

The Characteristic of Energy Metabolism Disorders and Its Correction in Children with Celiac Disease

Dustmukhamedova D. Kh., Kamilova A. T.

The Republican Specialized Scientific, Practical Medical Centre of Pediatrics of the Ministry of Health of the Republic of Uzbekistan

Abstract This article presents results of investigations of the disorders of energy metabolism and possibility of its correction with phytoecdysteroid ecdisten in children with celiac disease. Investigation was performed during the period from January 2009 to December 2012 in the Department of Gastroenterology of the RSRPMC of Pediatrics. There were studied 45 children with celiac disease at the age of 3 to 14 years. The investigations performed showed that in patients with celiac there were damaged processes of energy production: the synthesis of ATP and ADP was reduced, increased their ratio, 4-time reduction of LTT and GTT, there has been registered gain of the parameter of the state lactat/pyruvat, that indicated about prevalence of tissue hypoxia in children. In contrast of basic therapy the treatment of patients with celiac disease with use of phytoecdysteroid (ecdisten) decreases in duration of clinical-laboratory symptoms among the patients with celiac disease.

Keywords LTT, GTT, ATP, ADP, Children, Metabolism, Celiac

The significance of the problems connected to chronic bowel diseases is explained by their wide distribution among the children's population, and also by frequency of development of the heavy forms with unfavoured outcomes and unpredictability of the prognosis. The special place among them is occupied by celiac disease, which is most unfavourable in relation to prognosis of disease, characterized by diffusive atrophy of the intestinal mucosa developing due to gluten (protein of cereals) intolerance [1,2,3,4,5,7,18]. The previous researches showed that celiac disease © in children in our region progresses with marked metabolic disorders, that requires correction of these conditions [5].

Now the constant diet free of gluten appeared to be single method of C treatment. The adherence to this very restrictive diet is rather inconvenient because of presence of gluten in the contents of many products. Even at strict keeping to diet involuntary gluten usage fluctuates from several milligrams up to two gr a day [17,20]. The receiving even of such insignificant quantity of gluten induces clinical signs and histological changes, such as atrophy of the intestinal mucosa and increase in intraepithelial lymphocytes [14,22].

Therefore many patients, even if they follow strictly to gluten-free diet they do not reach clinical remission, and thus there is no complete restoration of the intestinal mucosa even on a background of gluten-free diet [15,19].

Thus, only keeping to gluten-free diet is not sufficient for the complete control of a health state of many patients with

celiac disease.

Attempts of revealing of new parts of pathogenesis of the enteric insufficiency and development on their basis of the pathogenic approaches to treatment of this heavy pathology now proceed. Over the last decade in medicine the metabolic direction has been developed intensively with purpose of performance of theoretical and applied analysis of metabolic processes of different levels as a basis or a background for many illnesses. The knowledge about a role of disturbances of the cellular energy metabolism in development of various pathological processes has been actively formed. The key part in this complex are mitochondria which are structures presenting in the cytoplasm of all the cells and performing functions vital for every cell. With the account of abovementioned it is clear, that the disorders of cellular energy metabolism on the basis of which, first of all, the mitochondrial insufficiency is found leading to the wide spectrum of clinical expressions.

The level of adenyly nucleotides, and first of all, ATP, reflecting final stage of energy accumulation in the tissue, may be considered as indicator of energy state of cells. The energy level of tissue is also characterized by the sum of all adenyly nucleotides and their ratio [9].

The fact of confirmation of efficiency of phytoecdysteroids in stimulation of protein-synthesizing processes in the body seems to be important [11]. As the modulators of energy metabolism there are of great interest investigators of the native researchers on use of phytoecdysteroids isolated from *Leuzea carthamoides* and Turkestan lively creature for bioenergy of the liver cell under the conditions of hepatitis characterized first of all by sharp changes in the

mitochondria functioning. [12].

Our researches in vitro [6] present data about obvious dissociation of a respiratory circuit in the suspension of mitochondria in the model of enteral failure in the growing rats. While using Ecdisten as correcting agent it was revealed that practically all parameters of oxidative phosphorylation were nearer to control meanings.

The **purpose** of our research was to prove application of phytoecdisteroid ecdisten for correction of disorders of energy metabolism in celiac disease in children.

1. Materials and Methods

The clinical examinations were carried out in 45 children with celiac disease at the age of 3 till 14 years, the average age was $7,1 \pm 2,3$ years.

