

IMBALANCE OF THE HUMORAL COMPONENT OF THE IMMUNE SYSTEM AS A BASIS FOR THE PROGRESSION OF NON-ALCOHOLIC FATTY LIVER DISEASE IN PATIENTS WITH OBESITY AND CONCOMITANT BILIARY TRACT PATHOLOGY

O.Yu. Filippova

Dnipropetrovsk Medical Academy of Health Ministry of Ukraine, Dnipro, Ukraine

e-mail: Filippova-dma@i.ua

ДИСБАЛАНС ГУМОРАЛЬНОЇ ЛАНКИ ІМУННОЇ СИСТЕМИ ЯК ПІДГРУНТЯ ПРОГРЕСУВАННЯ НЕАЛКОГОЛЬНОЇ ЖИРОВОЇ ХВОРОБИ ПЕЧІНКИ У ХВОРИХ З ОЖИРІННЯМ І СУПУТНЬОЮ ПАТОЛОГІЄЮ БІЛІАРНОГО ТРАКТУ

Філіппова О.Ю.

ДЗ «Дніпропетровська медична академія МОЗ України», м. Дніпро

e-mail: Filippova-dma@i.ua

Abstract. The objective of the research was to study the features of the indicators of the humoral component of the immune system depending on the body mass index in patients with non-alcoholic hepatic steatosis, non-alcoholic steatohepatitis, concomitant obesity and biliary tract pathology.

Material and methods. 200 patients with non-alcoholic fatty liver disease, concomitant obesity and biliary tract pathology including 100 patients with non-alcoholic hepatic steatosis and 100 with non-alcoholic steatohepatitis were examined. 70 out of 100 patients with non-alcoholic steatohepatitis had the minimum level of alanine transaminase activity and 30 patients had a moderate alanine transaminase activity. The control group included 30 apparently healthy persons. The body mass index was determined using the Quetelet formula. All the patients with non-alcoholic hepatic steatosis and non-alcoholic steatohepatitis were divided into three groups depending on the increase in the body mass index and the presence of biliary tract pathology. The humoral immune system state was evaluated by the levels of immunoglobulins A, M and G and the content of circulating immune complexes.

Results. In patients with non-alcoholic hepatic steatosis and non-alcoholic steatohepatitis, concomitant obesity and biliary tract pathology, there were observed abnormalities in the humoral component of the immune system with possible increase in the levels of major immunoglobulin classes as well as in the content of circulating immune complexes being more pronounced in patients with non-alcoholic steatohepatitis compared to patients with non-alcoholic hepatic steatosis ($p < 0.05$) and apparently healthy persons ($p < 0.001$). The increase in the body mass index led to a significant increase in the levels of Ig A, M, G and the activation of circulating immune complexes. More significant changes in humoral indices were observed in patients with chronic non-calculous and calculous cholecystitis in the presence of inflammatory biliary tract changes during the exacerbation of the pathology compared to patients who underwent cholecystectomy on the background of the aggravation of postcholecystectomy syndrome.

Conclusions. The obtained data indicated that one of the elements in the pathogenesis of non-alcoholic fatty liver disease with concomitant obesity and biliary tract pathology is a significant change in the indicators of humoral immunity, namely the increase in the levels of Ig (A, M, G) and circulating immune complexes which depend on the clinical form (non-alcoholic hepatic steatosis or non-alcoholic steatohepatitis), increase in the body mass index and the presence of biliary tract comorbidity.

Keywords: non-alcoholic hepatic steatosis; non-alcoholic steatohepatitis; obesity; body mass index; humoral immunity.

Резюме. Мета роботи - вивчити особливості показників гуморальної ланки імунітету залежно від індексу маси тіла (ІМТ) у хворих з неалкогольним стеатозом печінки (НАСП) та неалкогольним стеатогепатитом (НАСГ) у поєднанні з ожирінням (ОЖ) і патологією біліарного тракту (БТ).

