

Serum levels of chemerin, omentin and vaspin in children with cystic fibrosis

Stężenie chemeryny, omentyny i waspiny w surowicy u dzieci z mukowiscydozą

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Key words

cystic fibrosis, chemerin, omentin, vaspin, children

Słowa kluczowe

mukowiscydoza, chemeryna, omentyna, waspina, dzieci

Abstract

Introduction. Patients with cystic fibrosis (CF) present numerous pathological conditions such as malnutrition, depletion of fat-free mass, metabolic disturbances (abnormal glucose metabolism, increased insulin resistance, chronic energy deficit, local and chronic inflammation), which could affect or be associated with altered adipokines concentration. **The aim** of the study is to evaluate serum concentration of chemerin, omentin and vaspin in children with cystic fibrosis. **Material and Methods.** The study group included 21 children (mean age 11.3±0.4 years) with stable CF. The diagnosis of CF was established by sweat test and later confirmed by genetic examination in all subjects. Patients with pulmonary exacerbation were excluded from study. In all children history, physical examination, anthropometric parameters, sputum, blood samples, and lung function tests were assessed. The control group consisted of 22 healthy children (mean age 10.9 ±4.4 years). **Results.** The mean serum levels of chemerin and omentin were higher ($p<0.001$) in CF children than in healthy children. The mean serum vaspin concentration was significantly lower than in controls ($p<0.001$). Concentrations of examined adipokines showed no correlation with BMI, BMI-SDS,

Streszczenie

Wstęp. Pacjenci z mukowiscydozą (cystic fibrosis, CF) prezentują liczne patologiczne stany, jak niedożywienie, zmniejszenie masy tłuszczowej ciała, zaburzenia metaboliczne (zaburzony metabolizm glukozy, wzrost insulinooporności, przewlekły deficyt energii, miejscowe i chroniczne zapalenie), które mogą mieć związek z zaburzeniami stężeń adipokin. **Celem** badań jest ocena stężenia chemeryny, omentyny i waspiny w surowicy krwi u dzieci z mukowiscydozą. **Materiał i metody.** Badaniem objęto 21 dzieci (średni wiek: 11,7± 1,59 lat) ze stabilną CF. Diagnozę CF u tych dzieci potwierdzono badaniem genetycznym. Pacjentów z zaostrzeniem choroby wykluczono z badań. U wszystkich dzieci przeprowadzono wywiad, badanie fizykalne i antropometryczne, zbadano płwocinę, pobrano krew, wykonano czynnościowe badania płuc. Grupę kontrolną stanowiło 22 zdrowych dzieci (średni wiek: 10,9 ± 4,4 lat). **Wyniki.** Średnie stężenie chemeryny i omentyny w surowicy krwi było istotnie wyższe ($p<0.001$), a waspiny znacząco niższe ($p<0,001$) u dzieci z mukowiscydozą aniżeli u zdrowych. Nie stwierdzono znamiennych statystycznie korelacji pomiędzy stężeniem badanych adipokin we krwi a BMI, BMI-SDS, glukozą, cholesterolem całkowitym, LDL i HDL we krwi. FEV1 i FVC

and glucose, total cholesterol, LDL-, HDL-cholesterol, triglycerides serum levels. FEV1 and FVC correlated positively with BMI – SDS (R:0.58, $p<0.01$; R:0.5, $p<0.036$, respectively). **Conclusions.** Chemerin and omentin may be involved in the inflammatory process underlying the disease but they do not correlate with disease severity.

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Introduction

Cystic fibrosis (CF) is an untreatable and life-shortening inherited autosomal recessive disease with multiorgan manifestation. It is caused by different mutations in a single gene, localized on the long arm of chromosome 7 at position q31.2., which codes Cystic Fibrosis Transmembrane Conductance Regulator (CFTR). CFTR protein is a cAMP-activated chloride channel expressed at the apical membrane on the surface of epithelial cells lining the airways, gastrointestinal tract, cells of exocrine pancreas, airway submucosal and sweat glands [1]. The defective or absent CFTR protein results in poor transport of salt and water into and out of the cells in number of organs. The extent of clinical manifestations is highly heterogeneous in distinct organs. Leading symptoms of typical CF include increased electrolytes concentration in sweat, exocrine pancreatic insufficiency and progressive pulmonary dysfunction, which is responsible for more than 80% of CF-related deaths [1]. CF associated bronchopulmonary disease is characterized by multiply alterations including mucostasis, mucus hypersecretion, and chronic neutrophilic inflammation with recurrent bacterial infections, mainly caused by *Pseudomonas aeruginosa* and *Staphylococcus aureus* [2,3]. Other CF clinical manifestations comprise chronic rhinosinusitis, hepatic and intestinal disorders, diabetes mellitus, male infertility [1]. Cystic fibrosis is associated with malnutrition, depletion of body fat, but increased percentage of visceral adipose tissue [4,5]. Adipokines are protein mediators secreted by the adipose tissue, which were found to be associated with the chronic low-grade inflammation process present in inflammatory diseases and chronic disturbances of metabolism. With related receptors extensively dispersed throughout the body, including the lungs, adipokines may be a contributing factor underlying the complications of CF. We have planned to investigate serum levels

