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Concentrations of Ghrelin and Leptin in Children with Cystic Fibrosis

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Abstract

Ghrelin and leptin are peptide hormones which, working antagonistically, regulate the energy balance of the body. Abnormal concentrations of these hormones are observed in the course of gastrointestinal diseases, where the clinical picture is characterized by nutritional disorders. Approximately 70% of patients with cystic fibrosis have body weight deficiency due to exocrine pancreatic insufficiency, respiratory failure, and secondary circulatory disorders as well as eating disorders.

The aim of the study was to evaluate the levels of ghrelin and leptin in the blood serum of patients diagnosed with cystic fibrosis, in relation to their nutritional status and function of liver cells.

Patients and methods: The study group consisted of 34 patients, 17 girls (50%) and 17 boys (50%), aged from 3 months to 18 years (mean age 4.5 years) who were diagnosed with cystic fibrosis on the basis of screening and/or diagnostic tests. The analysis included the nutritional status (body weight and height, BMI), CFTR gene mutation, assessment of the exocrine pancreas function (albumin and glucose concentration in the blood serum, acid steatocrit in stool), abnormal lipid metabolism (cholesterol and triglyceride levels in blood serum), as well as liver cell function parameters and cholestasis (serum activity amino-transpherase, gamma-glutamyl transpeptidase, concentration of bile acids, coagulation parameters). In all children, serum ghrelin and leptin levels were measured by means of an *immunoenzymatic* test, using reagents from DRG Instruments. The results were statistically analyzed.

Results: Serum ghrelin levels were significantly lower in the youngest patients (<1 year of age) compared with older age groups. Ghrelin concentration was significantly lower in patients with salt wasting syndrome ($p<0.05$). The statistically lower serum leptin levels were observed in patients with growth deficiency and increased parameters of cholestasis, particularly in the youngest age group.

Conclusion: Ghrelin and leptin levels in children with cystic fibrosis correlate with the nutritional status and can be an early marker of exocrine pancreatic insufficiency.

Keywords: Ghrelin; Leptin; Cystic fibrosis; Children

Introduction

Ghrelin and leptin are peptide hormones which are antagonistic towards each other and thus regulate the energy balance of the body [1-3]. Ghrelin, whose secretion intensifies as the negative energy balance increases, augments the feeling of hunger and reduces energy expenditure [4-6]. Leptin activates the processes responsible for the reduction of energy reserves through the intensification of energy expenditure and a decrease in food intake [3]. Ghrelin affects both the exocrine and endocrine functions of the pancreas and the cardiovascular system. It encourages the motor activity of the stomach, increases the secretion of bile acids, participates in control of the energy balance, and in maintaining the normal physiological processes of sleep and wakefulness. Disorders in the concentration levels of these hormones can be seen in the course of gastrointestinal conditions, where malnutrition is often one of the symptoms [7-9]. It seems that such abnormalities can be observed in children with cystic fibrosis. Insufficient body weight due to the exocrine functions of the pancreas, respiratory failure with secondary circulatory failure and appetite disorders are observed in about 70% of patients with cystic fibrosis. In about 30-40% of children with CF features of damaged liver cells, most commonly in the form of hepatic steatosis, focal or multiple cirrhosis and/or portal hypertension are reported. It appears that liver malfunctions may also have an impact on the functions of the ghrelin-leptin balance [10-13].

Aim of Study

The aim of the study was to assess the concentration levels of ghrelin and leptin in the blood serum of patients with diagnosed cystic fibrosis in relation to their nutritional status and liver functions.

Patients and Methods

The study included 34 patients, 17 girls (50%) and 17 boys (50%), aged from 3 months to 18 years (the average of 4,5 years) with cystic fibrosis diagnosed on the basis of screening tests and/or conducted diagnostic process.

The following subgroups were extracted from the group:

- Subgroup 1-19 patients (19/34 patients – 55.8%), with cystic fibrosis concluded following the screening of newborns (the average age of the test was 13 months)
- Subgroup 2-15 patients (15/34-44.2%) not included in the screening tests and whose cystic fibrosis was diagnosed at a later age, following the diagnostic procedures in the Department (the average age was 7.5 years).

