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Regular paper

Serum chemerin level, cytokine profile and nutritional status in children with cystic fibrosis

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Background: Cystic fibrosis (CF) is characterized by malnutrition and chronic inflammation predominantly occurring in lungs. Evidence suggests a relation between inflammatory activity and nutritional status. Proinflammatory cytokines, playing crucial role in pulmonary destruction in CF, are regarded as a component of the pathogenesis of illness-related malnutrition. Chemerin – a novel marker of a crosstalk between nutrition and inflammation, has not been investigated in children with cystic fibrosis. The aim of this study was to determine serum level of chemerin, interleukin-1b (IL-1b), interleukin-6 (IL-6), tumor necrosing factor α (TNF-α) and interleukin-10 (IL-10) and to verify if they correlate with the nutritional status in children with CF. Methods: The study included 72 pediatric patients with cystic fibrosis. The control group was comprised of 30 healthy children. Nutritional status parameters: Body Mass Index (BMI), fat mass percentage (FM%) and fat free mass percentage (FFM%) have been assessed in all the subjects basing on bioimpedance and anthropometry according to Slaughter. Serum concentrations of chemerin and cytokines were estimated with ELISA. Results: No statistically significant difference in serum chemerin was found between the studied and the control group. We have documented a significantly higher level of IL-1b, IL-6, TNF-α and IL-10 in CF patients when compared to healthy controls. Neither the chemerin nor the cytokine levels correlated with parameters of nutritional status in our cohort. No statistically significant correlation was found between the serum chemerin and the inflammatory cytokines: IL-1b, IL-6, and TNFα. Conclusions: Our results show that chemerin is not associated with the nutritional status in children with cystic fibrosis. Chemerin has no impact on the levels of IL-1b, IL-6, TNFα in CF patients. IL-1b, IL6, TNFα and also IL10 are upregulated in cystic fibrosis.

Key words: chemerin, interleukin-1b, interleukin-6, tumor necrosis factor α, interleukin-10, cystic fibrosis

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Abbreviations: CF, cystic fibrosis; IL, interleukin; TNFα, tumor necrosis factor α; BMI, Body Mass Index; FFM%, Fat Free Mass percentage; FM%, Fat Mass percentage; hsCRP, highly sensitive C-reactive protein; SDS, standard deviation score; BIA, bioimpedance analysis

INTRODUCTION

Cystic fibrosis (CF) is the most commonly inherited fatal disease affecting Caucasians. This multiorgan progressive disorder is characterized by chronic inflammation and malnutrition, which has been proven to have an impact on the course and prognosis of the disease (Culhane *et al.*, 2013; Roesch *et al.*, 2018).

Malnutrition in CF is related to several factors, such as reduced energy intake resulting from anorexia or lipid maldigestion, increased energy loss associated with gastroesophageal reflux, and increased energy requirement due to pulmonary destruction increasing the respiratory effort (Pencharz & Durie, 2000). Also, inflammatory activity is suggested as a component of the pathogenesis of illness-related malnutrition (Olveira *et al.*, 2015). Nutritional assessment, early identification of malnutrition, and prompt initiation of supportive treatments are essential parts of the CF patients' care (Gaskin, 2013).

Activation of inflammation predominantly takes place in the CF lungs. Cystic fibrosis pulmonary disease was primarily believed to result from failure of airways to clear bacteria due to retention of thick, sticky mucus, as a result of the exocrine dysfunction (Ratjen, 2009). Evidence suggests that airway inflammation in CF is also associated with increased production of pro-inflammatory cytokines by airway epithelial cells, macrophages, and predominantly neutrophils (Courtney *et al.*, 2004). Several studies have found elevated concentrations of proinflammatory cytokines ,such as interleukin-1 (IL-1), interleukin-6 (IL-6), interleukin-8 (IL-8), and tumor necrosis factor-alpha (TNFα) in the sputum, bronchoalveolar lavage fluid (BALF) and also in the serum of patients with CF (Richman-Eisenstat *et al.*, 2004). Moreover, there is an existing evidence for the presence of increased inflammatory markers also in the absence of CF-related pathogens (Khan *et al.*, 1995; Balough *et al.*, 1995). Some authors have postulated that proinflammatory- anti-inflammatory imbalance in the lungs responsible for sustaining inflammation in the pulmonary tissue is an important element of pathogenesis of the disease (Bonefield *et al.*, 1995; Saadane *et al.*, 2005).

