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ASSOCIATION OF THE INDICES OF CIRCULATING LEPTIN WITH GASTRITIS CLINICAL MORPHOLOGICAL SIGNS DEPENDING ON BODY MASS INDEX IN SCHOOLCHILDREN WITHOUT OBESITY

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ABSTRACT

Aim: to study the association of leptin circulating in blood with gastritis clinical morphological signs in schoolchildren with normal and excessive body mass index.

Materials and methods: we have examined 46 schoolchildren with gastric intestinal complaints, patients of Gastroenterologic Division with preliminary diagnosed gastritis, followed by morphological tests, which confirmed the diagnosis in all the children. There were two cohorts of the subjects: with normal body mass (1st cohort, n = 31), with excessive body mass (2nd cohort, n = 15). All the subjects have passed: gastroscopy, including biopsy sampling, identification of the level of leptin circulating in blood serum by immune enzyme method fasting.

Results: The analysis of the results of the tests showed the increase of leptin level in schoolchildren in the 1st cohort with the clinical signs of dyspepsia (2.2 (0.1 – 8.4) ng/ml as compared to 0.1 (0.1 – 0.1) ng/ml in children without dyspeptic complaints; p = 0.443), that proves the strengthening of the hormone regulating role. At the same time the dynamics of leptin indices and their association with destructive changes in gastric mucosa, gastritis activity and *Helicobacter pylori* infection hadn't been marked. In the 2nd cohort no associations with gastritis clinical morphologic signs had been revealed. Besides, in the schoolchildren of the 2nd cohort we didn't find any increase of the level of circulating leptin in the presence of dyspepsia clinical sympathocomplex. That is why in the 2nd cohort the level of leptin in blood serum was considerably higher, than in the 1st cohort.

Conclusion: In children with excessive body mass the gastritis and associated pathologic processes in gastric mucosa are being formed and developed under the conditions of hyperleptinemia, because the level of its secretion into blood substantially depends on the volume of fat tissue in an organism. Leptin involvement and the strengthening of its regulating role, which is determined in children with normal body mass with dyspeptic symptoms are balanced under the conditions of the increase of fat tissue quantity in an organism.

Keywords: leptin, dyspepsia, gastritis, children, *Helicobacter pylori*, body mass index.

During the last years the list of the factors which considerably influence the course of gastroduodenal diseases involve obesity [15, 18]. In different regions of Russian Federation from 45 to 62 % of adult population suffer from obesity or overweight. The prevalence of obesity and overweight in Russia is rather high, but this index is different in different populations [5]. Among children the index is lower and it is 5.6 % (obesity) and 19.9 % (overweight) on average with considerable variations in accordance with gender and age [9]. Traditional understanding of the functions of fat tissue in an organism had changed. Active role of adipocytes of fat tissue in the synthesis of many peptides had been determined, including those with hormone activity. One of them is leptin [7, 17], a hormone, which has wide functional application in an organism [20]. Up to the present moment it has been shown that in addition to the control over nutrition behavior this hormone (leptin) influences the state of central nerve system, it also influences pancreatic gland, kidneys, immune and sympathetic nerve system. High level of leptin in plasma is accompanied by the activation of sympathetic nerve system, endothelial dysfunction, oxidative stress and so on [20]. The level of the indices of leptin which circulates in blood is associated with the volume of fat tissue in an organism [6]. During the last years scientists have marked negative influence of obesity on the development of diseases, including those of digestive tract [18] with hyperleptinemia as pathogenetic link. Now its role in the gastric cancer development is being actively studied [15, 18]. At the same time many aspects of hyperleptinemia association with digestive tract diseases are not studied well-enough.

Considering regulatory role of leptin, including pathology processes, definite interest is paid to the issues related to the association of circulating hormone with dyspepsia, pathophysiologic mechanisms of many aspects of its formation are still not clear [3, 8]. The data in regard to the ratio blood leptin indices/ gastritis clinical morphological signs in children, especially on the initial stage of gastritis formation in association with body mass. These became the basis for carrying out the present research.