pozytywnie korelowało z BMI-SDS (R:0,58, $p<0,01$; R:0,5; $p<0,036$, odpowiednio). **Wnioski.** Chemeryna i omentynamogą mieć związek z procesem zapalnym w mukowiscydozie ale nie korelują z ciężkością tej choroby.

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of selected adipokines such as chemerin, omentin, and vaspin to demonstrate their application as possible markers of inflammation.

Chemerin is a multifunctional protein implicated in chemotaxis of immune cells, regulation of adipogenesis and adipocyte metabolism. Chemerin plays a role in angiogenesis, myogenesis, and glucose homeostasis regulation [6,7].

Chemerin attracts leukocyte populations expressing high affinity functional receptor (ChemR23), particularly on immature plasmacytoid dendritic cells (DCs), but also immature myeloid DCs, macrophages and natural killer cells. ChemR23 expression was also described in a growing number of non-leukocyte cell populations. These include preadipocytes and adipocytes, osteoclasts, chondrocytes, skeletal muscle and endothelial cells [6].

Chemerin is synthesized as an inactive precursor (prochemerin), which circulates in the bloodstream. Various proteases are able to generate bioactive chemerin from prochemerin including neutrophil serine proteases and proteases from coagulation and fibrinolytic cascades. Prochemerin is expressed at particularly high levels in liver, white adipose tissue and placenta, but is also present in skin, adrenal glands, all parts of the gut, pancreas, the airways, and the kidney [6,7].

Omentin discovered in 2005, a secretory protein of 313 amino acids is an anti-inflammatory adipokine that is abundant in human visceral fat tissue. It is encoded by two genes with omentin-1 being the major circulating form [8,9]. Omentin has been reported to exert anti-inflammatory, pro-survival and pro-angiogenic functions in various cells via Akt-dependent mechanism. Higher circulating omentin levels are present in lean and healthy individuals compared with obese and diabetic patients [10].

Vaspin was identified as serpin A12, a member of the serine protease inhibitors family [11]. Human vaspin protein consists of 415 amino acids

and has 40% identity with α -1 antitrypsin [12]. It has been demonstrated that vaspin can play role in insulin resistance and metabolic syndrome, type 2 diabetes mellitus and is involved in vascular inflammation and remodeling [13]. It has been also suggested that an elevated level of vaspin is a compensatory factor in subjects with obesity or insulin resistance [13].

Only a few reports conducted in adult patients with CF focus on the pro-inflammatory role of leptin and anti-inflammatory of adiponectin, which potentially may affect inflammation and glucose tolerance as well as nutritional status in this group [5,14,15]. Recently we suggested the role of resistin and apelin in inflammatory processes in children with CF [16]. However, the potential association between CF severity and chemerin, omentin, and vaspinserum levels has not been explored in CF so far, and remains obscure. We have hypothesized, that chemerin, omentin and vaspin also participate in CF pathophysiology and may be associated with the intensity of CF clinical features.

The aim of the study is to evaluate the concentration of chemerin, omentin and vaspin in children with cystic fibrosis.

Material and methods

The study group, previously described [16], comprised 21 children (aged 4.5-18 years; mean age 11.3 ± 0.4 years) with stable CF. The diagnosis of CF was established by sweat test and later confirmed by genetic tests in all subjects. All patients were treated according to European and U.S. guidelines [17]. Patients with pulmonary exacerbation were excluded from this study. In all children the following parameters were assessed: patient history and physical examination, anthropometric parameters, sputum and blood samples, and lung function tests. The control group consisted of 22 healthy children (aged 4-17 years; mean age 10.9 ± 4.4 years). Children from the control group attended the outpatient pediatric clinic for non – immunological, non – inflammatory health problems and needed venous puncture. The present study was approved by Ethics Committee of the Medical University and written informed consent was obtained from children's parents.

