Body weight, body composition, and serum ghrelin in epileptic children receiving levetiracetam monotherapy

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Introduction

Epilepsy is a common neurological disorder in the pediatric population, affecting up to one percent of children.1,2 Nowadays there are many pharmacological choices for treatment of pediatric epilepsy. However, despite the frequent use of antiepileptic drugs (AEDs), remarkably little is known about the safety and efficacy of most of these medications in pediatric epilepsy population. Many types of endocrine and metabolic abnormalities are associated with epilepsy and its medications.3,4 AEDs may be associated with either increases or reductions in body weight.5 Epilepsy and AEDs may alter weight homeostasis regulating process including the two important homeostatic hormones; leptin and insulin.6 Ghrelin regulates the secretion of leptin and insulin.7 Ghrelin is a gastric hormone, known to initiate food intake; prolonged treatment with ghrelin causes increased body weight.8 Levetiracetam (LEV) is a second-generation anticonvulsant drug that has been evaluated in the pediatric population, gaining FDA approval in 2004 for adjunctive therapy in children from 4 years of age with partial onset seizures, and most recently, in 2012, as adjunctive therapy for partial onset seizures in infants and children one month of age and older with epilepsy. Some studies demonstrate its effectiveness as a monotherapy in partial epilepsy.9–11 Recently Weijenberg and his colleagues systematically searched the literature using Web of Science, PubMed and Embase up to August 2014 for articles on levetiracetam monotherapy in children, and they found that the evidence for levetiracetam monotherapy in children is minimal however; its efficacy and tolerability seemed to be good and comparable to other AEDs.12

Data regarding the impact of LEV on body weight were adapted mainly from studies done on adult epileptic.13–17

To the best of our knowledge, there are no previous reports that examined the effect of LEV monotherapy on body weight in pediatric epilepsy population. Therefore, the aim of the present study is (1) to prospectively investigate the changes in body weight, BMI, and body composition using bioelectrical impedance analysis (BIA) technique,18 and (2) to evaluate serum ghrelin level and insulin resistance after 6 months of LEV monotherapy in children with idiopathic focal epilepsy to test their contribution in weight changes.

Methods

Participants

This is a prospective comparative case-control study that was conducted from April 2013 to June 2015. Patients’ ages ranged between 6 and 10 years. They were recruited consecutively during their initial presentation at Neurology Outpatient Clinic (OPC), Mansoura University Children Hospital (MUCH), Mansoura, Egypt. The study population was restricted to those with newly diagnosed idiopathic focal epilepsy. Epilepsy was defined according to the guidelines of the International League against Epilepsy.19 Electroencephalogram (EEG) and MRI were done to all patients at presentation to exclude secondary causes of epilepsy. Exclusion criteria included: (1) Children who previously received any AEDs or medications known to affect growth (e.g., steroids). (2) History of an overt medical disorder before the onset of epilepsy that affect the process of growth, physical development, and body composition (e.g., thyroid disorders, hepatic, renal, muscle or bone diseases). (3) Patients with physical or neurological impairments prevented normal physical activity. In addition, 22 healthy controls recruited from the general outpatient clinic at MUCH matched for age, sex, and socioeconomic status were also included in this study. The periodic estimation of dietary habit and physical activity were done at the beginning and at the end of the study. The dietary habits including the characteristics of meals and snacks were checked by a general questionnaire. The physical activity was evaluated by the duration and frequency of specific exercises and daily activities.

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Written informed consent before participation in the study was obtained from parents of included patients and controls. The protocol of the study was approved by the Institutional Research Board (IRB) of Mansoura Faculty of Medicine.

