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# Lipid and thyroid hormone levels in children with epilepsy treated with levetiracetam or carbamazepine: a prospective observational study

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**Abstract**

Although previous studies have investigated the influence of antiepileptic drugs (AEDs) on lipid profiles and thyroid hormone levels, there is little evidence regarding the effects of levetiracetam (LEV). Therefore, we conducted a prospective longitudinal study to evaluate the effects of LEV and carbamazepine (CBZ) treatment on lipid profile and thyroid hormone levels in patients newly diagnosed with epilepsy. Inclusion criteria were as follows: (a) age between 4 and 15 years, (b) diagnosis of epilepsy with at least two focal seizures within a year, (c) newly treated with LEV or CBZ monotherapy. Serum lipid profile and thyroid hormone levels were measured before and after 1 and 6 months of AED initiation. Among the 21 included patients (LEV: 13 patients, CBZ: 8 patients), all but one patient in the LEV group continued AED monotherapy during the study period. Although triglyceride levels tended to be increased in the CBZ group (baseline: 58.3 ± 22.0 mg/dl, 1 month: 63.8 ± 21.6 mg/dl, 6 months: 92.3 ± 63.6 mg/dl, $p = 0.22$, ANOVA), there were no significant changes in total cholesterol, triglyceride levels, high-density lipoprotein cholesterol, or low-density lipoprotein cholesterol in either group. Serum free thyroxine levels were significantly decreased in the CBZ group (baseline: 1.15 ± 0.06 ng/dl, 1 month: 1.00 ± 0.16 ng/dl, 6 months: 0.98 ± 0.14 ng/dl, $p = 0.03$, ANOVA). In contrast, there were no significant changes in free thyroxine or thyroid-stimulating hormone levels in the LEV group. The results of the present study suggest that LEV monotherapy does not affect lipid profile or thyroid function, while CBZ monotherapy may cause thyroid dysfunction.

**Keywords:** antiepileptic drugs; levetiracetam; carbamazepine; children; thyroid hormone; lipid

## 1. Introduction[1]

Carbamazepine (CBZ) and levetiracetam (LEV) are among the first-line agents used in the treatment of partial seizures [1]. While previous studies have demonstrated that CBZ and LEV are equally effective for the treatment of newly diagnosed epilepsy in both adults and children [2,3], long-term adverse effects also play a role in the choice of antiepileptic drug (AED) [4]. CBZ is associated with potent induction of the cytochrome P450 (CYP450) enzyme system as well as increases in serum lipid levels, particularly total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) [5]. Most previous studies were cross-sectional in nature [5-10]; however, a few prospective longitudinal studies have also reported that CBZ monotherapy increases serum TC, LDL-C, triglyceride (TG), and lipoprotein (a) levels in children [11-13]. CBZ has also been associated with adverse effects on thyroid function [14]. Previous studies have reported that CBZ monotherapy is associated with a significant decrease in triiodothyronine (T3), thyroxine (T4), and free thyroxine (fT4) levels [14]. In contrast, dyslipidemia and altered levels of thyroid hormone have rarely been reported in patients taking LEV, and research regarding this matter remains inconclusive [15-20]. Although two cross-sectional studies and one longitudinal study analyzed the association between serum lipid levels and LEV, they have produced conflicting results [15-17]. Furthermore, no prospective studies have examined the association between thyroid hormone levels

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[1] Abbreviations: CBZ: carbamazepine; LEV: levetiracetam; CYP450: cytochrome P450; TC: total cholesterol; LDL-C: low-density lipoprotein cholesterol; TG: triglyceride; T3: triiodothyronine; T4: thyroxine; fT4: free thyroxine; AED: antiepileptic drug; HDL-C: high-density lipoprotein cholesterol; TSH: thyroid stimulating hormone; AST: aspartate aminotransferase; ALT: alanine aminotransferase; GGT: gamma-glutamyltransferase; CRP: C-reactive protein; LC/MS/MS: liquid chromatography tandem mass spectrometry.

and LEV use [17-20].

The primary aim of the present prospective study was to evaluate changes in lipid levels in children undergoing CBZ or LEV monotherapy. We further aimed to examine changes in thyroid hormone levels in these patients, and to determine the potential associations involving lipid and thyroid hormone levels.

## 2. Materials and Methods

### 2.1. Study design and patients

This prospective, multicenter, observational study was conducted with the approval of the Ethics Committee of Kobe University Graduate School of Medicine (No.1788). Written informed consent was obtained from the parents/guardians of each patient. Patients were recruited from Kobe University Hospital, Japanese Red Cross Society Himeji Hospital, Kobe City Hospital Organization Kobe City Medical Center West Hospital, Hyogo Prefectural Kobe Children's Hospital, Hyogo Prefectural Kaibara Hospital, and Saiseikai Hyogoken Hospital between September 2015 and December 2017. Inclusion criteria were as follows: (a) age between 4 and 15 years, (b) diagnosis of epilepsy with at least two focal seizures within a year [21], (c) newly treated with LEV or CBZ monotherapy. Patients with (a) previous neurological history such as intellectual disability or chromosomal abnormality, (b) those diagnosed with structural/metabolic epilepsy [21], (c) those with other medical conditions requiring continuous medication, and those (d) with unbalanced diets or taking supplements were excluded. Following enrollment, patients were excluded from the main analysis if they had discontinued initial AED monotherapy, or they had taken any medication known to affect liver or thyroid function prior to the final evaluation period.