Laboratory assays were described with details in our previous study [16]. Blood samples for assays were collected in the fasting state between

8-9.30 am. After centrifugation at $1000 \times g$ for 15 min at 4 C, the serum samples were frozen at – 20 C until analyzed. The absorbance measurements for all samples were performed using the Quant Universal Microplate Spectrophotometer (BioTek Instruments Inc., Winooski, VT, USA) determined on the basis of the standard curve made for a series of dilutions of the standards available in the kit. Acquired data were analyzed using KC Junior Software (v.1.31.5, Bio Tek Instruments, Winooski, VT, USA).

Serum concentrations of chemerin was determined using the immunoenzymatic method with the application of the Human Chemerin ELISA kit (BioVendor, Czech Republic) according to the manufacturer's protocol. The sensitivity of the kit was 0.1 ng/ml. The intra – and inter-assay CV was 6.1% and 7.5%, respectively. Serum omentin-level was determined using the immunoenzymatic method with the application of the Human Omentin-1 ELISA kit (BioVendor, Czech Republic) according to the manufacturer's protocol. The sensitivity of the kit was 0,5 ng/ml. The intra – and inter-assay CV was – 3,6% and 4,6%, respectively. Serum vaspinconcentration was determined using the immunoenzymatic method with the application of the Human Vaspin ELISA kit (BioVendor, Czech Republic) according to the manufacturer's protocol. The sensitivity of the kit was 0,01 ng/ml. The intra – and inter-assay CV was – 7,6% and 7,7% respectively.

All statistical analyses were performed using (MedCalc ver. 12.4.0.0) and p values of < 0.05 were considered to be significant. To compare the characteristics of the subgroups the MannWhitney U-test was applied. Correlations were analyzed with Spearman tests.

Results

The characteristics of 20 children with CF and 22 healthy control subjects is presented in table I. Mean values of BMI in CF group were significantly lower than in control group. The mean values of serum levels of chemerin, omentin and vaspinin all children are shown in figures 1–3.

The mean serum levels of chemerin (201.3 ± 2.5 ng/ml) and omentin (41.90 ± 2.95 ng/ml) were significantly higher than in healthy children (184.8 ± 3.2 ng/ml; $p=0.0003$ and 32.09 ± 3.48 ng/ml; $p=0.0001$ respectively). The mean values of serum vaspin concentrations were significantly lower in

Table I. Characteristics of examined children

Tabela I. Charakterystyka badanych dzieci

Characteristics	Children with CF(n=21)	Healthy Children (n=22)	p
Age [years]	11.67 ± 1.596	10.9 ± 4.4	ns
Sex [n]	F:11; M:10	F:12; M:10	
Height [cm]	144± 9.84	144.9 ± 21.7	ns
Weight [kg]	36.84 ± 15.7	39.5 ± 13.0	0.02
BMI [kg/m ²]	17.1 ± 1.4	18.3± 0.98	0.03
BMI-SDS	-0.58± -0.71	0.95±0.82	0.01
CRP [mg%]	3.43±1.77	0.54 ± 0.17	0.05
BWC	8.9±1.42	6.63±0.85	0.01
Fasting Glucose [mg%]	94.43±4.12	84.36 ± 2.67	0.003
TC [mmol/l]	3.42± 0.36	3.14±0.28	ns
LDL [mmol/l]	1.76 ± 0.26	1.79± 0.41	ns
HDL [mmol/l]	1.2 ± 0.12	1.27± 0.28	ns
TG [mmol/l]	1.08±0.23	1.26±0.77	ns
AspAT [IU/ml]	32±0.8	25.41± 4.16	ns
AlAT[IU/ml]	33.47±72	15.88±3.02	0.001
FEV1 [% predicted]	65.62±9.73	95.82±1.7	0.0001
FVC [% predicted]	67.11±8.6	94.11±2.8	0.0001
FEV1/FVC [%]	78.87±6.28	90.03±1.5	0.0001

Data are shown as mean ±SE; BMI – body mass index; BMI-SDS – body mass index standard deviation score; CRP – C-reactive protein; HDL-C – high-density lipoprotein cholesterol; IU – international unit; LDL-C – low-density lipoprotein cholesterol; SE – standard error; TC – total cholesterol; TG – triglyceride; FEV₁ – forced expiratory volume in 1 second; FVC – forced vital capacity