It has been now clearly demonstrated that nutritional status influences the immune cell function and that, conversely, the immune cell function determines the cellular metabolic state (Alwarawrah *et al.*, 2018). Although the mechanisms explaining relations between the pulmonary inflammation and malnutrition in CF have not been yet elucidated, proinflammatory cytokines are proposed to be the main players (Alwarawrah *et al.*, 2018). A positive relation between cytokines

and malnutrition has been previously demonstrated in other conditions – predominantly in malignancies (Seruga *et al.*, 2008). Studies concerning the impact of malnutrition on cytokine secretion produced conflicting results, but majority of them report an immunosuppressive influence of weight loss (Gonzales Torres *et al.*, 2013; Azavedo *et al.*, 2005; Muñoz *et al.*, 1994).

In obesity, which contrary to malnutrition has been proven to promote inflammation, many substances produced by the adipose tissue have been shown to exert proinflammatory activity.

One of the novel markers involved in the specific crosstalk between metabolism and immunity is chemerin, regarded as a stimulator of inflammation in obese subjects (Ernst & Sinal, 2010; Hart & Greaves, 2010). Chemerin has not been yet investigated in non-obese patients with cystic fibrosis.

The aim of the study was to assess serum concentrations of chemerin, proinflammatory cytokines and interleukin 10, and to verify if they are related to nutritional status in patient with cystic fibrosis.

PATIENTS AND METHODS

Patients and controls. Seventy two children, aged 9 months to 18 years (median age 9 years 5 months), previously diagnosed with cystic fibrosis, and being under specialist outpatient unit care, were enrolled into the study. Diagnosis was based on the chlorine sweat test and confirmed by genetic testing. Patients did not present with the signs of acute infection at evaluation, all had stable disease and no prior systemic steroid treatment. Thirty healthy children (9 months to 17 years, median age 10 years) constituted the control group.

Peripheral venous, 5-ml, blood samples were collected from all the subjects to determine the chemerin and cytokines levels. Highly sensitive C-reactive protein (hsCRP), was also tested in all the participants. Anthropometric measurements and bioimpedance analysis were performed for all subjects. Clinical and demographic characteristics of the subjects in the studied and control group are shown in Table 1.

Table 1. Clinical and demographic characteristics of the subjects in the studied and control group.

	CF patients (n=72) median (range)	Healthy controls (n=30) median (range)
Age	9.4 years (9 months–18 years)	10 years (9 months–17 years)
Sex	girls n=40 (55%) boys n=32 (45%)	girls n=12 (40%) boys n=18 (60%
BMI percentile	34 (1–97)	66.5 (1–98)
BMI SDS	–0.39 (–2.32±1.88)	0.42 (–2.32±2.05)
FM% (anthropometric)	23.38 (8.54–42.86)	30.9 (17.74–55.62)
FFM% (anthropometric)	76.6 (57.13–91.45)	69.0 (44.37–82.25)
FM% BIA	16.21 (7.11–35.44)	17.93 (3.8–34.55)
FFM% BIA	83.73 (2.64–91.08)	82.06 (66.5–96.21)
<1.5SD	N=11 (15%)	N=3 (10%)
hsCRP	0.39 mg/l (0.2–31.79)	0.36 (0.2–6.25)
Stool elastase 1	15 µg/g (5-421)	Not performed
Cystic fibrosis mutations	ΔF508 N=65 nonΔF508 N=7	Not applicable

METHODS

Nutritional status. The following parameters were used to evaluate nutritional status: BMI, the percentage of body fat (FM%) and fat free mass percentage (FFM%).

BMI was expressed as BMI percentile (BMI pc) and as standard deviation score (SDS). Nutrition of all patients was assessed according to the WHO criteria (World Health Organization, 2006). As only 4 patients in the studied group presented with malnutrition in this meaning finally, for the purpose of presented analysis the subjects demonstrating BMI<1.5 SD were regarded as undernourished.

