. Kanemura H, Sano F, Maeda Y, Sugita K, Aihara M. Valproate sodium enhances body weight gain in patients with childhood epilepsy: a pathogenic mechanisms and open-label clinical trial of behavior therapy. *Seizure*. 2012 Sep;21(7):496-500. PubMed PMID: 22694920.
26. Kurtoglu S, Hatipoglu N, Mazicioglu M, Kendirici M, Keskin M, Kondolot M. Insulin resistance in obese children and adolescents: HOMA-IR cut-off levels in the prepubertal and pubertal periods. *Journal of clinical research in pediatric endocrinology*. 2010;2(3):100-6. PubMed PMID: 21274322. Pubmed Central PMCID: 3005684.
27. Martin CK, Han H, Anton SD, Greenway FL, Smith SR. Effect of valproic acid on body weight, food intake, physical activity and hormones: results of a randomized controlled trial. *Journal of psychopharmacology*. 2009 Sep;23(7):814-25. PubMed PMID: 18583434. Pubmed Central PMCID: 2753432.
28. Rakitin A, Koks S, Haldre S. Valproate modulates glucose metabolism in patients with epilepsy after first exposure. *Epilepsia*. 2015 Nov;56(11):e172-5. doi:10.1111/epi.13114.
29. Yedulla NR, Naik AR, Kokotovich KM, Yu W, Greenberg ML, Jena BP. Valproate inhibits glucose-stimulated insulin secretion in beta cells. *Histochem Cell Biol*. 2018 Oct;150(4):395-401. doi: 10.1007/s00418-018-1713-6. Epub 2018 Aug 25. PMID:30145684.
30. Huan Zhang , Ping Lu , Hui-Ling Tang, Hua-Juan Yan, Wei Jiang, Hang Shi et al. Valproate-Induced Epigenetic Upregulation of Hypothalamic Fto Expression Potentially Linked with Weight Gain. *Cell Mol Neurobiol*. 2020 Jun 4. doi: 10.1007/s10571-020-00895-2.



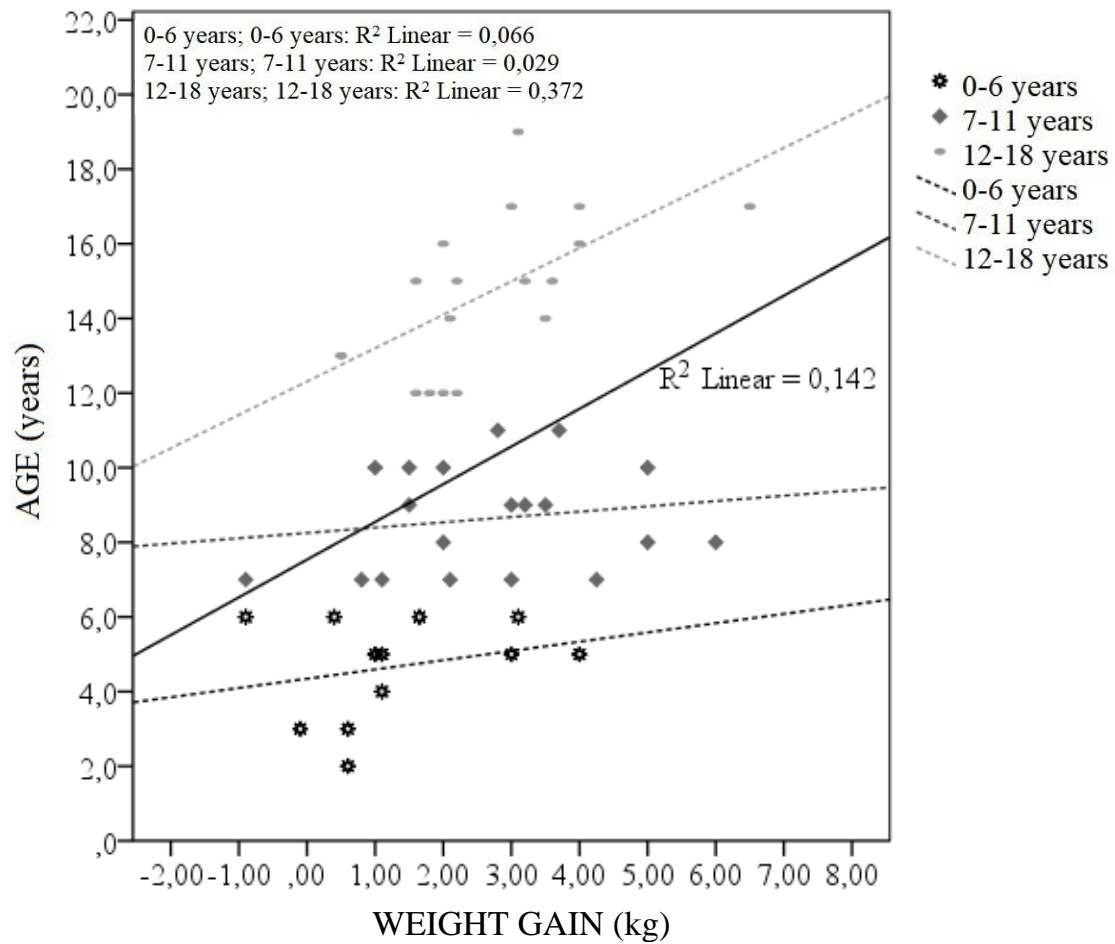
**Figure 1.** Median values of body mass index distribution of patients at the initiation of therapy, after 6 and 12 months of continuous anti-epileptic drug therapy



**Figure 2.** Average serum insulin levels distribution at the initiation of therapy, after 6 and 12 months of continuous anti-epileptic drug therapy



**Figure 3.** Average homeostasis model assessment – insulin resistance (HOMA) values distribution of patients at the initiation of therapy, after 6 and 12 months of continuous anti-epileptic drug therapy



**Figure 4.** Weight change after 12 months of anti-epileptic drug in correlation to age

**Table 1.** Correlation of weight change after 12 months of AED therapy between three group of patients in correlation to their age.

Age group (years)	Age group (years)	Mean Difference	SE	p	95% CI
					Lower boundary
0–6	7–11	-1.36469*	0.56736	0.020	-2.5067
	12–18	-1.33750*	0.57343	0.024	-2.4918
7–11	0–6	1.36469*	0.56736	0.020	0.2227
	12–18	0.02719	0.50610	0.957	-0.9915
12–18	0–6	1.33750*	0.57343	0.024	0.1832
	7–11	-0.02719	0.50610	0.957	-1.0459

SE – standard error;

\*the mean difference is significant at the 0.05 level