Procedures

All patients and healthy controls underwent the same research protocol, which included medical, neurological, and endocrinological histories and examinations. Pubertal staging was evaluated according to the Tanner method.20,21

Data collection included age, sex, and seizure related variables including: age at onset, duration of illness, frequency of seizures, and degree of patients’ control. Patients with focal seizure were selected consecutively at their first presentation in Neurology OPC. All patients were assigned to LEV monotherapy with start doses of 15 mg/kg/day with increment of 5 mg/kg/day till they achieve complete clinical control of fits (mean dosage of 30 mg/kg/day) and were followed up monthly over 6-months period. The drug dosage was individually adjusted to obtain appropriate balance between seizure control and tolerability. They were subjected to detailed clinical examination and laboratory evaluation before LEV monotherapy (month 0) and the 6th months of therapy. Seizure frequency and adverse effects were documented with a mother-recorded seizure diary when the patient visited the outpatient clinic. Patients were considered controlled if they remained seizure free for the entire study period.

Anthropometric measures

Anthropometric data were collected including: standing height to the nearest 0.1 cm in bare feet using portable Harpenden stadiometer and weight to the nearest 0.1 kg using digital weight scale, the measurements were repeated twice and the average was recorded. Body mass index (BMI) was calculated as weight in kilograms divided by the square of the height in meters.22 Height, weight, and BMI were expressed as Z-scores using published age- and sex-specific reference data of these parameters in healthy Egyptian children.23

Waist circumference (WC; cm) is measured using a tape at midpoint between lateral iliac crest and lowest rib margin at the end of normal expiration where hip circumference (HC; cm) is measured at the level of greater trochanter and symphysis pubis. Waist to Hip ratio (WHR) is used as a marker of central adiposity.

Body composition assessment

Whole-body and segmental body composition were determined using a bioelectrical impedance analysis (BIA) technique, using body composition analyzer “Tanita BC-418 MA” (Tanita Corp., Tokyo, Japan). Measurements were obtained on the morning after an overnight fast, after being requested to void their bladder. The subject stood on the two foot plates with legs apart catching the two hand electrodes for one minute. The BIA data include, body fat mass (kg), body fat free mass (FFM) (kg) both for total body, and segmental analysis (legs, arms and trunk).

Laboratory investigations

Fasting blood samples were taken between 8 and 10 am to avoid bias due to diurnal variations. All whole blood samples (3 ml) were centrifuged to obtain serum and then immediately frozen at −20 °C within 1 h after sampling, and stored until the analysis was carried out. Serum fasting blood glucose (FBG) was measured by end point colorimetric reagents supplied by SPIN-REACT (S.A./S.A.U Ctra. Santa Coloma, 7 E-17176 SANT ESTEVE DE BAS (GI SPAIN). Insulin was measured using enzyme- linked immune sorbent assay (ELISA) kit supplied by Cal Bio Tech (1046 Austin Dr, Spring Valley, CA 91978, USA). Serum ghrelin levels were measured by the enzyme-linked immune sorbent assay (ELISA) kit supplied by Ray Bio tech, Inc. (3607 Parkway Lane, Suite 200 Norcross, GA 30092, USA) and were expressed as ng/ml. Insulin resistance index (IRI) was calculated according to homeostasis model assessment insulin resistance (HOMA-IRI), through Matthews et al.24 formula where IR is considered at values ≥2.5. [HOMA-IR = fasting blood glucose (mg/dl) × fasting insulin (μU/ml)/405.]

Statistical analysis

All data analysis was performed using a statistical package for social science program (SPSS) version 17. Non parametric data were expressed in median and range (minimum–maximum). Parametric data were expressed in Mean ± Standard deviation. Frequency (Number-%) used to represent categorical variables (sex). Inter-group comparison of categorical data was done by using chi square test ($X^2$-value). Student’s t-test (Unpaired) was used to compare between the mean of numerical data (parametric) of two groups, while Student’s t-test (Paired) was used to compare between the mean of numerical (parametric) data of two related groups. Mann–Whitney U test was used to compare between numerical (non-parametric) data of two different groups. While Wilcoxon signed rank test was used to compare between the mean of numerical (non-parametric) data of two related groups. Spearman correlation coefficient test was used for correlating different parameters. A p value <0.05 was considered statistically significant in all analyses.