For each enrolled patient, blood tests were performed between 8 AM and 10 AM after at least 10 h of fasting on three separate occasions. Values were obtained prior to AED treatment (baseline), after 1 month of AED initiation (defined as 4 to 12 weeks after AED initiation), and after 6 months of AED initiation (defined as 26 to 39 weeks after AED initiation). Type and dosage of AED were selected by the physician based on the type of epilepsy and the physician's experience, although the study recommended that doses of AED align with the ethical guidelines outlined in the package inserts for each medication. AEDs were discontinued, added, or altered based on the clinical judgment of the physician.

**2.2. Outcomes and assessments**

The change in serum lipid values (TG and TC) from pretreatment to 1 and 6 months was regarded as the primary outcome. Secondary outcomes included changes in other serum lipid values (high-density lipoprotein cholesterol [HDL-C], LDL-C), thyroid-stimulating hormone (TSH), and fT4 between baseline and 1 and 6 months. We also evaluated differences in patient demographics, the seizure free rate between 1 month and 6 months, AED dosages and peak concentrations, adverse events, and other serum values (aspartate aminotransferase [AST], alanine aminotransferase [ALT], gamma-glutamyltransferase [GGT], uric acid, C-reactive protein [CRP], and glucose). Each variable was also compared between the LEV and CBZ groups. We also examined the correlation among changes in serum variables from pretreatment to 6 months and serum AED concentrations after 6 months. TG, TC, and AED concentrations after 6 months were selected for correlation analysis, along with variables exhibiting significant changes between baseline and 6 months.

All serum tests were performed in our hospital or by a commercial company (LSI Medience Co., Japan) in accordance with the manufacturer's instructions. TG and TC were measured with commercial enzymatic methods using a JCA-BM8040G system (JEOL Co., Ltd., Japan). LDL-C and HDL-C were directly measured using a JCS-BM8040G system (JEOL Co., Ltd., Japan). Serum TSH and fT4 were measured via chemiluminescent immunoassay using an ARCHITECT i2000SR system (Abbott Core Laboratory, U.S.A.). Serum CBZ concentration was assayed via enzyme immunoassay, while serum LEV concentration was assayed via liquid chromatography tandem mass spectrometry (LC/MS/MS).

### 2.3. Statistics

All analyses were performed using JMP (version 11.0) statistical software (SAS, Inc., Japan). Data are presented as the mean ± SD. Student's t-test was applied when comparing values between two patient groups. Repeated-measures analyses of variance (ANOVA) were used to compare values among different study points (baseline, 1 month, 6 months). Associations among all parameters were examined using Spearman correlation coefficients. *P* values less than 0.05 were considered significant.

## 3. Results

### 3.1. Patient demographics and treatment

Among the 21 patients (LEV: 13 patients, CBZ: 8 patients) initially included in the study, all but one continued taking AED monotherapy during the study period. One patient discontinued taking LEV within 1 month from the start of treatment due to aggression, and he was thus excluded from main analysis. The remaining 20 patients completed the study (LEV: 12 patients; CBZ: 8 patients). We observed no significant differences in age, sex, height, weight, Rohrer index, or epilepsy syndrome between the LEV and CBZ groups (Table 1).

The mean initial dosage of LEV was 9.1 ± 2.1 mg/kg. Dosages of LEV after 1 month and 6 months were 13.2 ± 4.9 mg/kg and 16.9 ± 10.6 mg/kg, respectively (Table 2). The mean initial dosage of CBZ was 4.4 ± 1.7 mg/kg. Dosages of CBZ after 1 month and 6 months were 6.5 ± 2.3 mg/kg and 8.5 ± 4.2 mg/kg, respectively. Nine patients (75%) in the LEV group and three patients in the CBZ group (38%) remained seizure free between 1 month and 6 months. With the exception of the one patient who discontinued taking LEV, no patient experienced severe adverse events. Although one patient in the LEV group experienced mild and temporary aggression, he continued taking the drug. Two patients of the LEV group and one patient of the CBZ group experienced mild somnolence. Dizziness and abnormal pitch perception were detected after 1 month in one patient in the CBZ group; however, both symptoms resolved after 6 months.