Матеріал і методи. Обстежено 200 хворих з неалкогольною жиророю хворобою печінки (НАЖХП) у поєднанні з ОЖ і патологією БТ, в тому числі у 100 хворих – НАСП, у 100 – НАСГ. Зі 100 пацієнтів з НАСГ у 70 спостерігалася мінімальна активність процесу за рівнем аланінової трансамінази, у 30 – помірна активність. Контрольна група – 30 практично здорових осіб (ПЗО). ІМТ визначали за формулою Кетле. Залежно від ступеня збільшення ІМТ та наявності різної патології з боку БТ всі хворі з НАСП чи НАСГ були розподілені на три групи. Стан гуморальної імунної системи оцінювали за рівнем імуноглобулінів класів А, М та G та вмістом циркулюючих імунних комплексів (ЦІК).

Результати. Встановлено, що у хворих з НАСП та НАСГ у поєднанні з ОЖ і патологією БТ спостерігаються виражені порушення з боку гуморальної ланки імунітету з вірогідним підвищенням вмісту основних класів імуноглобулінів і збільшенням вмісту ЦІК і було більш вираженим в групах НАСГ в співставленні з НАСП ($p < 0,05$) та по відношенню до ПЗО ($p < 0,001$). При збільшенні ІМТ фіксувалася виражена реакція зі збільшенням Ig A, M, G і виражена активація ЦІК. При наявності запальних змін у БТ в період загострення патології у хворих з хронічним некалькульозним холециститом та хронічним калькульозним холециститом відбуваються більш істотні вірогідні зміни гуморальних показників, ніж у пацієнтів після проведення холецистектомії на тлі загострення післяхолецистектомічного синдрому.

Висновки. Отримані дані свідчать, що однією з патогенетичних ланок у патогенезі НАЖХП у поєднанні з ОЖ і патологією БТ є суттєва зміна показників гуморального імунітету: збільшення Ig (A, M, G) та ЦІК, які залежать від клінічної форми (НАСП чи НАСГ), збільшення ІМТ та наявності супутньої патології з боку БТ.

Ключові слова: неалкогольний стеатоз печінки, неалкогольний стеатогепатит, ожиріння, індекс маси тіла, гуморальний імунітет.

Problem statement and analysis of the recent research

In recent years, the role of the liver as one of the major organs of the immune system has been widely recognized due to the population of macrophages and killer cells it contains. They are components of the innate immune system [1, 4, 6]. However, the humoral immune response in case of non-alcoholic fatty liver disease (NAFLD) with concomitant obesity (OB) and biliary tract (BT) pathology is insufficiently studied; in the

literature there some data about changes in the liver innate immunity and the role of acquired immunity in the progression of NAFLD [5].

In NAFLD, the process of disease progression is of great importance. Recurrent, and in some cases continuous exacerbations are caused by both humoral [7] and cellular [8] immune disorders. Therefore, the study of the causes and progression mechanisms of fatty liver disease from the

perspective of immunology is one of the relevant problems. The understanding of the disorders of immunological reactivity, which determine the pathological process activity has both diagnostic and prognostic value.

The study of the humoral component of the immune system in patients at different stages of NAFLD has not been conducted and the mechanisms responsible for the development and progression of NAFLD with concomitant OB and BT pathology are not fully understood. There is a need in more detailed study of changes in the humoral immune system caused by immunoregulatory disorders and concomitant NAFLD to improve the efficiency of diagnosing the disease.

The objective of the research was to study the features of the indicators of the humoral component of the immune system depending on the body mass index (BMI) in patients with non-alcoholic hepatic steatosis (NASP), non-alcoholic steatohepatitis (NASH), concomitant OB and BT pathology.