Results

Initially, the study included 26 pre-pubertal Egyptian children with newly diagnosed idiopathic focal epilepsy of whom 20 patients (76.9%) completed the study protocol. This was not possible for the other six patients because five patients were excluded due to treatment failure, and one patient was lost the follow up. The duration of epilepsy (between appearance of symptoms and initiation of LEV treatment) ranged between 1 and 2 months.

A. Baseline clinical and laboratory characteristics of control and patients groups:

There was no difference between patient and control groups at baseline as regards age and sex. In addition, no significant differences were detected between the two groups as regards anthropometric measurements (Table 1 and Fig. 1). Moreover, no significant differences were observed between the two groups as regards body composition parameters (Table 2). Serum ghrelin level was decreased in the patient group compared to control group, although this decrease was not significant. No significant differences detected in fasting serum levels of blood glucose, insulin, and insulin resistance (assessed by HOMA-IR) (Table 3).

B. Clinical and laboratory characteristics of patient groups before and after 6 months of LEV treatment:

There were significant decreases in body weight (with a mean loss of 3.42 kg and ranged between 2 and 4.20 kg) (Fig. 1), BMI and their Z-scores (p < 0.001), and WC ($p = 0.021$) after 6 months of LEV treatment compared to the pretreatment values. In addition, there were significant increases in WHR ($p < 0.001$) and height ($p = 0.042$) after 6 months of LEV treatment (Table 1).
children with idiopathic focal epilepsy.

In body weight in patients after six months of levetiracetam monotherapy in patient body weight at baseline than controls and a significant decrease (\( p < 0.001 \)) with significant decrease in total free fat mass (FFM) (\( p < 0.001 \)) and segmental fat mass (FM) that was only significant in legs FM (\( p = 0.002 \)) with significant increase in trunk:leg ratio FFM (\( p = 0.005 \)) with significant decrease in trunk:leg ratio FM (\( p < 0.001 \)) were observed after six months of treatment (Table 2).

As regards body composition, we observed a decrease in total and segmental fat mass (FM) that was only significant in legs FM (\( p = 0.041 \)) with significant increase in trunk:leg ratio FM (\( p < 0.001 \)). In addition, significant increase in total free fat mass (FFM) (\( p = 0.002 \)) and segmental FFM [trunk (\( p < 0.001 \)) and legs (\( p = 0.005 \))] with significant decrease in trunk:leg ratio FFM (\( p < 0.001 \)) were observed after six months of treatment (Table 2).

As regards laboratory investigations, non-significant increase in fasting insulin (\( p = 0.191 \)), and non-significant decrease in FBG (\( p = 0.642 \)), fasting insulin (\( p = 0.771 \)), and insulin resistance index (IRI) (\( p = 0.825 \)) were observed in patients after 6 months of therapy and none of them had insulin resistance (Table 3).

C. Correlations between evaluated parameters among studied groups:

Among control group, there were significant positive correlations between both fasting serum ghrelin and IRI and all the following parameters: WC, body FM (total and segmental including trunk, legs, and arms) and body FFM (total and segmental including trunk and legs only). In addition, IRI was negatively correlated with fasting serum ghrelin \( [r = -0.716; p < 0.001] \) (Table 4).

Regarding patient group after 6 months of LEV treatment, no significant correlation was detected between fasting serum ghrelin and IRI with anthropometric measurements and body composition parameters (Table 4).

Discussion

The impact of LEV monotherapy on body weight in prepubertal children has not been defined until now. To the best of our knowledge, this is the first report to estimate the effect of LEV monotherapy on body weight and body composition in pediatric epilepsy population.

At baseline evaluation, no significant differences were detected between patient group (with 1–2 months epilepsy duration) and control group as regards anthropometric measurements and body

### Table 1
Baseline demographic and clinical data of control group and patients groups at baseline and 6 months after Levetiracetam (LEV) treatment.