Aim: search for the association of circulating leptin with gastritis clinical morphologic signs in schoolchildren with normal and excessive body mass index.

Materials and Methods. We carried out clinical examination for 46 schoolchildren, all of them being the patients of Gastroenterology Division including interviewing in regard to dyspeptic complaints. Tests had been carried out in the Clinical Division of «Scientific Research Institute for Medical Problems of the North» with the permission of ethics authorities. All the patients who took part in the research had signed the informed concern form related to the experiment in accordance with World Medical Association's Declaration of Helsinki, regularizing scientific research.

All the children have been performed gastroscopy with biopsy sampling from the antrum of the stomach for morphological tests of the mucosa. Gastritis as diagnosis was confirmed by the said tests.

Criteria for the subjects to take part in the research: 1. Gastritis in different forms diagnosed by endoscopic test (erythematosus, nodular, gastritis with erosions), morphologically confirmed; 2. Ages from 7 to 17 years; 3. Absence of acute inflammatory diseases within the last month; 4. Absence of chronic diseases in other systems of an organism in the acute stage; 5. Absence of functional insufficiency in other organs and systems; 6. Conformity with normal body mass index (BMI) and/or excessive body mass.

Criteria for rejecting from the research: 1. Age younger than 7 years or elder than 17 years; 2. Acute diseases of inflammatory genesis within the previous month; 3. Chronic diseases in other systems of an organism in an acute stage; 4. Functional insufficiency in other organs and systems of an organism. 5. BMI is lower than under norm or in obesity.

Taking into account body mass index we have analyzed two cohorts of children: 1st – with normal BMI indices;

2nd – with BMI corresponding to excessive body mass. BMI calculation was carried out using BMI formula = Weight (kg) / Height $(m)^2$ [11]. Gender and age in schoolchildren were the same between cohorts. Evaluation of body mass indices was performed according to corresponding indices, shown in WHO percentile tables and BMI standard deviations. We took into account height, body mass, gender and age of a child. Considering WHO recommendations and in accordance with federal clinical recommendations, obesity in children and adolescents in the ages from 5 to 19 years was identified as BMI equal or over +2.0 SDS BMI, and excessive body mass as BMI from +1.0 to +2.0 SDS BMI [1, 4, 16].

The majority of the examined children with gastritis (82.6 %) showed dyspepsia clinical signs. The presence of dyspepsia syndrome (non-examined dyspepsia) was evaluated when there were complaints related to pain or discomfort feeling in epigastrium, nearer to median line. When estimating clinical course of dyspepsia we used the variants offered by Rome criteria. We recognized two variants of the course of the disease: 1) syndrome of epigastric pain – when schoolchildren had pains or burning sensations in epigastrium, without permanent character, which was found in 52.6 % of dyspepsia children; 2) postprandial distress syndrome – when after meals with accustomed quantity of food children fell postprandial fullness in epigastrium or early saturation, which were found in 47.4 % of the children with dyspeptic complaints [13]. The present research didn't touch gastrointestinal tract functional disorders according to Rome criteria, because all the children had verified gastritis.

Morphologic tests for bioptats of gastric mucosa involved light microscopy after gematoxyllin-eosin coloring. Gastritis diagnostics was carried out in association with the presence of neutrophil infiltration of epithelium and/or own plates in accordance with Sydney classification, which involves determination of 3 stages in the activity of inflammatory process. The 1st stage matches to moderate leucocyte infiltration of own plates of mucosa. The 2nd stage matches to more expressed infiltration and it covers epithelium in addition to own plates. The 3rd stage matches to expressed infiltration and in addition «abscesses» [2]. According to Modified Sydney Classification we estimated the presence of atrophic gastritis [12]. We haven't found any cases among the examined subjects. *H. pylori* presence was determined after the Gimza coloring of biopsy sections of antral mucosa [2].