**3.2. Serum variables**

Serum lipid levels, thyroid hormone levels, and other values are shown in Table 2. With the exception of glucose, we observed no significant differences in serum variables between the LEV and CBZ groups at baseline. All but one patient (TG: 328 mg/dl in the LEV group) had serum TG, TC, HDL, LDL values within normal limits prior to treatment. No significant changes in serum TG, TC, HDL-C, or LDL-C were noted in either group, although serum TG levels tended to be increased in the CBZ group after 6 months (baseline: 58.3 ± 22.0 mg/dl, 1 month: 63.8 ± 21.6 mg/dl, 6 months: 92.3 ± 63.6

mg/dl, $p = 0.22$, ANOVA).

All patients had normal thyroid function prior to treatment. Neither serum TSH nor fT4 changed in the LEV group. However, serum fT4 levels were decreased in the CBZ group (baseline: 1.15 ± 0.06 ng/dl, 1 month: 1.00 ± 0.16 ng/dl, 6 months: 0.98 ± 0.14 ng/dl, $p = 0.03$, ANOVA). Moreover, after 1 month and 6 months, fT4 levels were significantly lower in the CBZ group than in the LEV group (after 1 month: 1.00 ± 0.16 ng/dl vs. 1.17 ± 0.14 ng/dl, $p = 0.02$; after 6 months: 0.98 ± 0.14 ng/dl vs. 1.18 ± 0.14 ng/dl, $p = 0.008$). However, all patients exhibited normal serum fT4 values (0.70–1.48 ng/dl) and remained clinically euthyroid during the study period. Among other serum variables, GGT was increased in the CBZ group (baseline: 12.3 ± 3.6 U/l, 1 month: 24.0 ± 10.4 U/l, 6 months: 34.2 ± 23.0 U/l, $p = 0.02$, ANOVA) and remained significantly higher in the CBZ group than in the LEV group (after 1 month: 24.0 ± 10.4 U/l vs. 12.5 ± 2.5 U/l, $p = 0.001$; after 6 months: 34.2 ± 23.0 U/l vs. 12.9 ± 3.6 U/l, $p = 0.005$). Changes in TG, fT4, and GGT after 1 month and 6 months relative to baseline are shown in Figure 1.

We then examined correlations among the following parameters in both groups: changes in serum variables from pretreatment to 6 months (TG, TC, fT4, GGT) and AED concentrations after 6 months. No significant correlations between changes in serum variables and AED concentrations were observed in either group (data not shown). However, in the CBZ group, significant negative correlations were observed between changes in TG levels and changes in fT4 levels (r = 0.898, $p = 0.002$; Figure 2).

## 4. Discussion

To the best of our knowledge, the present study is the first prospective longitudinal study to evaluate serum lipid and thyroid hormone levels in children treated with LEV. Indeed, we observed no alterations in lipid or thyroid hormone levels in children treated with LEV; however, in the CBZ group, serum fT4 values were decreased at 1 and 6 months after treatment, while serum lipid levels remained unchanged.

To our knowledge, two cross-sectional studies and one longitudinal study have investigated the association between dyslipidemia and LEV monotherapy [15-17]. Two studies involving adults suggested that there is no association between serum lipid levels and LEV [15,16]. In contrast, one cross-sectional study involving children reported that LDL and HDL levels are higher in patients treated with LEV than in healthy children [17]. Considering the pharmacokinetic features of LEV, which does not induce liver enzyme increases and does not require dose adjustment in patients with mild to moderate liver dysfunction [22], our findings support the notion that LEV does not affect serum lipid levels.

In contrast to the findings of previous studies [5-8,11-13], our results indicated that CBZ did not increase serum TC and LDL-C levels. Because previous systemic reviews and prospective studies have reported that CBZ use is associated with dyslipidemia [5,11-13,23,24], these findings may have been due to the low number of patients in the present study. Indeed, although the result was not significant, TG levels tended to increase in patients treated with CBZ. Significant increases (>50 mg/dl) in TG levels were observed in two patients taking CBZ, suggesting that noticeable increases may occur in select patients [5].

In the present study, neither fT4 nor TSH levels were changed after 1 and 6 months of LEV treatment, consistent with the findings of two previous retrospective longitudinal studies [18,20]. However, two previous cross-sectional studies have reported an association between LEV and low fT4 levels [17,19]. El-Farahaty et al. reported that fT4 levels were lower in children treated with LEV than in healthy children or those treated with CBZ [17]. Shih et al. reported that, among 298 adults with epilepsy, LEV was associated with low fT4 (odds ratio: 2.432 [95% confidence interval: 1.325–4.464]) [19]. Given these conflicting results and the low number of patients in the present study, further investigation is required to determine the association between fT4 and LEV use.