<table>
<thead>
<tr>
<th></th>
<th>Controls (( n = 22 ))</th>
<th>Patients (At baseline) (( n = 20 ))</th>
<th>Patients (6 months after LEV) (( n = 20 ))</th>
<th>P1</th>
<th>P2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>8.25 ± 1.29</td>
<td>7.43 ± 1.72</td>
<td></td>
<td>0.085</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male (%)</td>
<td>9 (40.9%)</td>
<td>8 (40.0%)</td>
<td></td>
<td>0.951</td>
<td></td>
</tr>
<tr>
<td>Female (%)</td>
<td>13 (59.1%)</td>
<td>12 (60.0%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height (cm)</td>
<td>127.35 ± 11.51</td>
<td>122.70 ± 15.04</td>
<td></td>
<td>0.213</td>
<td>0.042</td>
</tr>
<tr>
<td>Weight-Z</td>
<td>–0.36 (–1.8 to 2)</td>
<td>0.48 (–1.76 to 1.65)</td>
<td></td>
<td>0.242</td>
<td>0.818</td>
</tr>
<tr>
<td>Weight-Z</td>
<td>–0.82 (–1.67 to 1.69)</td>
<td>–0.46 (–1.69 to 1.42)</td>
<td></td>
<td>0.134</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>15.83 ± 3.40</td>
<td>16.41 ± 2.93</td>
<td></td>
<td>0.564</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI-Z</td>
<td>–0.94 (–1.64 to 1.57)</td>
<td>–0.35 (–1.74 to 1.36)</td>
<td></td>
<td>0.352</td>
<td>0.001</td>
</tr>
<tr>
<td>WC (cm)</td>
<td>62.40 ± 5.83</td>
<td>61.9 ± 6.21</td>
<td></td>
<td>0.921</td>
<td>0.021</td>
</tr>
<tr>
<td>Waist:Hip ratio</td>
<td>0.89 ± 0.05</td>
<td>0.8 ± 0.05</td>
<td></td>
<td>0.183</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Data expressed as mean ± SD, as median and range [min–max], or as frequency [number (%)].

P1: test of difference between controls and patients at baseline.

P2: test of difference between patients at baseline and 6 months after LEV treatment.

\*p value <0.05 is significant.

### Table 2
Body composition parameters of control group and patients at baseline and 6 months after LEV treatment.

<table>
<thead>
<tr>
<th></th>
<th>Controls (( n = 22 ))</th>
<th>Patients (Baseline) (( n = 20 ))</th>
<th>Patients (6 months after LEV) (( n = 20 ))</th>
<th>P1</th>
<th>P2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fat Mass</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Body</td>
<td>5.41 ± 3.83</td>
<td>5.08 ± 3.19</td>
<td>4.71 ± 2.57</td>
<td>0.762</td>
<td>0.246</td>
</tr>
<tr>
<td>Trunk</td>
<td>2.17 ± 1.81</td>
<td>2.17 ± 1.62</td>
<td>2.07 ± 1.31</td>
<td>0.984</td>
<td>0.632</td>
</tr>
<tr>
<td>Legs</td>
<td>2.38 ± 1.61</td>
<td>2.26 ± 1.21</td>
<td>2.06 ± 1.02</td>
<td>0.783</td>
<td>0.041</td>
</tr>
<tr>
<td>Arms</td>
<td>0.71 ± 0.45</td>
<td>0.67 ± 0.43</td>
<td>0.63 ± 0.37</td>
<td>0.776</td>
<td>0.185</td>
</tr>
<tr>
<td>Trunk:Legs ratio</td>
<td>0.89 ± 0.33</td>
<td>0.96 ± 0.47</td>
<td>1.07 ± 0.63</td>
<td>0.527</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Free Fat Mass</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Body</td>
<td>21.31 ± 5.67</td>
<td>18.65 ± 6.78</td>
<td>20.19 ± 6.66</td>
<td>0.174</td>
<td>0.002</td>
</tr>
<tr>
<td>Trunk</td>
<td>13.4 ± 3.16</td>
<td>12.12 ± 3.55</td>
<td>12.74 ± 3.61</td>
<td>0.253</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Legs</td>
<td>6.263 ± 2.0</td>
<td>5.49 ± 2.4</td>
<td>5.93 ± 2.45</td>
<td>0.262</td>
<td>0.005</td>
</tr>
<tr>
<td>Arms</td>
<td>1.67 ± 0.58</td>
<td>1.55 ± 0.74</td>
<td>1.54 ± 0.68</td>
<td>0.561</td>
<td>0.922</td>
</tr>
<tr>
<td>Trunk:Legs ratio</td>
<td>2.2 ± 0.3</td>
<td>2.46 ± 0.98</td>
<td>2.31 ± 0.65</td>
<td>0.262</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data expressed as Mean ±SD.