In all the children, involved into the research, we identified the concentration of leptin in blood serum. Blood sampling for determining the concentration of circulating leptin was performed from 8 to 10 hours a.m. after night fasting. Leptin content in blood serum was calculated by immune enzyme method with the help of manual pad using the set of chemical agents Human Adiponectin ELISA, producer BioVendor. Leptin indices in the samples have been defined according to the producer's instructions. Leptin indices in children and adolescents didn't exceed the reference meanings separately for boys and girls in four age groups (6-9 years, 9-12 years, 12-15 years, 15-20 years).

Statistical analysis of the results was carried out with the help of program pack Statistica 6.1 (StatSoft, the USA). Checking for the distribution of the indices with the help of Shapiro – Wilks test showed their distinctions as compared to the norm, which caused the implementation of non-parametric methods of statistics. Cohorts were compared with the help of Mann-Whitney criterion. Statistical meaningfulness of the differences between the signs was evaluated under $p<0.05$ [10].

Results and discussions. Our findings show that the indices of leprin circulating in blood were considerably higher in children with excessive body mass (25.8 (13.9 – 43.5) ng/ml) as compared to the children with normal body mass (0.1 (0.1 – 6.5) ng/ml; p= 0.0001). This is quite explainable because at present it is well-known that leptin producers are adipocytes and the level of hormone, which secrets into an organism is directly associated with fat tissue mass. It is very important to mark that as a whole children with excessive body mass show wider fluctuations of leptin indices (from 0.1 to 52.6 (ng/ml)). There is scientific data specifying that as a rule obese subjects demonstrate insulin-resistance, which allows supposing that the increase and expressed range of the indices of leptin circulating in blood serum in children with excessive body mass can serve as the first sign of the formation of leptin-resistance in a range of them, which is associated with the lowering of slowing down influence of the hormone on appetite with the participation of central mechanisms.

From one side leptin is considered to play regulatory role in regard to physiological processes in an organism by influencing vegetative nerve system. From another side, numerous data had been accumulated related to its pathogenetic role in the formation of gastrointestinal tract diseases. In this connection we have analyzed the results in terms of the association between the level of the hormone circulating in blood and dyspeptic signs, that is with pathologic process. In its formation as it is known, the dysfunction of regulatory mechanisms plays not the last role with nerve system involved. At the same time we haven't found any association between leptin indices and dyspeptic syndrome, both with its presence and clinical course. But, we had some findings after analyzing the issue taking into account weight-height leptinh indices. In particular, in children with normal BMI dyspeptic complaints were associated with the increase of leptin circulating in blood (Table 1). This result proves leptin influence on the pathology in the way of its participation in the neuro-hormone regulation. At the same time in overweight children we didn't mark any association between leptin indices with dyspeptic syndrome. In them the indices of circulating leptin are considerably higher, despite the presence of dyspepsia symptomocomplex and its clinical course. That is why we didn't find any increase of the meaningfulness of leptin hormone regulation in an organism in excessive body mass children with dyspeptic syndrome, which is probably explained by its excessive production by fat tissue. So, leptin participation in the regulation of pathology process, which is the basis of dyspeptic syndrome in children, is associated with body mass. This can cause peculiarities in the risks of the formation and clinical course of pathology process in the subjects with different body mass. Taking into account leptin metabolic effect in the subjects with excessive fat tissue, its influence can be distributed to morphologic-functional state of a stomach, including its mucosa, but in the long-time course, with the formation of metabolic disorders.

Taking into account new data on the association between circulating leptin indices and carcinogenesis processes, it becomes very important to pay attention to the association between its level and gastric activity, *H. pylori* infection, which are considered to be ethiopathogenic links in the formation, atrophy and metaplasia of gastric mucosa, each with the meaningful influence upon the named processes. We believe those data is of interest in terms of the age, including childhood and adolescence period in the life of individuals.