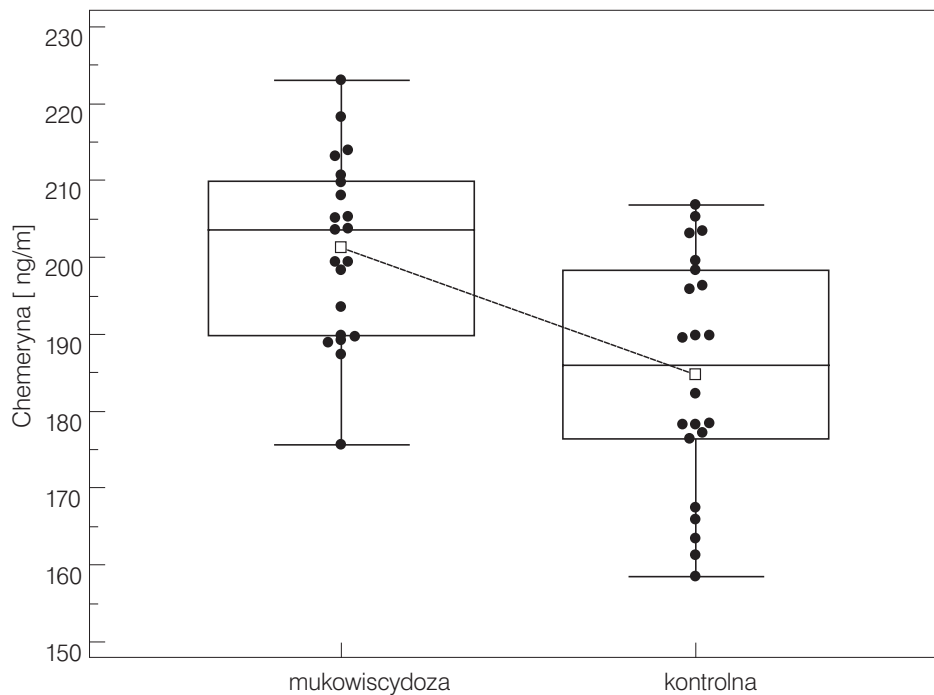


Fig. 1. Serum level of chemerin in children with cystic fibrosis and control group

Ryc. 1. Stężenie chemeryny w surowicy krwi u dzieci z mukowiscydozą i w grupie kontrolnej