P1: test of difference between controls and patients at baseline.

P2: test of difference between patients at baseline and 6 months after LEV treatment.

\*p value <0.05 is significant.
Correlation between HOMA-IR and fasting serum ghrelin and different evaluated parameters.

<table>
<thead>
<tr>
<th></th>
<th>Controls (n = 22)</th>
<th>Patients (At baseline) (n = 20)</th>
<th>Patients (6 months After LEV) (n = 20)</th>
<th>P1</th>
<th>P2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting blood glucose (mg/dl)</td>
<td>104.25 ± 3.95</td>
<td>104.21 ± 6.87</td>
<td>103.28 ± 7.52</td>
<td>0.981</td>
<td>0.642</td>
</tr>
<tr>
<td>Fasting insulin (mIU/ml)</td>
<td>5.85 (3.50–9.20)</td>
<td>5.70 (0.90–9.60)</td>
<td>5.25 (2.90–9.00)</td>
<td>0.623</td>
<td>0.771</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>1.48 (0.83–2.31)</td>
<td>1.42 (0.23–2.44)</td>
<td>1.38 (0.61–2.36)</td>
<td>0.674</td>
<td>0.825</td>
</tr>
<tr>
<td>Ghrelin (ng/ml)</td>
<td>2.30 (1.0–4.0)</td>
<td>1.90 (0.70–4.50)</td>
<td>2.95 (0.10–4.80)</td>
<td>0.695</td>
<td>0.191</td>
</tr>
</tbody>
</table>

Data expressed as Mean (±SD) and median (min–max).

FBG, Fasting blood glucose; IR, Insulin resistance.
P1: test of difference between controls and patients at baseline.
P2: test of difference between patients at baseline and 6 months after LEV treatment.

### Table 4

Correlation between HOMA-IR and fasting serum ghrelin and different evaluated parameters.

<table>
<thead>
<tr>
<th></th>
<th>HOMA-IR</th>
<th>Fasting serum ghrelin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Patients at baseline</td>
</tr>
<tr>
<td>Weight</td>
<td>r 0.339</td>
<td>0.044</td>
</tr>
<tr>
<td></td>
<td>P 0.123</td>
<td>0.855</td>
</tr>
<tr>
<td>BMI</td>
<td>r 0.237</td>
<td>0.200</td>
</tr>
<tr>
<td></td>
<td>P 0.288</td>
<td>0.397</td>
</tr>
<tr>
<td>WC</td>
<td>r 0.525</td>
<td>0.204</td>
</tr>
<tr>
<td></td>
<td>P 0.012</td>
<td>0.388</td>
</tr>
<tr>
<td>Waist:Hip ratio</td>
<td>r -0.031</td>
<td>-0.188</td>
</tr>
<tr>
<td></td>
<td>P 0.892</td>
<td>0.427</td>
</tr>
<tr>
<td>Body FM</td>
<td>r 0.565</td>
<td>0.022</td>
</tr>
<tr>
<td></td>
<td>P 0.006</td>
<td>0.927</td>
</tr>
<tr>
<td>Trunk:Legs FM</td>
<td>r 0.036</td>
<td>-0.200</td>
</tr>
<tr>
<td></td>
<td>P 0.875</td>
<td>0.399</td>
</tr>
<tr>
<td>Fasting insulin</td>
<td>r 0.975</td>
<td>0.986</td>
</tr>
<tr>
<td></td>
<td>P &lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fasting ghrelin</td>
<td>r -0.716</td>
<td>-0.034</td>
</tr>
<tr>
<td></td>
<td>P &lt;0.001</td>
<td>0.886</td>
</tr>
</tbody>
</table>