FM% and FFM% were assessed based on both: the anthropometric and bio-impedance analysis. Anthropometry was performed using skinfold thickness measurements and standard equations, as described by Slaughter (Slaughter *et al.*, 1998).

Bioimpedance analysis (BIA) was applied using the Maltron model BIO SCAN 920-2.

Cytokines and chemerin. Serum samples from subjects (72 patients with CF and 30 healthy controls) were tested with commercially available enzyme-linked immunosorbent assays (ELISA) for IL-1b, IL-6, TNFα, IL-10 (R&D Systems, USA) and for chemerin (Merck Millpore, Germany) in line with the manufacturer's instructions.

Statistics. The significance of differences between the studied and control groups was verified with Mann-Whitney U-test. Correlation analysis was performed by Spearman rank sum test. Chi square test was used to search for associations between categorical variables. The results of all tests were considered significant at $p<0.05$. All analyses were performed with Statistica 10 software (Stat Soft. Inc., USA).

Ethics. The protocol of the study was approved by an independent institutional bioethical board. The study was conducted according to the principles of the Declaration of Helsinki. Informed consent was obtained from legal guardians of all the study participants and from patients older than 15 years.

RESULTS

Nutritional status

We found a statistically significant difference for BMI, BMI pc, FM% and FFM% between the studied and the control group. BMI, BMI pc and FM% was

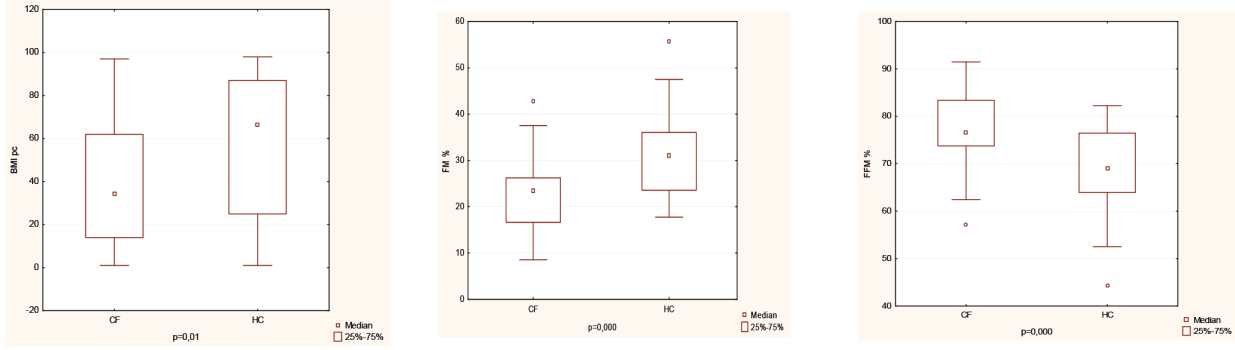

Figure 1. Differences between parameters of nutritional status between the studied group of cystic fibrosis patients (CF) and healthy controls (HC).
BMI pc, body mass index percentile; FM%, fat mass percentage measured by anthropometry; FFM%, fat free mass percentage measured by anthropometry

lower, while FFM% was higher in the studied than in the control group, as shown in Fig. 1.

The differences were noted only for FM% and FFM% determined by the means of anthropometry, while bioimpedance measurements results revealed no statistically significant differences (p=0.29 and p=0.40, respectively).

Only 4 children in the studied group, and 3 in the control group presented with BMI<–2 SD, which is defined as malnutrition according to the WHO criteria (World Health Organization, 2006). BMI<–1.5 SD was found in 11 (15.2%) children with CF, while in the control group the rate of undernourished children amounted to 10% (N=3). The difference was not statistically significant (p=0.56).

Cytokines

Statistically significant differences were demonstrated for all the investigated cytokines: IL-1b, IL-6, TNFα and IL-10, showing higher median concentrations of cytokines in CF patients (Fig. 2).

Chemerin

No statistically significant difference was found between median serum concentration of chemerin in the studied and the control groups (p=0.87).