We also observed that serum fT4 was significantly decreased at 1 and 6 months in patients treated with CBZ. Our findings are consistent with those of a previous meta-analysis, which reported that CBZ use was associated with low serum fT4 without alterations in TSH levels in children [14]. Previous researchers have proposed several mechanisms to explain the association between CBZ and abnormal thyroid function [25-27]. Some authors have suggested that low fT4 levels are caused by a CBZ-induced increase in hepatic clearance of thyroid hormones [27]. However, this explanation is insufficient, as valproate—which does not induce such increases—has also been associated with low fT4 [14]. Others have speculated that CBZ increases competitive binding of thyroid hormones to thyroxine-binding globulin [26,27], along with interference with the hypothalamic-pituitary axis [25,27]. Because we observed no association between changes in fT4 and GGT levels in our study, altered levels of thyroid hormones cannot be explained by the enzyme-inducing effect of CBZ alone.

In addition, we observed no correlation between AED concentration and changes in TG, TC, fT4, or GGT levels, consistent with the findings of several previous studies [27-29]. However, one study did report a negative correlation between thyroid hormone levels and CBZ concentration [30]. In our study, changes in TG levels exhibited a strong negative correlation with changes in fT4 in children treated with CBZ. Indeed, few studies have investigated the correlation between serum lipid and thyroid hormone levels in children treated with AEDs [31]. Garoufi et al. reported a significant positive correlation between TC and TSH levels in patients treated with oxcarbazepine monotherapy [31]. We hypothesized that TG levels may increase due to decreases in fT4, as proposed in previous reports [31]. In addition, similar to findings observed in previous studies, our patients remained clinically euthyroid despite these changes [27,29,31].

The present study possesses several limitations of note, including its small sample size. For ethical reasons, we were unable to include a control group of children with epilepsy who had not been treated with AED. In addition, while baseline clinical data did not significantly differ between the LEV and CBZ groups, we did not evaluate Tanner developmental stage or endocrinological function including levels of sex hormones. Finally, the dosage and concentration of AED were relatively low in the LEV group. However, because the seizure free rate in the LEV group was similar to that reported in previous studies [2,3], the treatment strategy selected by the physician was considered clinically appropriate.

In conclusion, the results of the present non-randomized study suggest that LEV monotherapy does not affect lipid profile or thyroid function, while CBZ monotherapy may cause thyroid laboratory dysfunction. Based on these preliminary findings, LEV monotherapy may have advantages over CBZ monotherapy in children with non-structural/metabolic epilepsy. However, large, prospective studies are required to verify this hypothesis.

## Conflicts of interest

The authors declare no conflicts of interest.


## Acknowledgments

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**Figure legends**

**Figure 1**. Changes in serum variables (A; change in fT4, B; change in TG, C; change in GGT) in each patient after 1 month and 6 months relative to baseline. The diagonal lined-bar represents the change after 1 month, while the filled-bar represents the change after 6 months. Patients treated with LEV are displayed on the left, while patients treated with CBZ are displayed on the right.

fT4: free thyroxine; TG: triglyceride; GGT: gamma-glutamyltransferase; LEV: levetiracetam; CBZ: carbamazepine.

**Figure 2**. Scatterplot representing the negative correlation between changes in fT4 and changes in TG after 6 months of CBZ monotherapy in eight patients with epilepsy ($r = 0.898$, $p = 0.002$).

fT4: free thyroxine; TG: triglyceride; CBZ: carbamazepine.

## Tables

**Table 1. Demographic characteristics and baseline clinical data**

| | **LEV**<br>n=12 | **CBZ**<br>n=8 | ***P*** |
|---|---|---|---|
| Age (years) | 9.2 ± 2.8 | 8.8 ± 3.7 | 0.74 |
| Sex (female:male) | 6:6 | 5:3 | 0.67 |
| Height (cm) | 132.6 ± 18.8 | 128.3 ± 23.0 | 0.66 |
| Weight (kg) | 34.9 ± 16.3 | 29.3 ± 14.8 | 0.45 |
| Rohrer index | 141.8 ± 26.1 | 132.7 ± 23.4 | 0.44 |
| Epilepsy syndrome | | | 0.10 |
| BECT, n (%) | 2 (17) | 3 (38) | |
| Occipital epilepsy, n (%) | 0 (0) | 2 (25) | |
| Frontal lobe epilepsy, n (%) | 3 (25) | 0 (0) | |
| Other focal epilepsy, n (%) | 7 (58) | 3 (38) | |