The analysis involved the nutritional status (body weight, height and BMI), assessment of the exocrine functions of the pancreas (level of protein, albumins, the concentration of glucose in the blood serum and acid steatocrit in stool), abnormalities of the lipid profile (levels of cholesterol and triglycerides in the blood serum) and the parameters of

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the damage and functions of the liver (functions of aminotransferases and gamma glutamyl transpeptidase, the concentration of bile acids and the parameters of coagulation). The clinical picture of the patients is shown in Table 1.

The concentration levels of ghrelin and leptin in the blood serum were evaluated in all children through the immunoenzymatic method and using reagents manufactured by DRG Instruments GmbH Germany. The procedures outlined by the producer were followed and the results were given in ng/ml. The benchmark values of ghrelin and leptin were <100 ng/mL. The concentration levels of ghrelin and leptin were analysed depending on the patient's age. Groups of patients aged <1 year, 1-6 years old and over 6 years old were created. The thus obtained results were then analysed statistically. The statistical analysis was conducted following the procedures set forth in the MEdCalc software (v.13). Quantitative variables were presented as the arithmetic mean and standard deviation or median and Interquartile Range (IQR). The quantitative variables are presented as the absolute value and/or the percentage. The normality of distribution has been verified with the Kolmogorov-Smirnov test. The correlation between the quantitative values was assessed based on the Spearman rank correlation and its statistical significance. Intragroup differences have been verified using the Kruskal-Wallis test for quantitative variables and the chi-square test for qualitative valuables. The criterium of statistical significance was $p<0.05$.

The Bioethical Committee of the Silesian Medical University has given its consent to conduct the research.

Results

The concentration of ghrelin was statistically significantly lower in the youngest patients (<1 year) compared with older age groups. (6.63 vs. 9.48 vs. 11.85) $p<0.05$. Also the concentrations of leptin were lower in the subgroups of younger children, however this difference was not statistically significant (Table 2).

Clinical picture	Studied Group N=34	Subgroup 1- Patients Who Underwent Screening Tests N=19	Subgroup 2- Patients Who Did Not Undergo Screening Tests N=15
Average age	4.5 years	13 months	7.5 years
Mutation			
F508del/F508del	22/34 (64.7%)	11/19 (57.8%)	11/15 (73.3%)
F508del/another	6/34 (17.65%)	5/19 (26.3%)	1/15 (6.7%)
Other	6/34 (17.65%)	3/19 (15.9%)	3/15 (20%)
Gender			
distribution F/M	17/17	9/10	8/7
Pancreatic failure	31/34 (91.2%)	17/19 (89.5%)	14/15 (93.3%)
Deficiency body weight	20/34 (58.8%)	10/19 (52.6%)	10/15 (66.6%)
Symptoms from the respiratory tract	23/34 (67.6%)	9/19 (47.4%)	14/15 (93.3%)
Damage to the liver	16/34 (47.5%)	10/19 (52.6%)	6/15 (40%)
History of *meconium ileus*	5/34 (14.7%)	3/19 (15.8%)	2/15 (13.3%)
Electrolyte disturbances	3/34 (8.8%)	2/19 (10.5%)	1/15 (6.67%)
The Schwachman-Kulczycki scale (average)	76.3	76.8	75.6

Table 1: The clinical picture of the patients.

Age range	Range of concentrations Average concentration of ghrelin (ng/ml)	Range of concentrations Average concentration of leptin (ng/ml)
<1 year	2.8-10.2 (6.63)	2.9-24.3 (6.82)
1-6 years	6.8-14.3 (9.48)	2.4-17.1 (5.28)
>6 years	4.7-42.7 (11.85)	1.2-38.4 (12.8)
All the patients	2.8-42.7 (8.7) $p<0.05$ ($p=0.022$)	1.2-38.4 (10.0)

Table 2: Concentrations of leptin and ghrelin in relation to the age.

No differences between the concentration levels of ghrelin and leptin in the blood serum in relation to the gender and the type of CFTR mutation were shown.

Average concentrations of ghrelin in children with insufficient body weight (low BMI) were higher than in the subgroup with the normal level of nourishment (9.67 vs. 8.7), however, the differences were not statistically significant.

