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Evaluation of the relationship of leptin, adiponectin and carnitine levels with lung function, asthma severity and BMI in children with asthma

Astımlı çocuklarda leptin, adiponektin ve karnitin düzeylerinin akciğer fonksiyonları, astım şiddeti ve BMI ile ilişkisinin değerlendirilmesi

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Abstract

Purpose: The aim of this study is to evaluate the relationship between serum levels of leptin, adiponectin and carnitine with lung function, disease severity and BMI (Body Mass Index) in children with asthma.

Materials and methods: 97 Pediatric patients with not in acute attack period bronchial asthma and 40 healthy control subjects were included in the study. Pulmonary function tests were done to all asthma patients with a spirometer. Children with asthma were divided into 3 groups according to GINA criteria, mild intermittent, mild persistent, and moderate persistent, with using symptoms and spirometric parameters according to the severity of airway obstruction. Leptin, total carnitine and adiponectin analyzes were performed from venous blood by ELISA method.

Results: Patient group serum leptin values were found to be significantly higher than the control group serum leptin values (p=0.001). Patient group serum total carnitine values were found to be significantly lower than the control group (p=0.001). Moderate persistent group adiponectin and total carnitine values were found to be significantly lower than mild intermittent group (p<0.05). A weak negative correlation was found between leptin and total carnitine, eosinophil, BMI values. A weak negative correlation was found between total carnitine and eosinophil, BMI values. A moderate negative correlation was found between age and leptin, adiponectin, total carnitine values.

Conclusions: It suggested that leptin levels increased, adiponectin and total carnitine levels decreased in children with asthma and at the same time the decrease in adiponectin and total carnitine levels may be associated with disease severity.

Key words: Asthma, leptine, adiponectine, carnitine.

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Özet

Amaç: Bu çalışmanın amacı astımlı çocuklarda leptin, adiponektin gibi adipokinlerin ve karnitin gibi mediatörlerin serum düzeylerinin akciğer fonksiyonları, hastalık şiddeti ve BMI ile ilişkisini değerlendirmektir.

Gereç ve yöntem: Çalışma kapsamına akut atak döneminde olmayan 97 bronşial astımlı çocuk hasta ve 40 sağlıklı kontrol bireyi alındı. Tüm astım hastalarına spirometre ile solunum fonksiyon testleri yapıldı. Astımlı çocuk hastalar hava yolu obstruksiyon şiddetine göre semptomlar ve spirometrik parametreler kullanılarak GINA kriterlerine göre hafif intermittan, hafif persistan, orta persistan 3 gruba ayrıldı. Venöz kandan ELİSA yöntemi ile leptin, total karnitin ve adiponektin analizleri yapıldı.

Bulgular: Hasta grubu serum leptin değerleri, kontrol grup serum leptin değerlerinden anlamlı düzeyde yüksek bulundu (p=0,001). Hasta grubu serum total karnitin değerleri kontrol grubuninkinden anlamlı düzeyde düşük bulundu (p=0,001). Orta persistan grup adiponektin ve total karnitin değerleri hafif intermitant gruptan anlamlı düzeyde düşük bulundu (p<0,05). Leptin ve total karnitin değerleri ile eozinofil ve BMI değerleri arasında zayıf negatif korelasyon bulundu. Yaş ile leptin, adiponektin ve total karnitin değerleri arasında orta düzey negatif korelasyon bulundu.

Sonuç: Astımlı çocuklarda leptin düzeylerinin arttığını, total karnitin düzeylerinin azaldığını, adiponektin ve total karnitin düzeylerindeki azalmamın hastalık şiddeti ile ilişkili olabileceğini düşündürdü.

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Anahtar kelimeler: Astım, leptin, adiponektin, karnitin.