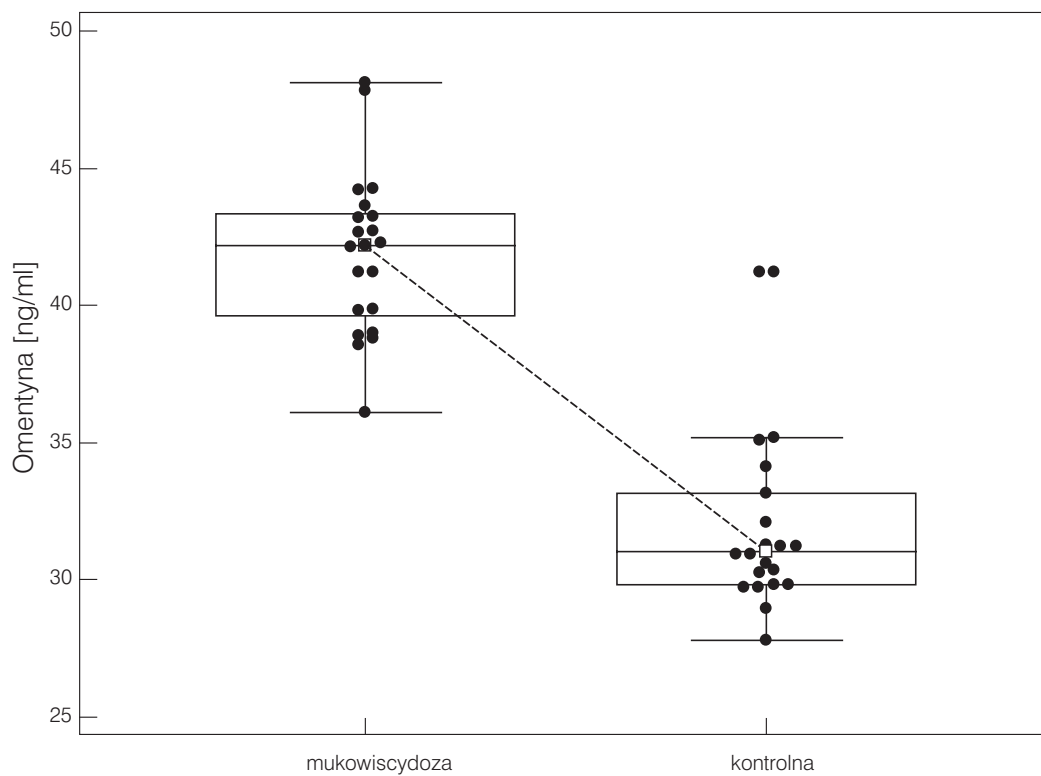


Fig. 2. Serum level of omentin in children with cystic fibrosis and control group
Ryc. 2. Stężenie omentyny w surowicy krwi u dzieci z mukowiscydozą i w grupie kontrolnej

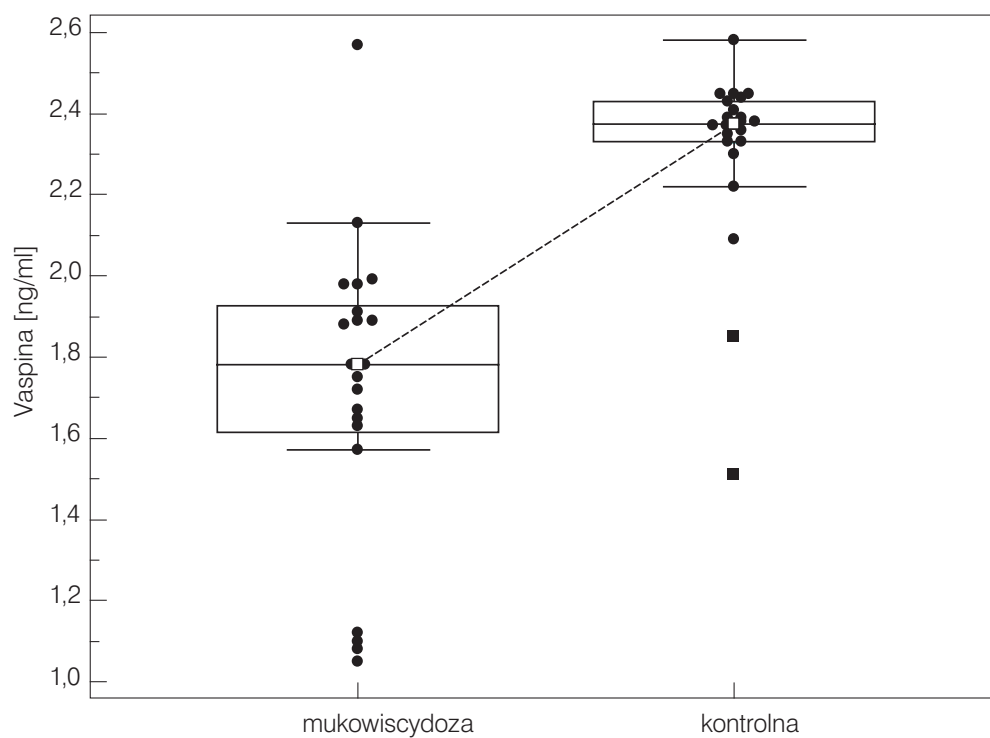


Fig. 3. Serum level of vaspinin children with cystic fibrosis and control group
Ryc. 3. Stężenie waspiny w surowicy krwi u dzieci z mukowiscydozą i w grupie kontrolnej

CF children (1.72 ± 0.38 ng/ml) than in healthy children (2.31 ± 0.23 ng/ml; $p=0.001$).

Age of CF patients correlated positively with chemerin levels ($r=0.43$; $p<0.042$). BMI of CF children correlated with TG ($R: 0.8$; $p<0.0001$) and CRP levels ($R:0.52$; $p<0.0017$). CRP correlated with chemerin levels ($R: 0.45$; $p<0.042$). Concentrations of examined adipokines showed no correlation with BMI, BMI-SDS, glucose, total and LDL, HDL cholesterol, triglyceride serum levels or spirometric parameters such as FEV₁, FVC, FEV₁/FVC.