Materials and methods

There were examined 200 patients with NAFLD, concomitant OB and BT pathology, who were hospitalized to the clinic of the Institute of Gastroenterology of NAMS of Ukraine (100 patients with NAHS and 100 patients with NASH). During sonographic or morphological examination of the liver biopate, the signs of hepatic steatosis were detected, including 100 patients with NAHS and 100 with NASH. 70 out of 100 patients with NASH had the minimum level of alanine transaminase activity (min. a.) and 30 patients had a moderate activity (mod. a.) of alanine transaminase. There were 59 (29.5%) males and 141 (70.5%) females. The average age was (52.57 ± 0.79) years. The control group consisted of 30 apparently healthy persons (AHP), compared by age (the average age – 49.4 ± 2.52 years) and sex (8 males – 26.7%, 22 females – 73.3%) with patients of the main groups ($p > 0.05$).

The diagnosis of NAFLD, OB and BT pathology was made according to standardized protocols for diagnosis and treatment of digestive diseases in accordance with the Order of the Ministry of Health of Ukraine of 13.06.2005 No 271 [2], standardized clinical protocols for primary, secondary (specialized) medical care “Non-alcoholic steatohepatitis” [3], ICD-10 and WHO criteria, as well as the World Gastroenterology Organization Global Guidelines (WGO Global Guideline Obesity) [10], on the basis of the patient’s medical history, clinical and instrumental (abdominal ultrasound, intraoperative liver biopsy) examinations with the obligatory consideration of the biochemical parameters and the increase in the level of liver enzymes. The patients included in the study, did not abuse alcohol (consumption < 50 g of ethanol/week by males and < 30 g of ethanol/ week by females during the past year). There were detected no serum markers of viral hepatitis B and C, autoimmune and hereditary liver diseases.

All the patients underwent anthropometric examination: they were weighted on an empty stomach, their height was measured, waist circumference (WC) and hip circumference (HC) were determined. The index of waist-to-hip ratio (WHR) was used to determine the type of body fat distribution. Women with the value of WHR > 0.88 and men with the value of WHR > 0.90 were considered as those having abdominal obesity [10]. The BMI was determined using the Quetelet formula. Depending on the decrease in the BMI, all the patients with OB and NAHS or NASH were divided into six groups: the BMI of 25–29.9 kg/m² – excessive body mass (Group 1 and Group 4); the BMI of 30–34.9 kg/m² – first-degree obesity (Group 2 and Group 5); the BMI of 35–39.9 kg/m² – second-degree obesity (Group 3 and Group 6). Depending on the presence of BT comorbidity, each group of patients with NAHS and OB or NASH with OB was divided into three subgroups: chronic non-calculous cholecystitis (CNC) – subgroups 1a and 2a, chronic calculous cholecystitis (CCC) – subgroups 1b and 2b,

concomitant postcholecystectomy syndrome (PCS) – subgroups 1c and 2c.

The status of the humoral immune system was evaluated by the levels of immunoglobulins A, M and G and the content of circulating immune complexes (CIC). Changes in the levels of immunoglobulins A, M, G in blood serum were determined using radial immunodiffusion (Mancini technique – 1965) [9]. CIC was determined using the method proposed by V. Haskova (1977) [11].

Licensed program STATISTICA 6.1 (No AGAR909E415822FA) was used for statistical analysis. The hypothesis of normal distribution of quantitative data was tested by the Kolmogorov-Smirnov test. The qualitative indices are given as the mean value and the standard error of the mean ($M \pm m$). For comparison of mean values in all subgroups the Student’s t-test was used considering homo- or heteroscedasticity of variances (the Fisher’s exact test) and univariate disperse analysis ANOVA; for comparison of relative indices the Pearson’s chi-squared test (χ^2) was used. To assess the relationship between signs the correlation analysis with the calculation of the Spearman’s rank correlation coefficient (r_s) was performed.

Results and discussion

The immunological examination of the humoral component of the immune system showed that patients with NAFLD and concomitant OB on the background of BT pathology had almost similar changes in the immunological parameters which depended on the presence of NAHS or NASH (Table 1). These changes in the humoral component of the immune system increased with the progression of NAFLD from NAHS to NASH (according to ANOVA from $p_F < 0.05$ to $p_F < 0.001$).