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Introduction

Characterized by chronic inflammation of the airways, asthma is one of the most common chronic diseases in children. Many studies show an increased prevalence of obesity and asthma, supporting the association between obesity and asthma in children [1]. Although it has been suggested that obesity may cause the development of asthma through its mechanical effects on the respiratory system and stimulating the inflammatory response, the relationship between asthma and obesity has not been fully explained in any of them [2, 3]. Metabolic active substances secreted by adipose tissue, they are called “adipocytokines” or “adipokines” [4]. Leptin, adiponectin, haptoglobin and other adipokines participate in many metabolic activities [4-6]. Because of these factors, obesity can be considered as a chronic systemic inflammatory syndrome [7]. Serum leptin functions as a proinflammatory in congenital and acquired immune response [8]. Adiponectin; It is an adipokine that exerts anti-inflammatory action by inhibiting pro-inflammatory cytokines such as TNF-α and IL-6 and inducing anti-inflammatory cytokines such as IL-10 and IL-1 receptor antagonists [8]. Carnitine is a cofactor involved in the mitochondrial oxidation of long-chain fatty acids, by increasing physical activity tolerance and reducing muscle fatigue [9]. It has been shown that L-carnitine treatment prevented subclinical bronchospasm and improved pulmonary function tests (PFT) in hemodialysis patients [10].

Although many studies have been conducted on the effect of obesity in the development of asthma, there is not enough data in the literature on the role of adipokines leptin, adiponectin and carnitine, which is involved in the oxidation mechanism of fatty acids, in children. The aim of this study is to evaluate the relationship between serum levels of adipokines such as leptin, adiponectin and mediators such as carnitine with lung function, disease severity and BMI in children with asthma.

Materials and methods

Study population

Among the patients who applied to a Tertiary University Hospital Pediatric Allergy outpatient clinic, a total of 97 patients, 66 males and 31 females, who were clinically diagnosed with bronchial asthma but did not have an acute attack period and did not have any other chronic diseases, constituted the “patient group”. A total of 40 individuals, 24 males and 16 females, who had no bronsial asthma and other acute or chronic diseases, and who had nonspecific complaints but no pathological findings, comprised the “control group”. Pulmonary function tests (1. Forced expiratory volume per second (FEV) and forced vital capacity (FVC)) of all asthma patients were performed with a spirometer (Minato Auto Pal Spirometry, Japan). Children with asthma were divided into 4 groups as mild intermittent, mild persistent, moderately persistent and severe persistent according to GINA criteria [11] using symptoms and spirometric parameters according to the severity of airway obstruction. Severe persistent patients were excluded, because there were not enough patients.

This study was approved by Cumhuriyet University Faculty of Medicine Clinical Trials Ethics Committee (20.05.2011 / 164).

Blood analysis

Venous blood was collected from each child included in the study between 08.00-11.00 a.m., following a 10-12 hour fasting, for routine hemogram and biochemistry analyzes and for leptin, total carnitine and adiponectin analysis. Samples were centrifuged 30 minutes after collection at 4000 rpm for 5 minutes. Serum was separated immediately. Serums were stored in a freezer at –80^{0}C until the day of analysis. Among the samples included in the study, serum total cholesterol level (mg/dl), triglyceride level (mg/dl), LDL level (mg/dl), HDL level (mg/dl) using Siemens AdviaChemistry (USA) ready-made commercial kits in the Siemens

Advia 2400 brand autoanalyzer device. dl) measurements were made. Serum leptin level was determined using DIA Source Belgium (cat. No. KAP 2281), serum adiponectin level by Invitrogen, USA (cat. No. KHP0041), and serum carnitine level using CUSABIO, China (cat. No. CSB-E13242h) branded commercial kit. Measurements were made in ChemWell Fully Automatic Elisa Device with ELISA (Enzyme-LinkedImmunosorbentAssay) method.

Statistical analysis

When the assumptions of parametric tests were fulfilled in the evaluation of the data recorded in a separate "Data Recording Form" for each case, the significance test of the difference between the two means was used when comparing two independent groups, and analysis of Variance was used when comparing more than two independent groups. When parametric test assumptions could not be fulfilled, the Kruskal-Wallis test was used when comparing more than two independent groups, and the Man Whitney U Test was used when comparing two independent groups. Correlation Analysis was used while investigating the relationships between variables. Our data were stated in the tables as arithmetic mean ± standard deviation, median, minimum and maximum value, and the level of error was taken as 0.05.