Association of blood leptin with gastritis (gastritis forms and macro morpho-

Table 1

Leptin level in blood in children due to the presence of dyspeptic complaints

Children		Leptin level						p1-2
		Normal BM		Excessive body mass		Total		
		n	Me (C25-C75)	n	Me (C25-C75)	n	Me (C25-C75)	
1. Without dyspepsia syndrome		7	0,1 (0,1-0,1)	1	52,6 (52,6-52,6)	8	0,1 (0,1-1,5)	
2. With dyspepsia syndrome		24	2,2 (0,1-8,4)	14	22,9 (13,9-35,2)	38	6,3 (0,1-20,1)	0,0003
Clinical course	Epigastric pain syndrome	14	0,5 (0,1-6,5)	6	28,5 (3,3-33,5)	20	3,0 (0,1-18,0)	0,0087
	Postprandial distress-syndrome	10	3,3 (0,1-15,2)	8	18,8 (14,7-39,9)	18	14,6 (2,2-20,1)	0,0266
P1-2	0,0443		0,0466					
P3-4	0,2847	0,9497	0,206					

logic changes in endoscopic tests) hasn't been revealed (Table 2).

The most actual moment in the analysis of the results of our study was the evaluation of the association between the level of leptin circulating in blood with the activity of inflammatory process in stomach mucosa, because it is high activity, which to a large degree causes unfavorable gastritis course. When analyzing the obtained data we haven't found any association between the two parameters (Table. 3). At the same time gastritis, which is the start of carcinogenesis, in children with deviations in height-weight indices in the stage of excessive body mass is developing under the conditions of the expressed liptinemia, which can contribute to the formation of atrophic changes in stomach mucosa. But critical level of hyperleptinemia and its duration, when cancer morphologic changes can be expected in stomach mucosa.

There is scientific data specifying that obesity increases the risk of stomach cancer diseases development, first of all it concerns atrophic gastritis, but the mechanisms of this association are still unclear to great extent. Nevertheless leptin involvement is demonstrated in the range of scientific works. So, some research with the implementation of experimental models had demonstrated that lipotoxicity is the factor of pre-cancer disorders, accompanied by the disturbance of organelle homeostasis, tissue integrity and the change in gene expression of stemness of stomach epithelium. As a result it was characterized by atrophic changes in gastric mucosa [15, 18].

It is likely that in addition to immune response in the time of the development of progressive inflammatory process, there can also exist metabolic aspects in the formation of atrophy in the stomach mucosa, by which leptin realizes its effect towards carcinogenesis risks, in the first turn under the conditions of hyperleptinemia. Unquestionably those points of view require proof and further studies.

In the course of the study we also didn't mark any association of the level of circulating leptin with *Helicobacter pylori (H. pylori)* infection in children both with normal and excessive body mass (Table 4). Pathogenic role of *H. pylori* bacteria in the formation of atrophic processes is a proven fact. Besides it is categorized as a factor, activating carcinogenesis process [14]. In this connection both infection and leptin are regarded as active participants of pathophysiological process of gastric carcinogenesis. However various research aimed at studying leptin involvement into the course and progress of infection-associated gastritis in adults show controversial results [19].

Undoubtedly all the above listed to greater extent concerns the issues of carcinogenesis in subjects with obesity. At the same time leptin production in gastritis in patients without obesity has not been studied enough. The data on the hormone influence on the gastritis course, especially on its progressing, would assist in the understanding of its pathophysiological role in carcinogenesis. In children this issue has not been studied as well. But to our minds, it is particularly relevant as pathology process is not from its source. While analyzing the results of our research aimed at the association of leptin level with gastritis clinical morphologic signs we marked that in children leptin influence on gastritis clinical morphological signs to great extent concerns regular processes. In this respect the evaluation of leptin involvement in hormone regulation of this or that pathological or physiological process in organism is difficult, because the level of its secretion into blood considerably depends from the volume of fat tissue in an organism [6, 7]. Certainly the issue requires further consideration.