The important indicator of humoral immunity is the content of the immunoglobulins (Ig) A, M and G in blood serum, which reflects the equilibrium between their synthesis and breakdown. Many bacterial products, endotoxins which are formed in hepatobiliary pathology enter the blood circulation as circulating antigens being able to activate the system of humoral immunity [1, 8].

According to the data presented in Table 1, an increased number of A, M, G immunoglobulins was observed in all examined groups. The indicators of IgA in patients with NAHS were 2.70 ± 0.11 g/l and increased by 1.6 times compared to the level of AHP being 1.73 ± 0.20 g/l, while in patients with NASH and min. a. and patients with NASH and mod. a. their level reached 3.16 ± 0.12 g/l and 3.46 ± 0.23 g/l increasing from 1.8 to

Table 1. Indices of humoral immunity in patients with non-alcoholic fatty liver disease, concomitant obesity and biliary tract pathology ($M \pm m$)

Index	AHP, n=30	NAHS, n=100	NASH, n=100		p _F between groups
			NASH, min. a., n=70	NASH, mod. a., n=30	
IgA, g/l	1.73±0.20	2.70±0.11 **	3.16±0.12 ***	3.46±0.23 ***	<0.001
IgM, g/l	1.56±0.12	1.79±0.06 *	2.10±0.07 ***	2.52±0.15 ***	<0.001
IgG, g/l	13.03±0.47	15.05±0.54 *	17.54±0.6 1***	19.82±0.53 ***	<0.001
CIC, optical density units	3.33±0.27	5.39±0.27 **	6.13±0.37 ***	7.03±0.66 ***	0.024

Notes: * – $p < 0.05$; ** – $p < 0.001$ compared to AHP; # – $p < 0.05$ compared to the group of patients with NASH and min. a.; " – $p < 0.05$; "" – $p < 0.001$ compared to the group of patients with NAHS; p_F – level of significance of difference in the indices between groups with NAFLD in total according to univariate disperse analysis ANOVA

2.0 times respectively ($p < 0.001$ for all comparisons). Intergroup comparison showed that the highest IgA levels were detected in patients with NASH and min. a. and patients with NASH and mod. a. with the increase from 1.2 to 1.3 times compared to patients with NAHS ($p < 0.05$ and $p < 0.001$).

The indicators of IgM increased in all observation groups with a minimum increase by 1.15 times in patients with NAHS being 1.79 ± 0.06 g/l compared to 1.56 ± 0.12 g/l in AHP ($p < 0.05$). The maximum level of IgM— 2.52 ± 0.15 g/l was observed in patients with NASH and mod. a. with an increase by 1.6 times as related to AHP ($p < 0.001$), by 1.2 times as related to patients with NASH and min. a. ($p < 0.05$) and by 1.4 times compared to patients with NAHS ($p < 0.001$).

The study of IgG levels demonstrated the increase in this index in all groups of the observation with a tendency to the maximum parameters in patients with NASH and mod. a. The minimal elevation in IgG was observed in patients with NAHS: only by 1.15 times as related to AHP ($p < 0.05$), while patients with NASH and min. a. and patients with NASH and mod. a. had the increase by 1.3 and 1.5 times, respectively ($p < 0.001$). The maximum level of the indicator was observed in patients with NASH and mod. a. (19.82 ± 0.53 g/l) with an increase by 1.3 times compared to patients with NAHS ($p < 0.001$) and 1.13 times compared to patients with NASH and min. a. ($p < 0.05$).

An important function of immunoglobulins is the neutralization of the antigens with the formation of CIC and their subsequent elimination from the body, which is aimed at maintaining the immunological balance [1]. We considered it appropriate to determine the content of CIC in the blood serum as an important component in the pathogenesis of immune destruction in case of concomitant NAFLD.