The diagnosis of celiac disease was verified on the basis of the positive tests to tissue transglutaminase IgA (increase more 10 times from norms), and results of mucosa biopsy with evaluation of histological changes by March. Diagnosis of celiac disease was made in 26% of patients at the age before 12 months, in 43,5% - before 5 years of life, in 26,0% - to 8 years and in 4,5% of children at the age of above 8 years. In order to study the state of digestion and absorption of the disaccharides there were used tests with glucose - glucose tolerant test (GTT), which were given per orally in dose 1.75 g/kg with the following measurement of glucose content by glucose oxidant method 30 and 60 minutes later. The norm was considered as increase in glycemia for an hour more than 1,1 mmol/l. Measurement of ATP and ADP in the blood serum as performed with use of chromatography on the gas-liquid chromatograph "LKB" (Sweden), with following spectrometry on the SF "BEKMAN". The pyruvic and lactic acids were determined on the biochemical analyzer "Basis Secomam" (France). The contents of pyruvic acid was measured by method of Friedman F. et al [8].

For correction as a preparation improving processes of

oxidative phosphorylation, membrane digestion and absorption in the intestine there was used phytoecdisten as the natural substance of steroid structure isolated from roots of *Leuzea carthamoides*, made by Institute of Chemistry of Plant Substances of the Academy of Sciences of the Republic of Uzbekistan. There were developed the following doses of preparation: 2,5 mg/ kg body weight a day for 14 days taking into account its cumulative effect during a month [6].

For evaluation of the efficacy of preparation in the complex treatment of children with celiac disease in 2 groups of patients: group 1 included 20 children.

Received basic therapy (elimination diet, pancreatic enzymes, probiotics, partial parenteral feeding according to indications), 25 children were selected to the group of patients receiving modified treatment (basic therapy + ecdisten 2,5 mg/kg/day for 14 days). Efficacy of preparation was assessed by clinical manifestations as well as by laboratory investigations reflecting the state of membranous and cavitary hydrolysis and absorption, evaluation of the state of cellular energy by contents of lactic and pyruvic acid, their ratio, quantity of adenyl nucleotides in the blood in 3 months later.

The statistical processing of the received results was performed by a method of Student - Fisher criteria. There was calculated average arithmetic size (M), average mistake (standard mistake - m), and parameter of reliability (P). Size P less than 0,05 is considered as a parameter of reliable distinctions.

2. Results and Their Discussion

The research was carried out during the period since January 2009 till December 2012 in the department of gastroenterology of the Republic Specialized Research Practical Medical Center of Pediatrics. Among the patients with celiac disease the boys were prevailed (54%).

Table 1. The comparative analysis of glycemia gain

Parameter (mmol /l)	Before treatment	Basic therapy	Basic therapy + ecdisten	P	Control (norm)
Glucose tolerant test	$0,5 \pm 0,02$	$0,7 \pm 0,05$	$1,2 \pm 0,04$	<0,001	$1,64 \pm 0,18$
Lactose tolerant test	$0,4 \pm 0,03$	$0,5 \pm 0,05$	$1,0 \pm 0,05$	<0,001	$1,52 \pm 0,12$

Notes. P - reliability of differences of the basic and modified therapy

Table 2. Dynamics of the contents of adenyl nucleotides in the blood plasma of the children with celiac on the basis of treatment with ecdisten

Parameter nMol/l	Control group	Celiac disease					
		Before treatment	PI	Basic therapy	P2	Basic therapy + ecdisten	P3
ATP	$133,36 \pm 5,3$	$118,6 \pm 5,4$	<0,05	$124,52 \pm 6,1$	<0,10	$129,6 \pm 5,9$	<0,10
ADP	$20,22 \pm 4,35$	$11,09 \pm 1,69$	<0,05	$18,1 \pm 2,1$	<0,01	$19,3 \pm 3,2$	<0,01
ATP/ADP	6,6	10,7		6,88		6,71	

Note: PI- reliability of differences between data of control group and celiac disease. P2- reliability of differences between data in group with celiac disease and after basic treatment. P3- reliability of differences between the data of celiac disease and after modified treatment.

Table 3. Dynamics of the contents of pyruvic, lactic acids and oxidative- restoration potential of the system lactic-pyruvic acid

Parameter mg%	Control group	Celiac disease					
		Before treatment	PI	Basic therapy	P2	Basic therapy + ecdisten	P3
lactate	9,04±0,9	10,9±0,9	<0,10	9,56±3,1	<0,10	9,2±2,9	<0,10
pyruvat	0,71±4,1	0,32±1,3	<0,10	0,53±2,1	<0,10	0,65±2,2	<0,10
LPR	238	250		242		240	

Note: PI- reliability of differences between data of control group and celiac disease. P2- reliability of differences between data in group with celiac disease and after basic treatment. P3-reliability of differences between the data of celiac disease and after modified treatment.

The comparative analysis of the parameters of membranous digestion revealed almost 4 -time reduction of LTT and GTT (Table 1). After basic therapy in children there was noted tendency to increase in level of glycemia gained. The modified therapy positively influenced on the parameters of membranous digestion that was confirmed by reliable increase in glycemia gained in children ($P < 0,001$).