BECT: benign epilepsy of childhood with centrotemporal spikes

**Table 2. Serum lipid profile, thyroid hormone levels, and other values in patients taking LEV or CBZ**

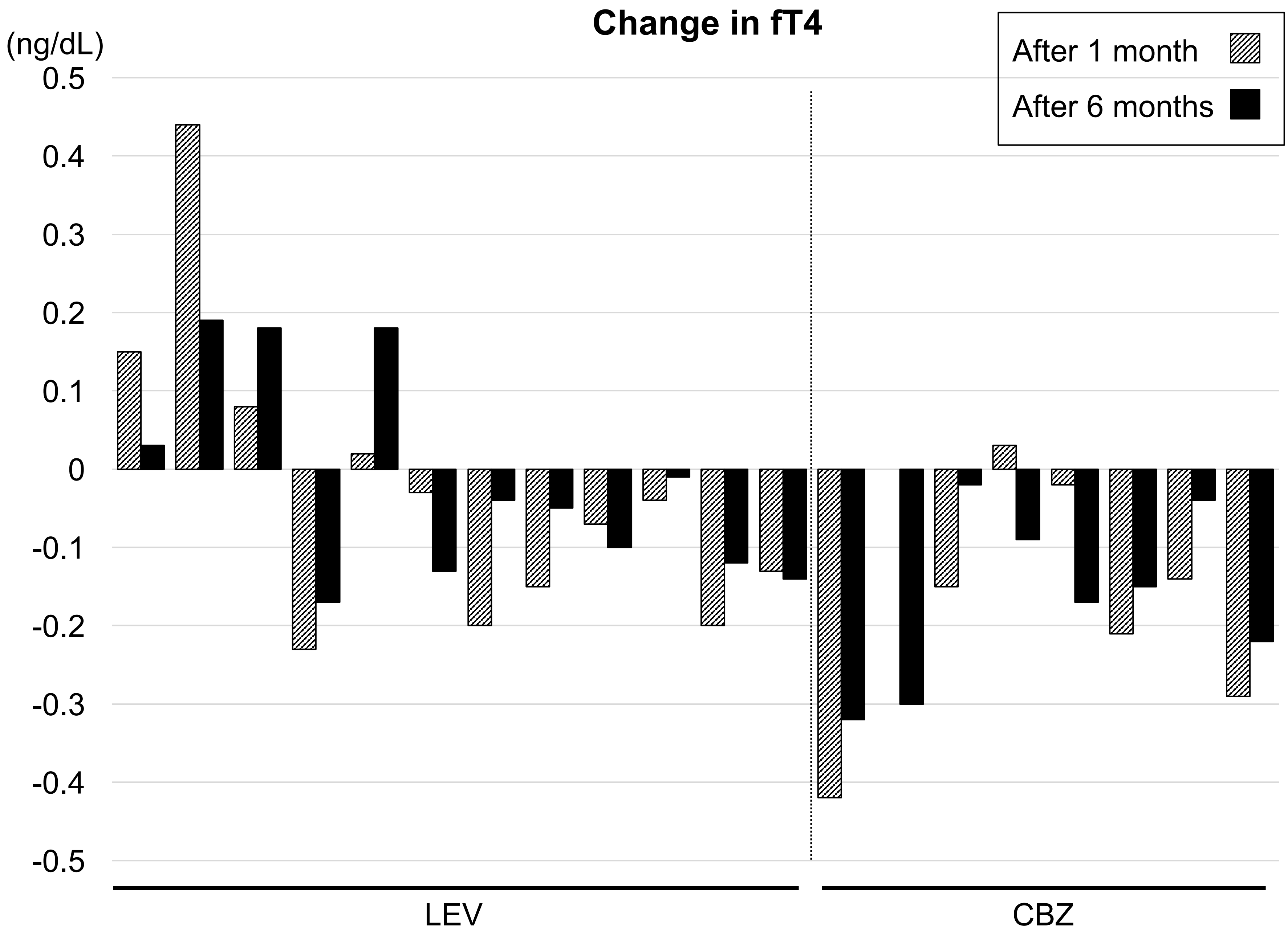
| | LEV-treated patients | | | CBZ-treated patients | | |
|---|---|---|---|---|---|---|
| | *Baseline* | *After 1 month* | *After 6 months* | *Baseline* | *After 1 month* | *After 6 months* |
| Duration after treatment (weeks) | | 6.0 ± 1.5 | 31.1 ± 4.2 | | 7.0 ± 2.5 | 32.3 ± 3.2 |
| Dosage of AED (mg/kg) | | 13.2 ± 4.9 | 16.9 ± 10.6 | | 6.5 ± 2.3 | 8.7 ± 4.2 |
| AED concentration (μg/ml) | | 9.2 ± 8.7 | 14.1 ± 15.2 | | 5.1 ± 2.2 | 7.1 ± 4.1 |
| Serum variables | | | | | | |
| TG (mg/dl) | 79.0 ± 81.8 | 51.3 ± 27.9 | 63.6 ± 51.2 | 58.3 ± 22.0 | 63.8 ± 21.6 | 92.3 ± 63.6 |
| TC (mg/dl) | 174.7 ± 17.8 | 176.1 ± 23.7 | 173.1 ± 20.5 | 163.8 ± 24.2 | 166.1 ± 19.8 | 159.1 ± 33.1 |
| HDL-C (mg/dl) | 64.0 ± 17.2 | 63.8 ± 13.6 | 64.3 ± 16.5 | 60.8 ± 19.2 | 59.0 ± 12.2 | 62.3 ± 19.6 |
| LDL-C (mg/dl) | 98.0 ± 14.2 | 101.6 ± 22.5 | 96.7 ± 18.1 | 90.3 ± 19.2 | 93.3 ± 17.3 | 83.1 ± 18.7 |
| TSH (μU/ml) | 1.60 ± 0.62 | 1.56 ± 0.51 | 1.35 ± 0.61 | 1.31 ± 0.82 | 2.13 ± 1.92 | 1.77 ± 1.12 |
| FT4 (ng/dl) | 1.20 ± 0.21 | 1.17 ± 0.14[a] | 1.18 ± 0.14[a] | 1.15 ± 0.06[*] | 1.00 ± 0.16[*a] | 0.98 ± 0.14[*a] |
| AST (U/l) | 23.7 ± 3.8 | 24.8 ± 6.2 | 23.7 ± 6.2 | 24.0 ± 4.1 | 22.6 ± 3.5 | 25.1 ± 4.7 |
| ALT (U/l) | 14.8 ± 7.1 | 19.2 ± 23.6 | 14.5 ± 10.5 | 14.1 ± 9.0 | 14.5 ± 8.0 | 17.3 ± 11.4 |
| GGT (U/l) | 12.7 ± 2.5 | 12.5 ± 2.5[a] | 12.9 ± 3.6[a] | 12.3 ± 3.6[*] | 24.0 ± 10.4[*a] | 34.2 ± 23.0[*a] |
| Uric acid (mg/dl) | 4.3 ± 0.9 | 4.3 ± 1.0 | 4.4 ± 0.7 | 4.6 ± 1.2 | 4.0 ± 1.1 | 4.0 ± 0.9 |
| CRP (mg/dl) | 0.13 ± 0.36 | 0.15 ± 0.23 | 0.06 ± 0.09 | 0.05 ± 0.08 | 0.02 ± 0.03 | 0.55 ± 0.81 |
| Glucose (mg/dl) | 95.6 ± 5.1[a] | 92.5 ± 3.0 | 93.7 ± 7.3 | 90.6 ± 2.8[a] | 89.0 ± 7.1 | 84.8 ± 14.4 |