r, Spearman correlation coefficient; P, probability.

WC, waist circumference; BMI, body mass index; FM, fat mass; IR, insulin resistance.

*p value <0.05 is significant.

composition parameters that exclude any possible effect of epilepsy per se on previously evaluated parameters. In contrast to our results, Daniels et al. found that obesity is a common comorbidity in a cohort of children and adolescents (2–18 years) with newly diagnosed untreated epilepsy who were evaluated within 10 days of referral. These contrary results are likely due to the smaller sample size and younger age of patients in the present study.

On the other hand, anthropometric parameters of the patient group after six months of LEV treatment showed a significant decrease in body weight, BMI, and their Z-scores compared to pretreatment values. However, the observed significant weight loss does not affect the patients' growth as significant increase in height and developmental stages, inclusion of patients with long history of LEV treatment with an average dose of 30 mg/kg/day did not adversely affect linear bone growth.

The significant weight loss that observed after 6 months of LEV treatment can be partially explained by appetite loss that reported after initiation of treatment in some patients (12 out of 20 epileptic children). Similarly, anorexia has been listed as a common side effect of LEV treatment and was reported in 1–18% of patients. Reviewing the literature showed that data regarding the impact of LEV on body weight were conducted mainly on adult population and their results have been conflicting. Similar to our results, Cramer and her colleagues found that weight loss was a treatment adverse event in a group of 97 elderly patients treated with LEV. In addition, intense weight loss (with a mean of 26.75 kg) has been reported in four patients under LEV co-therapy in a dose ranging between 2000 and 3000 mg/day. As well, Gelisse et al. found that LEV accompanied with marked weight loss at lower doses of 500–2000 mg/day. Contrary to our findings, LEV is considered a “weight-neutral” AED as documented by Gidal and his colleagues, and Briggs and French, as well. Alternatively, Pickrell and his colleagues noticed a significant weight gain associated with LEV and valproic.

These controversial results reported by previous studies may be related to different factors including: inclusion of different age groups (from adolescents to elderly patients) with different growth and developmental stages, inclusion of patients with long history of AEDs intake with different drug dosage and duration of treatment, and a possibility of other comorbidities that affect body weight.

It is well known that during mid-childhood, around the age of 8 years, a preadolescent “fat wave” or “adiposity rebound” occurs. After which, the total body fat continues to increase throughout puberty at an estimate rate about 1.4 kg/year in girls and 0.6 kg/year in boys. Adolescent girls add more fat on their arms, legs, and trunk, while the arm and leg fat of adolescent boys decreases. In contrast, LEV-associated weight loss was observed in our patients after 6 months of LEV therapy compared to pre-treatment level and was related mainly to reduction in body fat stores as evidenced by a decrease in total and segmental fat mass. This decrease in fat mass was only significant in legs with a significant increase in trunk:leg fat mass ratio. The observed changes in fat distribution cannot be explained by the effect of sex steroid as all patients included in the present study were pre-pubertal. Fortunately, neither the increase in trunk:leg fat mass nor the decrease in fat mass in the trunk area was significant.
mass ratio nor the increase in WHR showed significant correlation with insulin resistance, which has significant impact on body fat distribution. Contrary to body fat mass, the FFM (total body, trunk, and legs) increased significantly after six months of LEV therapy. This finding in part clarify that the growth of patients (as regards muscles) were not affected by LEV treatment.