The relation between cytokines and nutritional status

No statistically significant correlation was found between BMI, BMI percentile, FM%, FFM% and serum cytokines: IL-1b, IL6, TNFα and IL10. Comparing serum cytokine levels between the groups of different BMI:<–1.5 SD and BMI≥–1.5 SD revealed the difference only for IL-6, which was higher in undernourished children (p=0.01) (Table 2).

The relation between chemerin and nutritional status

No statistically significant correlation was found between BMI, BMI percentile, FM%, FFM% and chemerin. The groups of different nutritional status (BMI<–1.5 SD *vs* BMI≥–1.5 SD) did not differ significantly in terms of serum chemerin level (p=0.11) (Table 2).

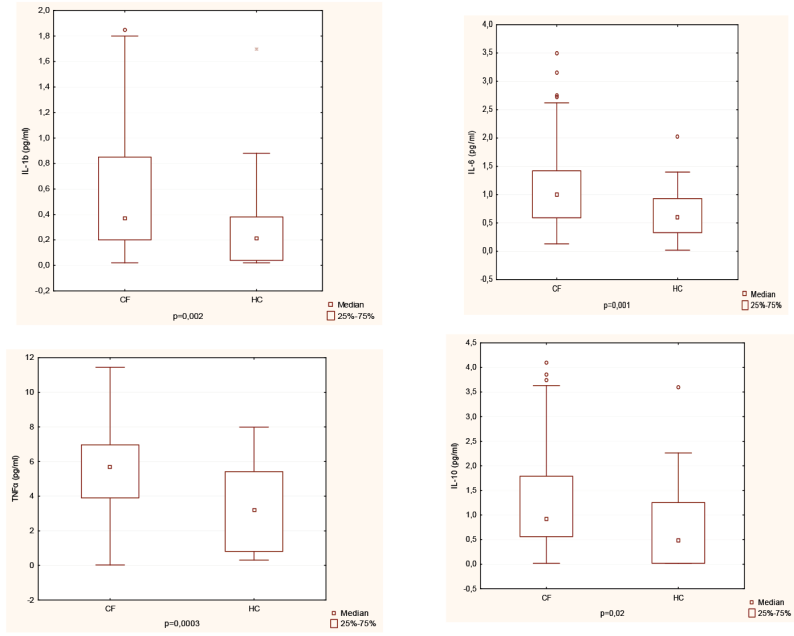

Figure 2. Differences in the levels of cytokines between the studied group of cystic fibrosis patients (CF) and healthy controls (HC).

Table 2. Differences in the investigated parameters: chemerin, interleukin 1b, interleukin 6, tumor necrosis factor α and interleukin 10 between the groups of different nutritional status.

	BMI<–1.5 SDS (N=14) median(range)	BMI≥–1.5SDS (N=88) median(range)	*p*-value
Chemerin	58.89 (44.04–69.84)	49.94 (24.7–103.32)	0.11
Interleukin 1b	0.63 (0.02–1.85)	0.29 (0.02–1.8)	0.05
Interleukin 6	1.52 (0.23–2.72)	0.78 (0.02–6.36)	0.01
TNFα	5.65 (1.49–8.6)	5.07 (0.03–11.45)	0.28
Interleukin 10	0.89 (0.02–4.51)	1.04 (0.02–7.47)	0.99

The relation between chemerin and cytokines

No statistically significant correlation was found between serum chemerin level and inflammatory cytokines: IL 1b, IL-6, and TNFα.

DISCUSSION

Our results confirm the obvious fact that the nutritional status in CF patients is worse than in healthy controls, although the proportion of malnourished children in the studied group is lower than it could have been expected. These findings reflect the progress that has been made during the last two decades in the treatment of cystic fibrosis (Gaskin, 2013). The impact of malnutrition on the course and the prognosis of the disease has been of great interest since it was proven that low BMI in CF was closely implicated in worsening the lung function, predicted worse outcome, and carried a higher risk of death in patients awaiting lung transplant (Steinkamp & Wiedemann, 2002; Belkin *et al*., 2006). Furthermore, improving the nutritional status of malnourished patients may ultimately improve lung function, even in the cohorts with relatively advanced lung disease (Stephenson *et al*., 2013).