mean ± SD

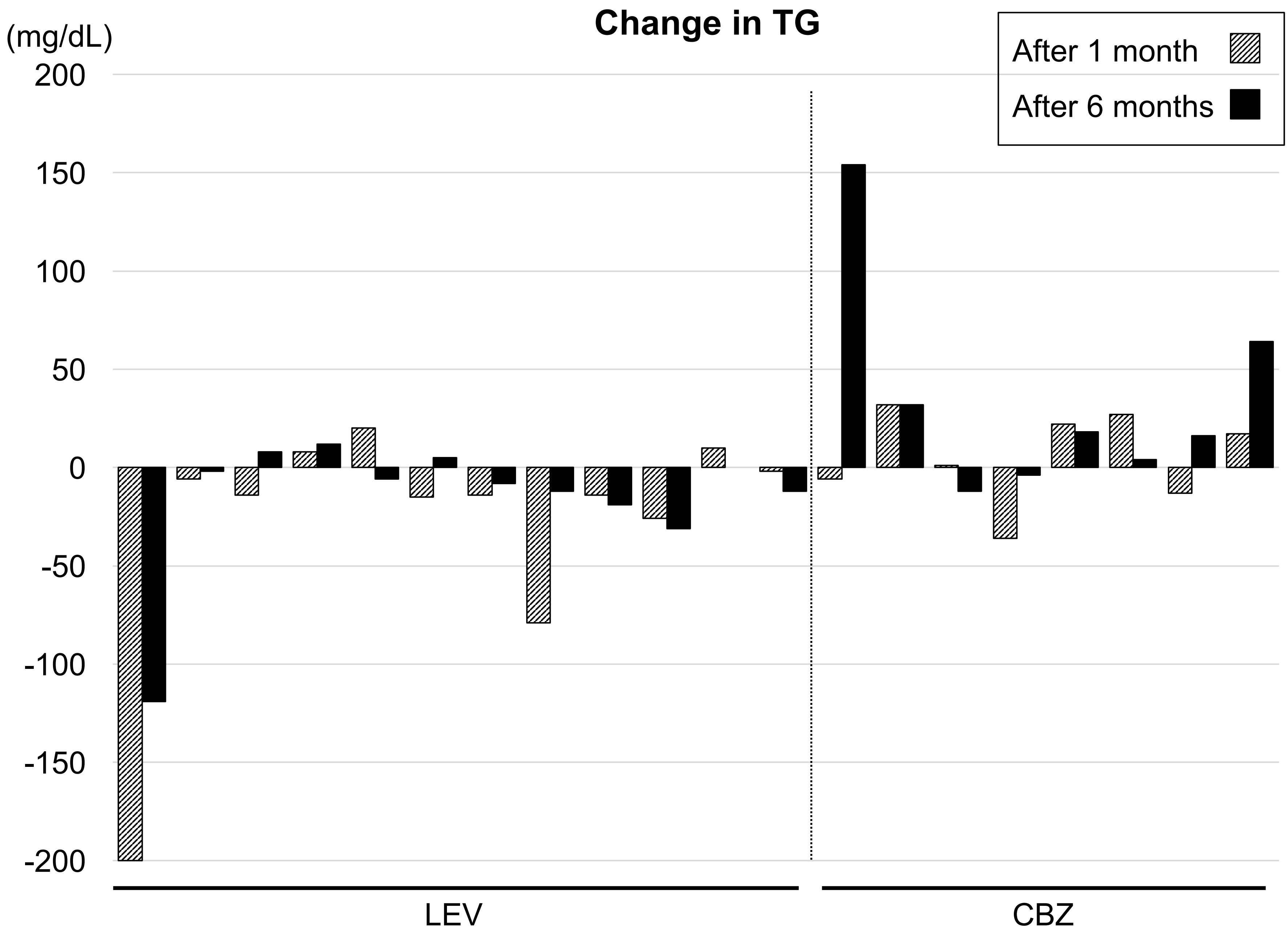
[*]P<0.05 with ANOVA among baseline, after 1 month, and after 6 months.