Results

The mean age of the children with asthma included in the study was 10.15±3.72, and the control group was 9.48±3.48 (p>0.05). The mean BMI values of the patient group were 18.29±3.95, while the mean BMI values of the control group were found to be 18.07±8.87 (p>0.05). There was no significant difference between the comparatively evaluated serum lipid parameters of the patient and control groups in terms of total cholesterol, triglyceride, LDL and HDL values (p>0.05). Patient group serum leptin values [median (min-max): 1.9 (0.1-11.6)], compared to control group serum leptin values [median (min-max): 0.6 (0.1-13, 6)] was found to be significantly higher (p=0.001). Serum total carnitine values (mean ± SD: 10.66±5.62) in the patient group were found to be significantly lower than the control group serum total carnitine values (mean±SD: 15.08±7.31) (p=0.001). There was no statistically significant difference between the serum adiponectin values of the patient and control groups (p>0.05) (Table 1).

When we divided the patient group into groups according to the severity of asthma, the

Table 1. Comparison of patient and control group demographic status and laboratory data

	Patient Group (n=97)	Control Group (n=40)	*p* Value
Age (years)	10.15±3.72	9.48±3.48	0.472
Gender (M/F)	66/31	24/16	0.925
Body Mass Index (kg/m^2)	18.29±3.95	18.07±8.87	0.339
Total Cholesterol (mg/dl)	166 (97-293)	160 (101-211)	0.187
Triglyceride (mg/dl)	95 (24-259)	93 (28-259)	0.899
LDL(mg/dl)	75.47±23.94	83.60±22.59	0.929
HDL(mg/dl)	46.20 (23.60-75.50)	48.10 (27.70-70.30)	0.375
Leptin (ng/ml)	1.9 (0.1-11.6)	0.6 (0.1-13.6)	0.001*
Adiponectin (µg/ml)	17.4±10.2	17.0±9.6	0.448
Total Carnitine (µg/ml)	10.66±5.62	15.08±7.31	0.001*

Normally distributed parameters are shown as "mean ± standard deviation", parameters not showing normal distribution are shown as "median (min-max)". * p<0.05 significant

MEF50 and MEF25-75 values of the moderate persistent group were found to be significantly lower than the mild intermittent group and the mild persistent group (p<0.05). No significant difference was found between the average PEF values of the disease severity groups (p>0.05) (Table 2).

Table 2. Comparison of demographic data and PFT findings of groups and control group according to asthma severity

	Mild intermitant (n=23)	Mild persistant (n=58)	Moderate persistant (n=16)	*p* Value
Age (Years)	9.35±3.27	10.34±3.86	10.63±3.86	0.513
Body Weight (kg)	32.92±12.37	37.69±17.99	44.13±19.13	0.140
Height (cm)	134.52±20.36	139.22±21.99	145.75±20.51	0.258
Body Mass Index (kg/m^2)	17.51±2.59	18.24±3.98	19.61±5.07	0.103
FEV1	90.61±18.93	88.98±12.68	88.75±12.53	0.962
FEV1/FVC	106.13±11.34	106.53±11.32	103.69±7.21	0.247
PEF	86.65±18.46	87.88±14.34	81.00±14.75	0.322
MEF50	89.43±22.18	93.53±88.50	75.25±16.37	0.017*
MEF25-75	95.26±24.62	98.26±23.49	78.2516.49	0.009*

*$p<0.05$ significant.