Based on these facts, the efforts of clinicians had focused on effective nutritional treatment strategy, what has been also illustrated by our results in a pediatric cohort. We would like to notice that the mentioned differences in the patients' body composition parameters were found only for anthropometric, and not BIA measurements of FM% and FFM%. The discrepancies between those two methods of body composition evaluation have been previously reported and have shown some advantage of anthropometry over bioelectrical impedance in CF patients (Alicandro *et al*., 2015). Consistently with previous results, our study provides further data that proinflammatory cytokines are upregulated in cystic fibrosis (Nicols *et al*., 2008; Courtney *et al*., 2004). We found all the investigated serum cytokine levels to be increased in the CF children, although none of the patients presented with acute infection, and hsCRP was not higher in the studied group when compared to healthy controls. This reflects the well-known fact that the persistent inflammatory state is a characteristic feature of cystic fibrosis, irrespective of the stage of the disease and presence of bacteria in the airways (Courtney *et al*., 2004; Wolter *et al*., 1999). Thus, proinflammatory cytokines can be regarded as inflammatory markers of an ongoing pulmonary progression in CF.

In the study presented here, we did not document statistical correlation between nutritional status and cytokine levels, although inflammatory cytokines are believed to be one of the factors contributing to the disease related malnutrition. However, it is difficult to demonstrate such association, if we realize the complex and multifactorial origin of malnutrition in CF. The role of cytokines as mediators of weight loss and anorexia has been previously proven in studies concerning malignancies, showing apparent relation between the level of IL-6, IL1 and TNF, and neoplasmatic cachexia (Patel & Patel, 2017; Kuroda *et al*., 2007). Comparison between the groups of opposed BMI SDS revealed statistically higher serum IL-6 level in the malnourished patients. Similar results were also presented by Santetti, who reported high level of IL-6 in children with chronic liver disease at nutritional risk (Santetti *et al*., 2015). We have to note that in our study the regarded sample of malnourished children was very small and comprised only 14 subjects presenting BMI<–1.5 SD. This observation needs to be verified in a larger cohort. Our results also showed an increased IL-10 – the main anti -inflammatory cytokine, which has not been so extensively investigated in CF patients. This may reflect the physiological immunoregulatory function of this cytokine in self-limiting of inflammation. This finding may stand in opposition to the opinion of some authors, who claim that proinflammatory-anti- inflammatory imbalance may be responsible for the pulmonary progressive destruction (Saadane *et al*., 2005).

Chemerin, the main parameter investigated here, also appeared to be not corelated with the nutritional status in our cohort. Majority of the studies dealing with this issue concerned adult obese patients and demonstrated relation between chemerin and BMI, waist circumference, as well as multiple components of the metabolic syndrome (Li *et al*., 2014). Results of several investigations confirm these associations also in obese children (Śledzińska *et al*., 2017). In the study presented here, we have aimed to compare malnourished children with the group of children of normal nutritional status, but we documented no statistically significant difference in the chemerin level. It could be expected that chemerin, regarded as a marker of the adipose tissue, should be decreased in children with low BMI. Our results also did not document the relation between chemerin and proinflammatory cytokines, as well as hsCRP, which is inconsistent with previous publications concerning obese children (Landgraf *et al*., 2012; Śledzińska *et al*., 2017). We have to note that cystic fibrosis itself is an inflammatory condition induced by strong local triggers, including detectable and undetectable infection or unproper CFTR gene products, which are the main stimulators of inflammation. Thus, the hypothesized association between chemerin and proinflammatory cytokines is difficult to document.

Discrepancies between our results and previous findings may indicate that the described connections between

chemerin and metabolism, as well as its proinflammatory activity, do not play a prominent role in non-obese patients.

CONCLUSIONS

Our results show that chemerin concentration is not associated with nutritional status in children with cystic fibrosis. Chemerin has no impact on the levels of IL 1b, IL-6, and TNFα in CF patients. IL-1b, IL-6, TNFα, as well as IL-10, are upregulated in cystic fibrosis.

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