There was a statistically significant correlation between the concentration of ghrelin and the activities of amylase and lipase. Also, low levels of the concentration of ghrelin correlated with low concentrations of the protein and albumins in the blood serum. The concentration of ghrelin was also significantly statistically lower in patients with salt-wasting syndrome ($p<0.05$).

Differences between the concentration of leptin and elevated activities of GGTP and height insufficiencies were close to being significant ($p=0.06$ i $p=0.09$) (Table 3).

Overview and Discussion

Ghrelin is produced mainly by the endocrine cells of the fundus of the stomach and is directly secreted into the bloodstream. The most important function of ghrelin is the regulation of energy homeostasis, which is an indicator of insufficient energy levels. The secretion of ghrelin increases when the energy balance is negative, during the process of food deprivation, before meals, during cachexia and at night. A lowered concentration of ghrelin occurs when the energy balance is positive in the course of obesity, food intake and/or hyperglycaemia. The level of ghrelin in blood plasma is correlated with the level of leptin. During the period of food deprivation the level of ghrelin in blood plasma increases while the level of leptin decreases. This process reverses during food intake [1,2,7,14]. The quality of food is of importance. The concentration of ghrelin drops more after carbohydrates rather than fats, while food poor in protein results in its increase. Ghrelin participates actively in glucose transformations; it integrates the hormonal and metabolic response to lower food intake, and prevents the development of diabetes. It also increases the amount of fatty tissue by stimulating adiposeness, reducing lipolysis and affecting the distribution of fatty tissue [7,15]. In our patients with diagnosed cystic fibrosis, we showed higher average concentrations of ghrelin in the blood serum in those patients with insufficient body mass, especially in the oldest age group. Ghrelin produced in the stomach plays the main role in regulating the secretion of growth hormone and food intake. It increases the secretion of bile acid and accelerates the emptying of the stomach through the activation of the vagus nerve. Therefore, the concentration of ghrelin could be expected to rise in the patients with cystic fibrosis, where the loss of appetite resulting from respiratory and circulatory failure is very often observed. Perhaps it acts protectively before the occurrence of the DIOS syndrome in patients with cystic fibrosis [2,6,9]. The observed lower concentration of ghrelin in patients with an elevated activity of lipase and lower activities of amylase is likely to be related to progressing pancreatic insufficiency.

Clinical picture	Number	Average concentration of ghrelin (ng/ml)	Average concentration of lepin (ng/ml)
Pancreatic failure	31/34 (91.2%)	8.51 NS	10.2 NS
Insufficient body weight	14/34 (41.2%)	9.67 NS	9.18 NS
Symptoms from the respiratory tract	23/34 (67.6%)	9.13 NS	9.65 NS
History of econium ileus	5/34 (14.7%)	8.64 NS	10.3 NS
Salt-wasting Syndrome	3/34 (8.8%)	4.0 p=0.04	6.4 NS
Elevated activities of alanine aminotransferase	16/34 (47%)	8.81 NS	8.14 NS
Elevated concentration of bilirubin	7/34 (20.5%)	10.94 NS	8.33 NS
Elevated activity of GGTP	13/34 (38.2%)	7.42 NS	7.65 p=0.06
Elevated concentration of bile acids	10/29 (34.5%)	6.75 NS	10.22 NS
Elevated concentration of lipase	15/34 (44.1%)	5.78 P=0.052	8.08 NS
Lowered concentration of protein in the blood serum	11/34 (32.3%)	5.75 p=0.051	9.4 NS
Lowered concentration of albumins in the blood serum	5/34 (14.7%)	5.14 p<0.05	7.82 NS
Abnormal concentration of cholesterol	3/34 (8.8%)	5.33 NS	10.9 NS

Table 3: Concentrations of ghrelin and leptin with regard to the clinical symptoms and selected biochemical parameters.