BMI, lipid and study parameters of the patient groups and the control group according to the severity of asthma are compared in Table 3. Although the BMI values of the middle persistent group were the highest group, the difference between the BMI values of the other groups was not statistically significant ($p>0.05$). Among the lipid parameters, only the moderate persistent group serum LDL values were found to be significantly higher than the other patient groups and the control group ($p<0.05$). When the eosinophil values of the patient and control groups were compared, no significant difference was found ($p>0.05$). When the total IgE levels were compared between the groups in pairs, only the difference between the mild persistent group and the control group was found to be significant ($p<0.05$). Serum leptin levels were higher in all patient groups than the control group ($p<0.05$), while adiponectin levels in the moderate persistent group were significantly lower than the mild intermittent group ($p<0.05$). Serum total carnitine levels were found to be the lowest in the middle persistent group. This decrease was statistically significant compared to other patient groups ($p<0.05$). There was a decrease in serum total carnitine levels in other patient groups, and the difference between the control group and total carnitine levels was statistically significant ($p<0.05$) (Table 3), (Figure 1).

When the relationship of leptin, adiponectin and total carnitine levels of the patients with study parameters was evaluated, a moderate positive correlation was found between adiponectin and total carnitine values. A weak negative correlation was found between leptin levels and adiponectin and total carnitine values. There was no significant correlation between leptin, adiponectin, total carnitine values and PFT values. A weak negative correlation was found between leptin, total carnitine values and eosinophil, BMI values. When the relationship between these three parameters and age is evaluated; A moderate negative correlation was found between age and leptin, adiponectin, total carnitine values (Table 4).

Table 3. Comparison of tests belonging to groups and control groups according to the severity of asthma

	Mild intermitant (n=23)	Mild persistant (n=58)	Moderate persistant (n=16)	Control (n= 40)
BMI (kg/m^2)	17.51±2.59	18.24±3.98	19.61±5.07	18.07±8.87
Total Cholesterol (mg/dl)	157 (111-218)	167 (97-293)	178 (116-224)	160 (101-211)
Triglyceride (mg/dl)	99.5 (37-187)	81.5 (24-529)	114 (50-219)	93 (28-384)
LDL (mg/dl)	71.87±14.25	72.38±24.37	92.31±27.72[a,b,c]	83.60±22.59
HDL (mg/dl)	47.15 (29.9-72.5)	45.85 (23.6-75.5)	46.4 (35.0-53.4)	48.10 (27.7-70.3)
Eosinophil	0.22 (0.03-1.1)	0.33 (0.01-1.51)	0.42 (0.03-1.00)	0.19 (0.0-1.70)
IgE	72.65 (0.5-2730)	125 (4.5-2720)	91 (4.5-1730)	30 (4.5-565)
Leptin (ng/ml)	2.4 (0.2-9.4)[c]	1.8 (0.1-11.6)[c]	2,1 (0.1-10.7)[c]	0.6 (0.1-13.9)
Adiponectin (µg/ml)	20.9 (3.1-31.9)	16.9 (0.0-38.5)	13.9 (0.1-30.8)[a,c]	18.03 (0.9-35.4)
Total Carnitine (µg/ml)	11.35 (3.5-23.5)[c]	9.94 (1.2-23.8)[c]	8.99 (1.6-28.3)[a,c]	13.48 (1.0-30.3)

ANOVA multiple comparison test (TUKEY test), * $p<0.05$ significant, BMI: Body mass index
a Significant difference from the mild intermittent group $p<0.05$
b Significant difference from mild persistent group $p<0.05$
c Significant difference from control group $p<0.05$

Table 4. Relationship between leptin, adiponectin and total carnitine levels in patients with study parameters (Leptin, Adiponectin, Total Carnitine)

	Leptin		Adiponectin		Total Carnitine	
	r	*p*	r	*p*	r	*p*
Adiponectin	-0.270	0.011*	-	-	-	-
Total Carnitine	-0.228	0.007*	0.544	<0.0001*	-	-
FEV1	0.002	0.983	-0.298	0.027	0.002	0.983
FEV1/FVC	-0.045	0.659	0.193	0.178	-0.045	0.659
PEF	-0.027	0.796	-0.001	0.993	-0.027	0.796
MEF50	0.046	0.653	0.013	0.923	0.046	0.653
MEF25-75	-0.013	0.902	-0.229	0.093	-0.013	0.902
Eosinophil	-0.261	0.003*	0.057	0.597	-0.261	0.003*
Total IgE	-0.126	0.151	-0.157	0.162	-0.126	0.151
BMI	-0.217	0.011*	-0.039	0.715	-0.217	0.011*
Age	-0.343	<0.0001*	-0.348	0.001*	-0.343	<0.0001*
LDL	0.088	0.318	0.090	0.419	0.167	0.056