CIC is a physiological product of the antigen-antibody reaction, which is the part of the protective immune mechanisms. The formation of immune complexes is an integral indicator of developing the humoral immune response [1]. A certain level of immune complexes must be constantly present in the blood for the implementation of physiological processes maintaining homeostasis. Moreover, it indicates an adequate reaction of the organism to external influence [5]. However, it should be noted that in case of excessive accumulation of CIC due to their increased production or insufficient removal from the body, a transition toward the pathology may occur, which is caused by the increase in biological activity of immune complexes which under special conditions play an undeniable role in the pathogenesis of autoimmune processes [8]. In patients with NAHS, the level of CIC increased by 1.6 times comparing to AHP while in patients with NASH and min. a. and patients with NASH and mod. a., it increased by 1.8 and 2.1 times, respectively ($p < 0.001$ for all comparisons). Intergroup comparison showed that the highest values of CIC were observed in patients with NASH and min. a. (6.13 ± 0.37 optical density units) and patients with NASH and mod. a. (7.03 ± 0.66 optical density units) exceeding those in patients with NAHS (5.39 ± 0.27 optical density units) by 1.14 and 1.3 times, respectively ($p < 0.05$ for all comparisons). The increase in serum levels of CIC in patients with NAFLD, concomitant OB and BT pathology was probably associated with the increase in the intensity of their formation and impaired mechanisms of their elimination.

The analysis showed that patients with NAHS and NASH with concomitant OB and BT pathology had the disorders of humoral immunity manifested themselves as a significant increase in the levels of the main immunoglobulins (A, M, G) and CIC content being associated with the increase in the intensity of their formation and impaired mechanisms of their elimination. They were more pronounced in patients with NASH and min. a. and patients with NASH and mod. a. compared to patients with NAHS ($p < 0.05$) and AHP ($p < 0.001$).

The results of the correlation analysis confirmed the aforementioned trends concerning different clinical forms of

NAFLD, namely NAHS and NASH. They led to different degrees of the increase in the level of IgA ($r_s = 0.423$, $p < 0.001$ and $r_s = 0.522$, $p < 0.001$), IgM ($r_s = 0.184$, $p < 0.05$ and $r_s = 0.395$, $p < 0.001$), IgG ($r_s = 0.174$, $p < 0.05$ and $r_s = 0.514$, $p < 0.001$) and CIC ($r_s = 0.375$, $p < 0.001$, and $r_s = 0.493$, $p < 0.001$) compared to AHP.

The comparison of humoral immunity indicators in patients with NAFLD, concomitant OB and BT pathology depending on the BMI allowed ascertaining the fact that the increase in body weight leads to significant changes in Ig A, M, G, and CIC (Table 2).

In Group 1, IgA level increased by 1.3 times only being 2.33 ± 0.18 g/l, compared to AHP - 1.73 ± 0.20 g/l ($p < 0.05$). In Group 2 and Group 3, the increase in IgA was more significant. The indicators were equal to 2.53 ± 0.15 g/l and 3.30 ± 0.20 g/l, i.e. by 1.5 and 1.9 times higher than the data of AHP ($p < 0.001$). The maximum value of IgA was observed in Group 3 with a probable difference by 1.3 and 1.4 times compared to patients of Group 2 and patients of Group 1 ($p < 0.05$ and $p < 0.001$).

Intergroup analysis showed that the highest IgM levels were observed in patients of Group 3 being 2.05 ± 0.10 g/l with an increase by 1.3 times compared to AHP ($p < 0.001$) and patients of Group 1 ($p < 0.001$) and by 1.15 times compared to Group 2 ($p < 0.05$; $p_F = 0.002$).

The maximum value of IgG was observed in patients of Group 3 being 17.61 ± 0.95 g/l with an increase by 1.4 times compared to 13.03 ± 0.47 g/l in AHP ($p < 0.001$) and 13.0 ± 0.90 g/l in patients of Group 1 ($p < 0.001$); with an increase by 1.2 times compared to Group 2— 14.63 ± 0.83 g/l ($p < 0.05$; $p_F = 0.002$).