[a]P<0.05 between LEV and CBZ groups.

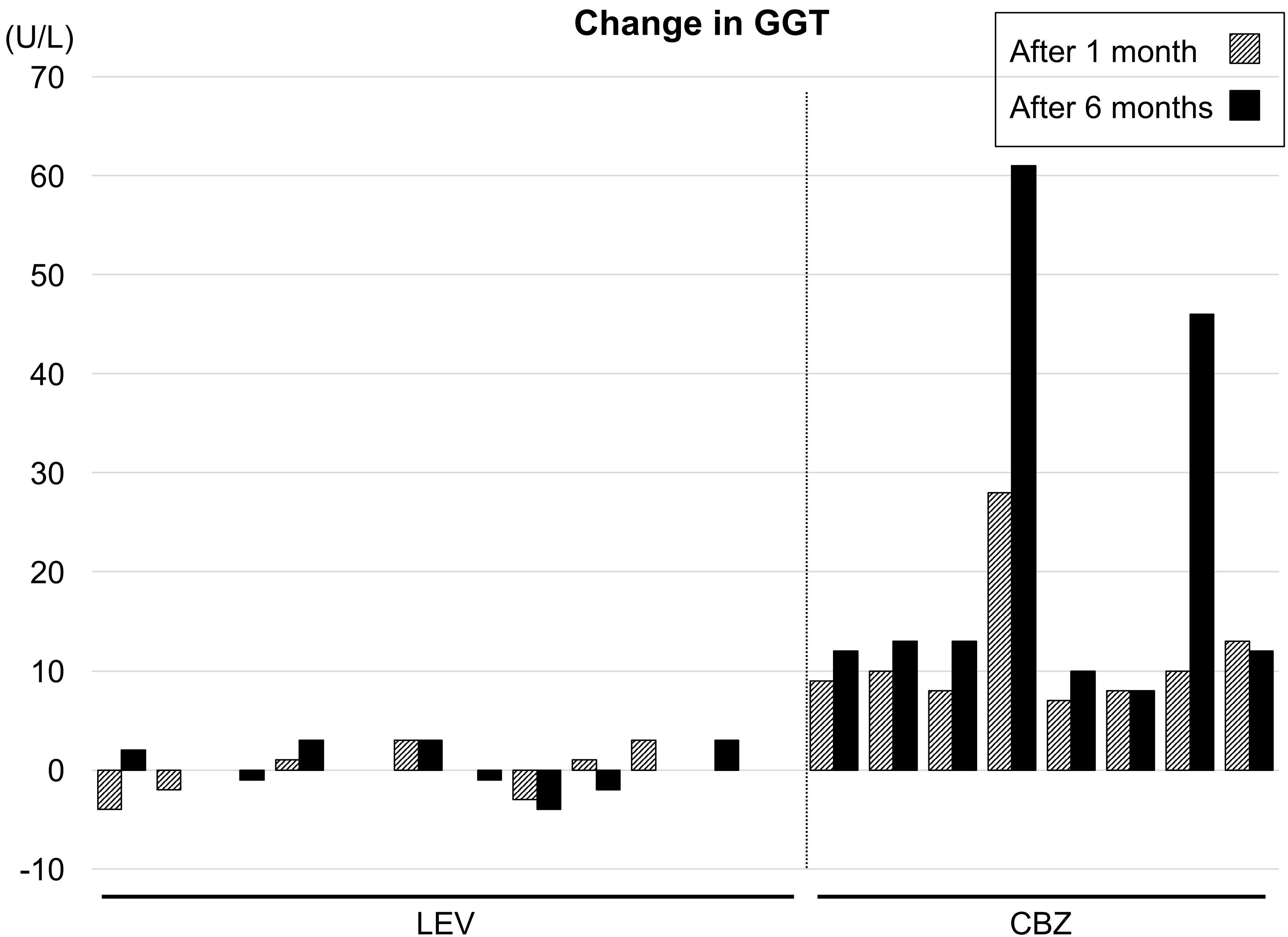
TG, triglyceride; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TSH, thyroid-stimulating hormone; FT4, free thyroxine; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma-glutamyltransferase; CRP, C-reactive protein