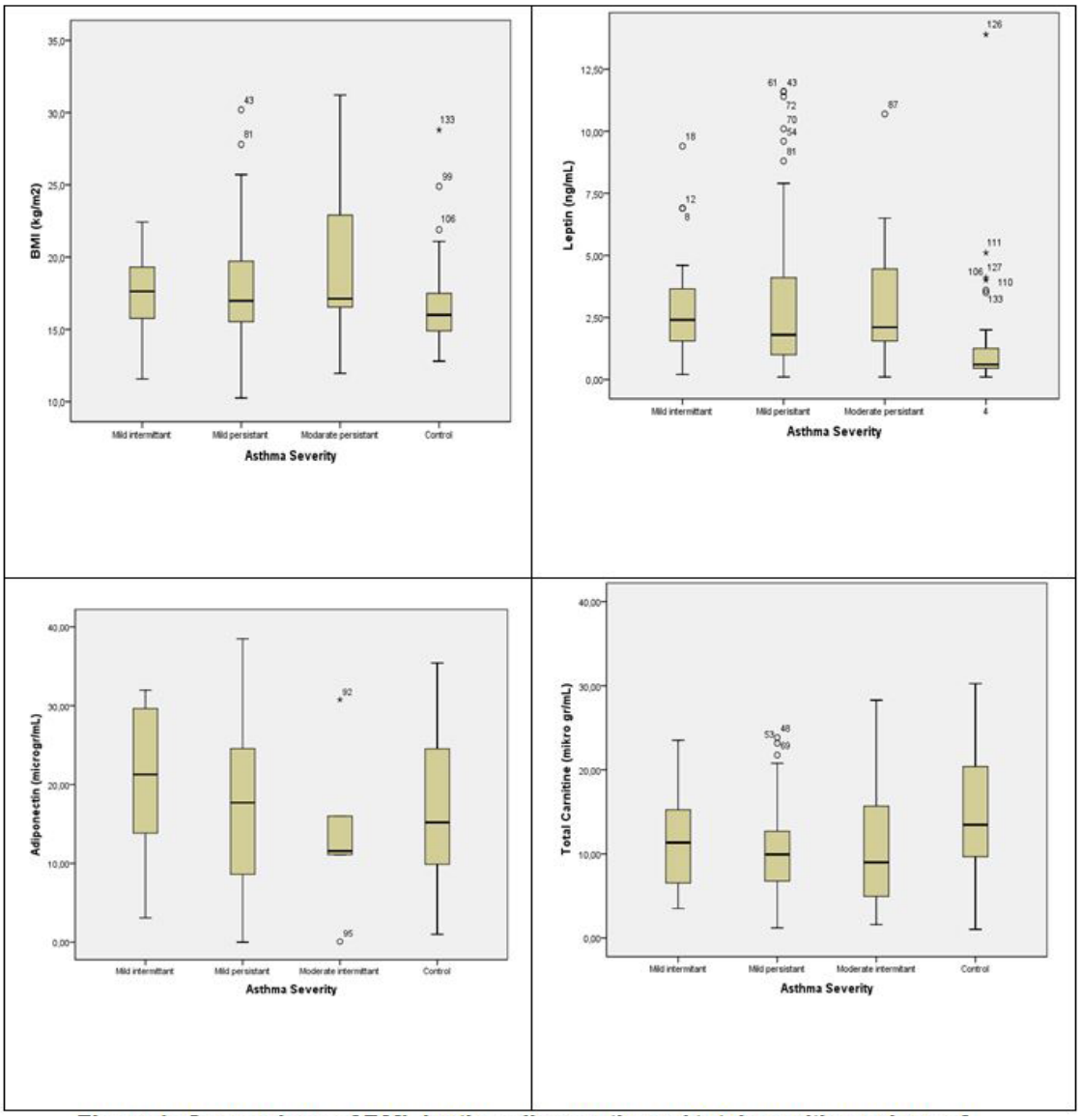

Figure 1. Comparison of BMI, leptin, adiponectin and total carnitine values of groups and control group according to asthma severity