During investigation of the contents of adenyl nucleotides in the blood plasma in the patients with celiac there was revealed reduction of the ATP content in comparison with control group, respectively $118,6 \pm 4,53$ nMol/l in norm $133,36 \pm 5,3$ nMol/l. Reduction of the ADP parameters was more significant ($11,93 \pm 2,3$ in norm $20,2 \pm 4,3$ nMol/l), that indicated not only about disorder about production ADP, but about transport mechanisms of cellular membranes. In group of children with celiac disease there was found increase in coefficient of the ratio ATP and ADP (ATF/ADF): this coefficient was 10,7 in norm 6,6 (Table 2).

After performance of basic therapy for celiac disease there was noted tendency for increase in the contents of ATP ($P < 0,10$) in blood plasma. Reliable increase in this parameter we noted only after use of modified complex treatment, however without achievement of control value. The same pattern we observed in relation to ADP in the blood serum. Under the effect of the modified complex treatment coefficient ATP and ADP reduced to normal values ($P < 0,01$): this coefficient was 6,71 in norm 6,6.

Investigation of the state of glycolytic processes in the body included: determination of lactic acid, pyruvic acid in the blood serum, oxidative-restoration potential of the system lactic-pyruvic acids.

In the celiac disease in children there were registered disorders in the energy metabolism, that is characterized by change of ratio between aerobic and anaerobic processes. In the patients activation of anaerobic processes is suggested due to accumulation in the blood of the glycolysis product, that is lactic acid to $10,9 \pm 0,9$ mg% in norm $9,04 \pm 0,9$ mg%. The content of pyruvic acid in children was 2 time lower than the control ($0,32 \pm 0,03$ mg%, in norm $0,71 \pm 0,02$ mg%, respectively) There is found increase in coefficient of the ratio of lactic and pyruvic acid (LPR): it accounted $250,2 \pm 2,1$ mB in norm $238 \pm 2,5$ mB (Table 3). Increase in parameters of glycolysis processes may indicate about activation of anaerobic way of energy producing as compensatory reactions to reduction of oxidative processes.

Increase in concentration of lactic acid in the studied children may be connected not only with intensification of glycolytic processes, but also with disorder of resynthesis of lactic acid into glycogen in the liver.

The results presented in the table showed that the contents of lactic acid in the blood serum after performance of basic therapy remained at the initial level. The reliable increase in this parameter was found after carrying of modified treatment. After basic therapy in these parameters there was noted positive dynamics, and after complex therapy the reliable improvement in the LPR.

In the literature there are single works reflecting a state of energy metabolism in the patients with celiac disease. A. Lemer, N. Gruener and coauthors suggested that [21], that C can be considered as the reason of camitin insufficiency.

The researches of Francoise Briet etc. [16] showed reduction of the activity of 1 complex of respiratory chain in the patients with chronic inflammatory intestinal diseases on the background of insufficient nutrition. The author suggested that mitochondrial insufficiency of 1 complex of respiratory chain, established in the mononuclears from the peripheral blood appeared to be marker of insufficiency nutrition.

The description of a case of atrophie of the small intestine in an infant at the age of 5 months is presented by Bonnemains S. and co-authors [13]. Diet without milk and gluten was not effective, but research of activity of 1, 111 and V complexes of a respiratory circuit was sharply reduced, that testifies to comparability of mitochondrial exhaustion with enteral insufficiency.

Nearly the same results were received at experimental researches of Nieto N. and co-authors [23]. The purpose of the research performed, was to estimate influence of serious undereating of protein on the antioxidative system of protection in the small and large intestine in the rats. The results have shown that chronic diarrhea and serious under eating of protein promoted suppression c antioxidizing system of protection both in small and in large intestine, w hich can play the important role in the pathogenesis of given pathology and maintenance of a v.cious circle of malabsorption-diarrhea-malnutrition in an infancy.

Thus, in the patients with celiac disease the processes of energy producing were damaged: the synthesis of ATP and ADP was reduced, and the ratio was increased. It is possible to assume, that chronic enteral insufficiency in the patients is

accompanied by the expressed damage of energy metabolism, both at a stage of oxidative phosphorylation, and at a stage of ADP transferring through cellular membrane by hydrogen ions. The disturbance of energy metabolism has unfavourable effect on all synthetic activity of the body because synthesis of any substance is accompanied by energy expenditure [10]. On one hand deficiency of energy production leads to damage of absorption in the intestine of the main food ingredients, on the other hand, damage of absorption results in negative shifts in the energy metabolism.

In children with enteral insufficiency there is established the gain of parameter of the state lactate/pyruvat, that testifies to prevalence of tissue hypoxia in children, that evidently connected to duration of the pathological process.

As against basic therapy the treatment of the patients with enteral insufficiency with use of phytoecdysteroid (ecdisten) reduces duration of clinical- laboratory symptoms among the patients with celiac disease.

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