The occurrence of low concentrations of ghrelin in our patients with decreased concentrations of protein, albumins and cholesterol as the biochemical indicators of undernourishment, and the after-effect of complex regulatory processes of the ghrelin-leptin-adiponectin complex have been puzzling. In her doctorate dissertation Musiol did not conclude any relationship between the concentration of ghrelin and the status of nourishment of patients with tumours of the central nervous system [16]. However, the tendency to higher concentrations of ghrelin in patients with malignant tumours at the beginning and at the end of the treatment was noticeable. In Baumann's research the low level of ghrelin in obese female patients rose as the body mass lowered. Interestingly, in the group of girls with anorexia a high level of ghrelin in the blood serum was reported [17-19].

In the group of the oldest patients with cystic fibrosis, in which the observed eating disorders caused by abnormal digestion and absorption were the highest, the values of ghrelin were the greatest. Additionally, in the children from the youngest age group and included in the screening test, the treatment in the form of pancreatic enzymes and vitamins protecting from significant energy insufficiencies was included from the age of 2 months. This seems to explain the statistically significant lower concentrations of ghrelin.

95% of leptin production takes place in the cells of white adipose tissue but also in the placenta, the stomach, the hypothalamus, the hypophysis, ovaries and skeletal muscles. It acts through the membrane cytoplasmic receptors. The most important role of leptin is the hypothalamic control of body weight. It constitutes the peripheral indicator of satiety and activates an anorexigenic pathway in the arculate nucleus of the hypothalamus and impedes the orexigenic pathway. This results in the suppression of appetite with a simultaneous increase in the pace of peripheral metabolism and thermogenesis [1,8,20]. In patients with cystic fibrosis, in whom insufficient body weight and loss of appetite is often observed low levels of leptin would be expected. In our patients these values did not differ in relation to the status of nourishment (the body mass index and protein and albumin concentrations in the blood serum) (9.18 vs. 10.0). The concentration of leptin is positively related with anthropometric indicators, the concentrations of glucose on an empty stomach, triglycerides, the c-reactive protein and uric acid, and negatively related with the concentration of HDL cholesterol. In our patients these values were not statistically significantly different. Other factors leading to an increase in the level of leptin in blood are oestrogens, glucocorticoids, TNF alpha, II-1 and impaired kidney functions [10,21,22].

Respiratory sufficiency in patients with cystic fibrosis has an impact on their status of nourishment. Peng reported statistically significantly higher concentrations of leptin in obese patients and those with POCHP [23]. In 67% of our patients, we observed symptoms from the respiratory tract; however the levels of ghrelin and leptin in the blood serum were not statistically different in those age groups. Leptin activates the synthesis of nitric oxide, increases its production and the production of cyclooxygenase, thus increasing the submucous blood flow. It regulates immunological processes by stimulating the phagocytosis and the production of pro-inflammatory cytokines in macrophages. Therefore, it acts pro- and anti-inflammatorily. Its concentration elevates under the influence of pro-inflammatory cytokines such as TNF-alpha, II-1and IL-6. It releases the antagonist of II-1 receptor from monocytes [8,10]. Perhaps in CF patients, recurrent / chronic infections of the respiratory tract and/or Pseudomonas Aeruginosa colonisation may be additional factors influencing the levels of ghrelin and leptin [21]. In his study Arumugam did not conclude lower concentrations of leptin in the blood serum of patients with cystic fibrosis compared with the healthy population. He found, however such correlation in relation to the content of fatty tissue [22]. Ghrelin influences not only food intake and growth but also physical activity. In our patients with cystic fibrosis, the physical activity may be lowered by respiratory insufficiency. On the other hand, such patients undergo quite an intensive rehabilitation [7,23]. Cohen showed that the level of ghrelin was elevated only in patients with an acute course of cystic fibrosis and concluded a negative correlation between the level of ghrelin , the function of the lungs and the BMI, and a positive correlation with pro-inflammatory cytokines. Lowered level of leptin, observed in advanced cystic fibrosis positively correlated with BMI and negatively with pro-inflammatory cytokines [10]. It was also shown that hyperopia increases the production of leptin probably through an increased amount of endogenous corticosterone [24]. Interestingly, in cystic fibrosis patients chronic hypoxia is often observed as a result of respiratory insufficiency, which may additionally cause a decrease in the production of leptin. The authors mention extremely low concentrations of leptin in the blood serum in chronic obstructive pulmonary disease and disorders accompanied by the fibrosis of the lung tissue [14,23,24] The same can be seen in the case of the acute course of the inflammatory process in cystic fibrosis.