Discussion

Asthma severity follows very different courses in children and these courses are affected by many factors. Studies on these factors raise new hopes in the treatment of asthma in children. This study was planned to explain the effects of adipokines and carnitine, which are parameters related to body fat and the relationship of body fat on asthma severity in children. The results of our study show us that there is an increase in leptin levels and a decrease in total carnitine levels in children with asthma. When BMI, blood lipid levels, total IgE, eosinophil values and leptin, adiponectin and carnitine levels were compared according to disease severity; Although BMI values were higher in the more severe group, there was no significant difference between the groups. Among the blood lipid parameters, serum LDL levels were found to be higher in the severe group than in the mild groups. The increase in leptin levels in patients was independent from the severity of disease. Adiponectin values showed a decrease with increasing disease severity. Total carnitine levels decreased in patients in proportion to disease severity. While there was a weak negative correlation between leptin and adiponectin and total carnitine values, there was a moderate positive correlation between adiponectin and total carnitine values. Eosinophils and BMI were weakly negatively correlated with leptin and total carnitine.

Age was a moderately negatively correlated parameter with these three study parameters in children with asthma.

Studies have suggested that adipokines play an important role in the inflammatory pathogenesis of asthma. Leptin is an inflammation-related adipose tissue hormone [12] and its level has been shown to be higher in patients with asthma compared to those without asthma [13, 14]. Leptin has a regulatory role in T cell proliferation and inflammation, monocyte activation, and angiogenesis [15]. It also plays a role in normal lung development [16]. In a study by Yüksel H et al. It was shown that the increase in leptin levels in children with asthma was more pronounced in obese patients. They also found adiponectin and ghrelin levels lower in obese asthmatic patients than in non-obese asthmatic patients. In this study, leptin levels were significantly higher in obese and non-obese children with asthma compared to the healthy control group [17]. In the study of Ma et al, Serum leptin levels were measured in asthmatic and healthy children, and a positive correlation was reported between BMI and leptin levels [18]. In a study evaluating 138 children, it was reported that serum leptin levels were significantly higher in obese patients compared to normal weight individuals, and serum leptin levels were 2 times higher in obese patients with asthma compared to those who were obese and did not have asthma [19]. There are few studies showing a relationship between serum leptin levels and FEV1 values. Sin et al.'s study, in which they screened 2808 healthy non-obese patients, showed that there is a significant inverse relationship between serum leptin levels and FEV1 values. It has been reported that FEV1 values of patients with high leptin levels are lower than those with normal leptin levels [20]. In the study of Güler et al. ıt was reported that no correlation was observed between serum leptin levels and spirometric parameters. However, in the previous study of the same investigator, a positive correlation was found between FEV1 reversibility after bronchodilator therapy and leptin levels [21]. In our study, leptin levels were found to be high in children with asthma. However, this increase was not associated with disease severity. There was no correlation between spirometry parameters and leptin levels. Leptin levels were negatively correlated with BMI, age and eosinophil values. These results made us think that the increase in leptin levels in children with asthma may be independent of disease severity, but may be an increase related to weight gain and age.