Conclusion. Gastritis children with dyspeptic complains show increased level of leptin in blood plasma, which can be explained by its regulating influence on vegetative nerve system and this relates to normal BMI only. Whereas the association of leptin indices with gastritis morphologic forms, its activity and *H. pylori* infection has not been found. In this context gastritis, which is the starting point of carcinogenesis in children with deviations related to height-weight parameters in the stage of excessive body mass is developing under the conditions of hyperleptinemia. Nevertheless there is no data available on hyperleptinemia level and duration, which could be regarded as critical for expecting pre-cancer morphological changes in gastric mucosa. Clear-

Table 2

Association of blood leptin indices with gastritis endoscopic forms

Children	Gastritis with erosions		Non-erosive gastritis forms (erythematosus + nodular)		p1-2
	n	Me (C25-C75)	n	Me (C25-C75)	
1. With excessive body mass	3	25,8 (15,4-49,1)	12	25,7 (8,6-39,4)	0,7341
2. With normal body mass	7	0,9 (0,1-3,5)	24	0,1 (0,1-6,6)	0,9448
3. Total	10	2,9 (0,1-15,4)	36	3,2 (0,1-18,8)	0,9895
p1-2	0,0167		0,0004		

Table 3

Association of blood leptin indices with the activities of antral gastritis in children

Children	Activity at 1st stage	Activity at 2nd – 3rd stages	p1-2		
	n	Me (C25-C75)	n	Me (C25-C75)	
1. With excessive body mass	6	38,5 (17,4-49,1)	9	22,9 (9,4-33,2)	0,2284
2. With normal body mass	10	0,5 (0,1-6,5)	21	2,2 (0,1-6,6)	0,7992
3. Total	16	10,2 (0,1-31,9)	30	3,1 (0,1-15,4)	0,4266
p1-2	0,0008	0,0008			

Table 4

Association of leptin indices in blood in *H. pylori* children

Children	*H. pylori* +	*H. pylori* -	p1-2		
	n	Me (C25-C75)	n	Me (C25-C75)	
With excessive BM	8	17,8 (8,6-30,5)	7	33,5 (17,4-49,1)	0,2319
with normal BM	18	0,1 (0,1-3,1)	13	0,9 (0,1-10,2)	0,4175
Total	26	2,8 (0,1-13,9)	20	8,4 (0,1-30,7)	0,2957
p1-2	0,0006	0,0007			

ly, carrying out further research aimed at meaningful mechanisms of hyperleptinemia influence on carcinogenesis in stomach mucosa is topical.

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A COMPARATIVE ANALYSIS OF THE EXPERIMENTAL INDICATORS OF INTRACUTANEOUS OXYGEN TENSION WITH MICROCIRCULATION PARAMETERS

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ABSTRACT

The article presents the results of the authors' research on the modern possibilities of studying a number of hemodynamic parameters – microcirculation and oxygen tension (PO2) in the skin of the abdomen in rats.

To conduct qualitative and quantitative analysis of microcirculation in experiments on animals using laser Doppler flowmetry and transcutaneous oxygemometer experiments have been performed in 25 mature male rats of Wistar line. The control group consisted of 5 rats. Animals of the experimental group were tired daily for 30 days by forced running from 0.5 to 1.0 hour at a speed of 10-15 km/h. A time of the rats' running on the treadmill depended on the intensity and productivity of their run. On the first day and in 5, 10, 20 and 30 days from the beginning of the experiment microcirculation speed was studied in the skin of the abdomen of the animals after the running load with «Transonic Systems Inc.»(Model BLF21) laser Doppler flowmeter as well as intradermal oxygen tension with Radiometer TCM-2 (Denmark) transcutaneous oxygemometer. It was found that during the experiment in animals of the experimental group the level of intracutaneous oxygen tension was lower than in control animals. It was found that in systematic running load the microcirculation in the skin of the animal's abdomen accelerated up to 10 days from the beginning of the experiment. Then, by 30th day there was a slowdown in the rate of microcirculation. But in all measurements during the experiment it was faster than in animals of the control group. The inverse dependence of PO2 from the rate of microcirculation was revealed, which was expressed by a decrease in the level of intracutaneous PO2 in all cases of increasing the rate of intracutaneous microcirculation.