Additional factors which may contribute to regulating the leptin-ghrelin balance are gastroesophageal reflux disease, diabetes, lesions to the liver and small intestinal bacterial overgrowth. The activity of

ghrelin affects the emptying and motor activity of the stomach, and has prokinetic properties and yet, in the group of CF patients, disorders of the motor activity of the gastrointestinal tract, in severe cases in the form of the DIOS syndrome, are often reported [9,25].

Also damage to the liver is a factor contributing to the status of nourishment. Children with cystic fibrosis and accompanying damage to the liver have a significantly lower weight, shoulder circumference and BMI. Low levels of Linoleic Acid (LA), Docosahexaenoic Acid (DHA) and Docosapentaenoic (DPA) acid, as well as insufficient level of antioxidants are observed in those children. The concentration of ghrelin rises significantly in patients with chronic liver diseases [26-29]. Among our patients with diagnosed cystic fibrosis, elevated parameters of damage to liver cell were observed in just less than half of the patients. High levels of ghrelin were not however seen in blood serum. On the other hand, low levels of ghrelin were observed with high parameters of cholestasis (elevated activity of GTP and high concentrations of bile acids). Leptin hinders the biosynthesis of triacylglycerols in the liver, adipose tissue and also in skeletal muscles, thus lowering the amount of lipids cumulated there. Can it be that leptin may have protective properties against hepatic steatosis in CF patients? In the studied children with elevated levels of damage to the liver cells, we did not report differences in the concentrations of leptin. However, its low levels were observed in patients with elevated parameters of cholestasis. It is known that the intensity of lipogenesis depends on the status of nourishment, the concentration of glucose and cholesterol in blood serum. In the analysed group of patients, abnormal concentrations of cholesterol and TG were concluded in only 9%, mainly in the form of increased levels of cholesterol [30]. El-Shehaby proved that significantly abnormal (higher) levels of ghrelin in patients with hepatic cirrhosis are related to eating and metabolic disorders; while the concentrations of leptin were relatively lower [28]. Elkabbany observed abnormalities in the concentrations of acylated ghrelin in the blood serum of children and adolescents with chronic liver diseases, however they mainly correlated with the nutritional status. Our observations also confirm this data [26,31,32]. Koch observed elevated levels of ghrelin in the blood serum of critically ill patients with acute sepsis – it was a factor for the necessity of hospitalisation in the A&E department [33] Ghrelin acts preventatively against the formation of stones in the area of the gallbladder and bile ducts, which are significantly more common in cystic fibrosis and concern 14-24% of patients. They are particularly common in cachectic patients and those with insufficient levels of essential unsaturated fatty acids, carnitine and choline. It is known that abnormal concentrations of ghrelin and leptin occur very frequently in those conditions [32,34,35] Our patients were not diagnosed with cholelithiasis either the gallbladder or bile ducts.

In our research we proved very low concentrations of ghrelin and leptin in children with accompanying salt-wasting syndrome. The syndrome is facilitated by factors like infancy, delayed diagnosis of cystic fibrosis, fever, advancement of pulmonary lesions or heat stroke in the summer months. The mechanism of those lesions is probably related to abnormalities in corticotropic hormones [9,36].

Both ghrelin and its agonists are hoped to contribute to a safe and effective therapy for cachexia, also in the course of cystic fibrosis. Perhaps in the future, ghrelin will be used in the treatment of disorders of the motor activity of the gastrointestinal tract by causing a prokinetic effect in gastropareses, post-operative occlusions, idiopathic constipation and abnormalities in the gastrointestinal tract, including DIOS [9,37].

Summary

1. Concentration levels of ghrelin and leptin in children with cystic fibrosis correlate with the status of nourishment and may be an early indicator of exocrine pancreatic insufficiency, especially in older children.

2. High levels of ghrelin in the blood serum of patients with cystic fibrosis are more likely secondarily related with undernourishment rather than being caused by the disorders.

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