In addition, lean mass is influenced by physical exercise or sports activity whereas constant physical activity increases the proportion of lean body mass and reduces the fat compartment, even without changes in body weight. Children with epilepsy tend to be less physically active before initiation of AEDs or control of seizures due to the fear of injuries and the fear that seizures may be provoked by exercise or blows to the head. However, once the patients’ seizures are well controlled, they were allowed to participate in group and total sports activities with some limitations.

To evaluate possible mechanisms of weight changes associated with LEV monotherapy, we studied serum ghrelin, fasting insulin, and fasting blood glucose levels at baseline and after six months after of LEV treatment. Ghrelin is a peptide-like hormone that is produced in the gastrointestinal system and contributes to positive energy balance. We observed that, ghrelin level tends to decrease in the patient group compared with a matched control at baseline. This finding was partially in accordance with Aydin and his colleagues who reported that, serum and saliva ghrelin levels were significantly (2-fold) lower in epileptic patients before treatment than in controls. These results can be explained by the association between ghrelin and etiopathogenesis of epilepsy, that has been confirmed in human and animal studies, despite the controversial results. In addition, the decreased ghrelin level before starting treatment might be related to the increased uptake of ghrelin in brain under effect of pathophysiological events to modify epileptic discharges. Bhatt and his colleagues, and also Hum and his colleagues explained that decreased ghrelin level in untreated rats was due to the detected high serum leptin levels and which might impede ghrelin secretion directly.

On the other hand, the levels of ghrelin increased non-significantly after six months of LEV treatment that might be due to feedback mechanism induced by the observed weight loss and reported anorexia or by direct effect of LEV on ghrelin secretion. This result is in accordance with Berilgen and his colleagues, and Aydin and his colleagues who found that, serum and saliva ghrelin levels were increased in epileptic patients under treatment with AEDS.

The previous studies were conducted on patients who were already on AEDs, so it is difficult to delineate whether increased ghrelin was due to the seizure or due to the effect of AEDs. However, in the present study ghrelin level was decreased prior to start of treatment and increased after six months of LEV monotherapy which highlights the possible modulation of ghrelin secretion by LEV treatment. In addition, all enrolled children were prepubertal and achieved complete control of the seizure on LEV monotherapy in order to exclude possible modulation of ghrelin secretion by pubertal stage, age, and seizure activity.

Finally, a non-significant decrease of FBG, and fasting insulin levels was found in the patient group after six months of LEV treatment which was in accordance to Heppner and Tong who found that increased ghrelin levels impede the insulin secretion stimulated by glucose. None of included epileptic children in the present study exhibited IR assessed by HOMA method.

Conclusion

LEV monotherapy in prepubertal children associated with a significant weight loss that is related mainly to decrease in body fat particularly from legs. However, statural growth was not affected as evident by a significant increase in patients’ height, total and segmental FFM after 6 months of LEV treatment compared with pretreatment level. Serum level of ghrelin tends to increase after 6 months treatment compared to pretreatment levels. This increased ghrelin level might be due to feedback mechanism induced by weight loss and anorexia or by direct effect of LEV on ghrelin secretion.

Study limitations

The present study was limited by the relatively small size of the cohort and also the lack of detailed dietary intake and physical activity assessment.

Recommendations

A future long-term large scale study is needed for more delineation of the effect of LEV monotherapy on body weight and its exact mechanism of weight affection with emphasis on the role of ghrelin as a contributing factor.

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Conflict of interest

None of the authors has any conflict of interest to disclose.

Authors’ contributions

SE, BH, NS, and DE participated in study concept and design, recruited and carried out clinical diagnosis of the study population. BH, NS, and DE carried out analysis and interpretation of data. BH and NS drafted and revised the manuscript. RE carried out the laboratory investigations. All authors revised and approved the final manuscript.

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