Discussion

CF patients present numerous conditions such as malnutrition and depletion of fat free mass, metabolic disturbances including abnormal glucose metabolism, increased insulin resistance, chronic energy deficit, local and chronic inflammation, all of which could affect or be associated with altered adipokines concentration [1–4]. In this study we observed a significant increase in serum levels of chemerin and omentin, but decrease in serum levels of vaspinas compared to healthy subject.

Major characteristics of CF airways is a state of chronic inflammation. The CF airways contain several proinflammatory mediators including TNF- α , IL-1 β , IL-6, IL-8, MIF [2,3]. We observed a strong positive correlation between chemerin and CRP levels. The secretion of chemerin is efficiently induced by pro-inflammatory cytokines, including TNF- α , IL-1 β and by cysteine protease (Staphopain B), secreted by pathogens such as *Staphylococcus aureus*, which are increased in CF patients [2,3].

In human plasma chemerin levels were higher in many chronic inflammatory disorders including rheumatoid arthritis, coronary artery disease, obesity, type 2 diabetes, Crohn disease or COPD (chronic obstructive pulmonary disease) [18–21]. Additionally increased expression of chemerin was found in various inflammatory sites including skin lesion of acute psoriasis, lupus and in kidney tissue in lupus nephritis [18–21]. In contrast, lower chemerin levels were found in children with anorexia nervosa [22]. Interestingly, in animal model, both pro-inflammatory and anti-inflammatory roles of chemerin have been reported. Chemerin suppresses murine allergic asthma, and exerts anti-inflammatory activities in experimental peritonitis and lung injury [23,24]. Chemerin is predicted to share similar tertiary structure with

antibacterial cathelicidins and is implicated in inhibition of bacteria growth [25]. In several studies was shown that chemerin correlated with BMI, fasting glucose, fasting insulin, cholesterol, TG, and inflammatory markers including CRP levels [20,21].

Also serum omentin was higher in CF children as compared to healthy ones. Omentin can inhibit inflammation via several signaling pathways. It suppresses CRP and TNF- α synthesis, NF- κ B induced ICAM-1, VCAM-1 expression, and increases eNOS. Therefore omentin has an anti-inflammatory effect on smooth muscle cells and endothelium [25]. Omentin protects against pulmonary arterial hypertension through vascular structure remodeling and abnormal contractile reactivity inhibition [26]. Moreover omentin protects against LPS-induced acute respiratory distress (ARDS) suppressing pulmonary inflammation and promoting endothelial barrier stabilization [27].

On the other hand the reduced omentin levels are related with atherosclerosis, hypertension, cardiovascular disease and obstructive sleep apnea [26,28]. Omentin is inversely correlated with BMI, insulin resistance and positively with HDL and adiponectin [29]. If omentin through the increase of insulin sensitivity and protective effect on the lung injury may be a “good adipokine” in CT patients remains to be elucidated.

The serum vaspin levels were decreased in CF children like in ischemic heart disease and girls with anorexia nervosa [30–32]. Decreased serum vaspin concentrations may simply reflect reduced fat mass in CF like in obese subjects after 12-weeks short term weight reduction program [33]. Interestingly the vaspin levels in sera were elevated in rheumatoid arthritis and obstructive sleep apnea-hypopnea syndrome [34,35].

The beneficial effect of vaspin on vascular cells was shown in several studies. It was demonstrated that vaspin exerted antiatherogenic effect on vascular cells and significantly decreased TNF α -induced activation of NF- κ B, as well as the expression of the adhesion molecules ICAM-1, VCAM-1, E-selectin, and MCP-1 [35].

In this study any correlation between examined adipokines and BMI and BMI-SDS, glucose, total and LDL, HDL cholesterol, triglyceride serum levels and spirometric parameters such as FEV₁, FVC, FEV₁/FVC were found.

In conclusion, a significant increase of chemerin and omentin serum levels accompanied by the

decrease in serum level of vaspin observed in children with CF may suggest that these adipokines are involved in the inflammatory process underlying the disease like resistin and apelin [16]. However chemerin and omentin seem not to be associated with the severity of CF and clinical features. To the best of our knowledge the role of these adipokines in CF has not yet been investigated in patients with CF so it is impossible to directly compare our results with others.

Although this was a cross-sectional study with a relatively small sample size we believe that our data may be a starting point for further studies evaluating the possible role of adipokines in CF pathogenesis.

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