The study has showed that the study of hemodynamic parameters of experimental animals with the research methods described above is a promising direction of modern physiology. The main advantages of these research methods are noninvasiveness, which provides the possibility of repeated use in the experiment and the implementation of dynamic control over changes in the studied parameters.

Keywords: microcirculation, oxygen tension, experimental study.

Introduction. Interest in the study of hemodynamics in animal experiments involves extrapolating the results to humans. The experimenter has an extensive arsenal of devices that record various parameters of tissue and organ hemodynamics. A particular interest are the devices that make it possible to perform noninvasive methods of hemodynamic studies in organs and systems of laboratory animals in the process of experimental exposure [1, 3, 4, 7, 8]. The simplest, most accessible, and noninvasive hemodynamic studies in animals are performed using Doppler ultrasound scanning [2, 5, 6, 9-11]. In addition, various analyzing systems based on laser Doppler flowmetry are used to study blood microcirculation in laboratory animals, and transcutaneous oxygemometers and polygraphs are used to determine intracutaneous oxygen tension [7, 8]. The choice of a device for the study of hemodynamics in a particular vascular pool depends on the goal of the study and the devices available to the experimentalist recording hemodynamics [5]. This raises the question of the aim of a particular device's use in a particular experimental study. In the literature, these issues are presented insufficiently, so it involves special studies aimed at conducting a comparative analysis of the results obtained with the use of different recording systems.

The aim of the study was to carry out a comparative analysis of intracutaneous oxygen tension indicators with parameters of microcirculation in the skin of the abdomen of the experimental animals.

Materials and methods of research. The study was performed in 20 mature male Wistar rats weighing 280-300 g or more. The control group consisted of 10 rats. Animals of the experimental group were tired daily for 30 days by forced running from 0.5 to 1.0 hour at a speed of 10-15 km/h. A time of the rats' running on the treadmill depended on the intensity and productivity of their run. On the first day and in 5, 10, 20 and 30 days from the beginning of the experiment oxygen tension (PO2) was measured in the animals' skin of the abdomen in the control and experimental groups under general anaesthesia (1% solution of thiopental sodium at the rate of 15 mg/kg of body weight intraperitoneal) in the supine position by means of transcutaneous oxygemometer Radiometer TCM-2 (Denmark) [7], and using «Transonic Systems Inc.»(model BLF21) lazer Doppler flowmeter (LDF) device. Parameters of intracutaneous microcirculation were determined [8].

To determine the PO2 wool in the rat's abdomen was shaved, the skin was treated with soap and water, dried with ether and degreased. The sensor retainer was glued to the skin the cavity of which was filled with a contact gel and sealed with a membrane. Calibration of the device sensor was performed, which was stopped after the appearance of a stable indicator on the display of the device. After the device calibration finishing, the sensor was fixed in the lock and a series of measurements were performed (Fig. 1).

When determining the parameters of intracutaneous microcirculation with the help of LDF, recording of indicators began after a 10-minute adaptation of the animal to an ambient temperature of 20°C. Indications of intracutaneous microcirculation were measured for 5 minutes in the area of the shaved part of the anterior abdominal wall (the site of determining the skin PO2) until a stable value was achieved.

Care of animals was carried out according to the orders regulating the organization of work with use of experimental animals.

Digital data were processed by meth-