Similar to leptin, adiponectin affects energy metabolism but has an anti-inflammatory effect [22]. It is negatively associated with obesity because its concentration increases with weight loss [23]. Adiponectin inhibits the proliferation of vascular smooth muscle cells [24]. If adiponectin has the same effect on airway smooth muscle cells, decrease in adiponectin in obese individuals may contribute to the increase of smooth muscle mass in asthmatic patients [25]. Adiponectin inhibits the activation, proliferation, and cytokine production of inflammatory cells, and also disrupts the interaction of T cells from inflammatory cells with other T cells and B cells. It has been suggested that decreased adiponectin levels in obese individuals may contribute to the increase of airway smooth muscle mass in remodeling in chronic asthma patients [26]. Holguin et al. found a significant increase in plasma leptin levels of these two groups in the obese asthmatic group, although BAL leptin levels of obese individuals in the asthmatic and healthy control groups were increased in both groups. While there was a negative correlation between BAL adiponectin levels and BMI of these patient groups, they did not find any relationship between plasma adiponectin levels and BMI [27]. In our study, no reduction in adiponectin levels was found in children with asthma. However, children with severe asthma were found to have lower adiponectin levels. This decrease in adiponectin levels was a decrease unrelated to spirometry parameters and BMI. It only showed a weak negative correlation with age. These results suggest that the decrease in adiponectin levels, which has an anti-inflammatory effect in children and prevents proliferation in airway smooth muscle cells, may be another factor that may be responsible for the exacerbation of asthma.

Carnitine deficiency causes toxic accumulation of long-chain fatty acids in the cytoplasm and acetyl coA in mitochondria. These accumulated sature and monounsature oils have different effects on airway inflammation [28]. In recent studies, it has been observed that total carnitine levels are lower in children with moderate persistent asthma compared

to the control group. Asilsoy et al. found that serum carnitine levels were low in children with moderate asthma after acute exacerbation [29]. Ergür et al. found that serum carnitine levels were low in children with recurrent respiratory tract infections [30].

Leukotrienes are among the mediators of inflammation in asthma and have a strong bronchoconstrictor effect. It is synthesized by eosinophils, basophils and mast cells in the bronchial mucosa. They play an important role in eosinophilic inflammation, airway mucus secretion, airway edema, collagen synthesis and airway remodeling [31]. Studies have reported that L-carnitine inhibits leukotriene synthesis by inactivation of the lipogenesis pathway and change in the ratio of fatty acids. Borghi-silva et al. showed that L-carnitine inhibits bronchospasm and improves obstructive findings in PFT [32]. Al-Biltagi et al found that L-carnitine levels were lower in children with moderate persistent asthma compared to the healthy control group [33]. In accordance with the studies conducted in our study, carnitine levels were found to be low in children with asthma. As the severity of the disease increases, so does the decrease in carnitine levels. This reduction was a weakly negatively correlated decrease in eosinophil values. There was also a moderate negative correlation between BMI and age and carnitine levels. However, there was no significant relationship between spirometer parameters. These results made us think that the decrease in carnitine levels associated with disease severity in children with asthma may be another factor that can be held responsible for the developing clinical picture. In this regard, it is necessary to conduct more comprehensive studies examining total carnitine and free carnitine levels, especially in children with obese asthma.

In our study, a comparison of blood lipids according to the severity of the disease was also made in children with asthma. Serum LDL levels were higher than the other groups only in the moderate persistent group. However, there was no relationship between serum LDL levels and leptin, adiponectin and total carnitine levels. This result made us think that the changes in leptin, adiponectin and carnitine levels in children with asthma may be a change unrelated to blood lipids.

In conclusion, the results of our study showed us that leptin levels, one of the adipokines associated with body fat mass, increased, L-carnitine levels, which are responsible for the transport of fatty acids to the mitochondria, decreased in children with asthma. At the same time, the decreases in adiponectin and total carnitine levels suggested that ıt was more in the moderate persistent group with high disease severity, and the changes in leptin, adiponectin and carnitine levels were more related to age than body fat.

Conflict of interest: No conflict of interest was declared by the authors.

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Author contribution

F.A.B.: Protocol/project development, Data analysis, Manuscript writing/editing

K.D.: Protocol/project development, Data analysis, Manuscript writing/editing

U.A.: Data collection or management

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