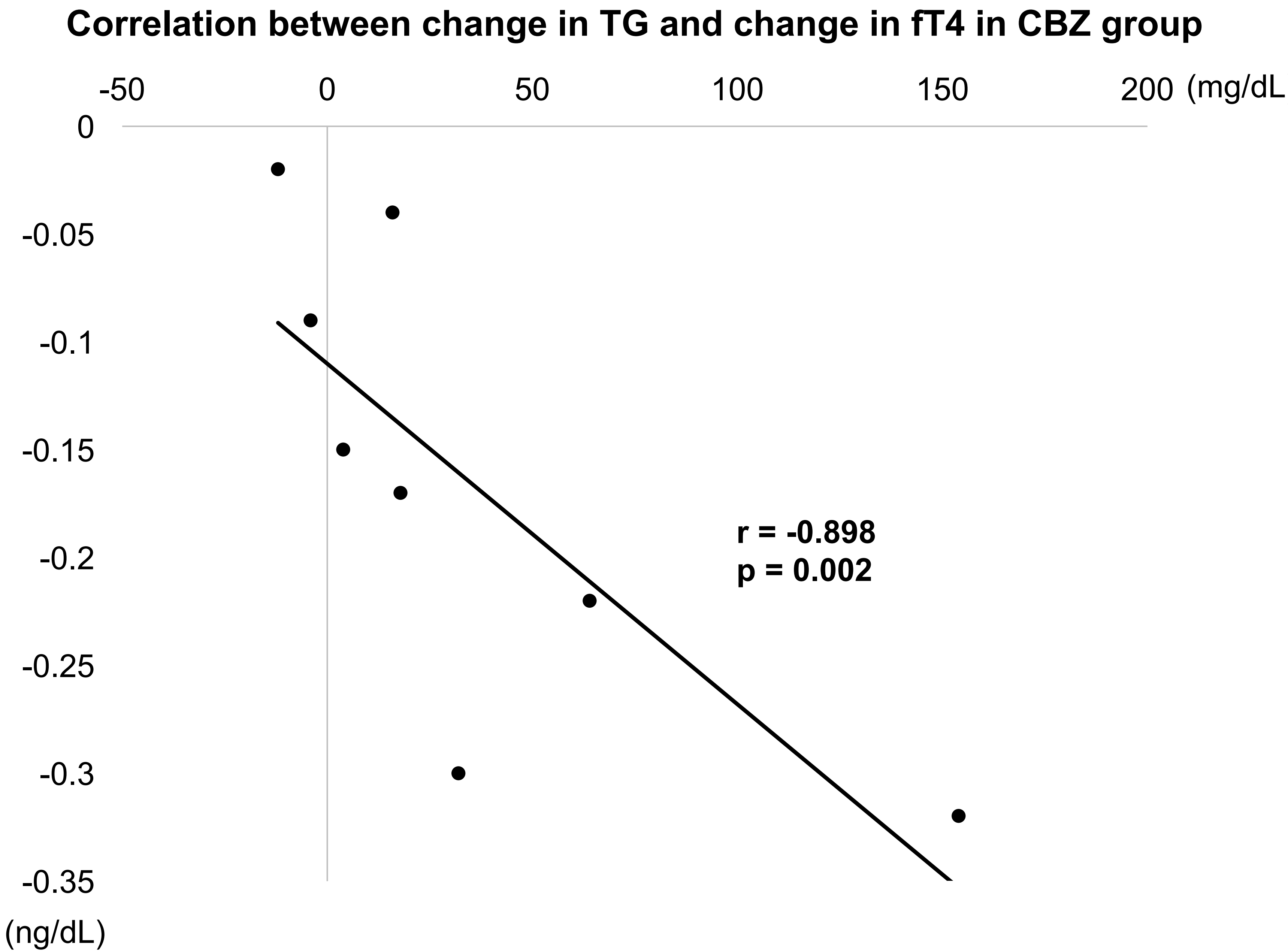


Change in fT4
(ng/dL)
0.5
0.4
0.3
0.2
0.1
0
-0.1
-0.2
-0.3
-0.4
-0.5
After 1 month
After 6 months
LEV
CBZ



Change in TG
(mg/dL)
200
150
100
50
0
-50
-100
-150
-200
After 1 month
After 6 months
LEV
CBZ


Change in GGT
(U/L)
70
60
50
40
30
20
10
0
-10
After 1 month
After 6 months
LEV
CBZ


Correlation between change in TG and change in fT4 in CBZ group
-50
0
50
100
150
200
(mg/dL)
0
-0.05
-0.1
-0.15
-0.2
-0.25
-0.3
-0.35
(ng/dL)
r = -0.898
p = 0.002