There was detected a significant increase in CIC in patients of Group 2 and Group 3: 5.80 ± 0.51 optical density units and 6.17 ± 0.39 optical density units with an increase by 1.7 and 1.9 times, respectively compared to AHP with CIC level of 3.33 ± 0.27 optical density units ($p < 0.001$) and increase by 1.4 and 1.5 times, respectively compared to Group 1 with the level of immune complexes of 4.11 ± 0.37 optical density units ($p < 0.05$ and $p < 0.001$).

Similar but more profound changes in humoral immunity were observed in patients with NASH (Table 2). Group indicators of IgA increased compared to AHP in all groups – from 1.7 times in Group 4 to 2.2 times in Group 6 ($p < 0.001$ for all comparisons). The highest level of IgA was observed in Group 6 being 3.81 ± 0.25 g/l with an increase by 1.3 and 1.2 times compared to patients of Group 4 and Group 5 ($p < 0.05$ for all comparisons; $p_F = 0.013$).

IgM indicators in all observed groups significantly exceeded those in AHP ($p < 0.001$). The maximum group increase in IgM by 1.15 times was noted in Group 6; the level of IgM was equal to 2.41 ± 0.12 g/l versus 2.10 ± 0.09 g/l in patients of Group 4 ($p < 0.05$).

Similar trends were observed when studying the concentration of IgG in blood serum of patients with NASH: there was detected a significant increase from 1.3 times in Group 4 to 1.6 times in Group 6 compared to AHP ($p < 0.001$); the maximum value of IgG was detected in Group 6 compared to patients of Group 4 and Group 5 ($p < 0.05$; $p_F = 0.016$).

The increase in CIC parameters in patients with NASH were statistically significant compared to AHP as well. The increase by 1.7 times was detected in Group 4; by 1.9 times – in Group 5; by 2.3 times – in Group 6 ($p < 0.001$ for all comparisons). As in the previous cases, the highest values of immune complexes were detected in patients of Group 6; they increased by 1.3 times compared to patients of Group 4 ($p < 0.05$).

Thus, the conducted research allowed us to detect the features of the humoral responses in patients with NAHS and NASH, concomitant OB and BT pathology, that were dependent on the BMI parameters. The increase in the BMI was found to be accompanied by more pronounced reaction of Ig A, M, G and more significant activation of CIC. The obtained data allowed us to assume a correlation relationship between indicators of humoral immunity and the BMI parameters in patients with comorbid NAFLD and OB on the background of

Table 2. Comparative characteristics of the indicators of humoral immunity in patients with non-alcoholic fatty liver disease, concomitant obesity and biliary tract pathology depending on the body mass index (M±m)

Group	CIC, optical density units	IgA, g/l	IgM, g/l	IgG, g/l	
AHP (n=30)	3.33±0.27	1.73±0.20	1.56±0.12	13.03±0.47	
NAHS	Group 1, BMI - 25-29.9 kg/m ² (n=31)	4.11±0.37	2.33±0.18*	1.54±0.11	13.0±0.90
	Group 2, BMI - 30-34.9 kg/m ² (n=38)	5.80±0.51**#	2.53±0.15**	1.79±0.09#	14.63±0.83
	Group 3, BMI - 35-39.9 kg/m ² (n=31)	6.17±0.39**###	3.30±0.20**##'	2.05±0.10**###'	17.61±0.95**###'
	p _F between groups	0.004	<0.001	0.002	0.002
NASH	Group 4, BMI - 25-29.9 kg/m ² (n=40)	5.67±0.47**	3.02±0.13**	2.10±0.09**	17.29±0.88**
	Group 5, BMI - 30-34.9 kg/m ² (n=37)	6.42±0.53**	3.16±0.19**	2.25±0.12**	17.74±0.65**
	Group 6, BMI - 35-39.9 kg/m ² (n=23)	7.65±0.74**#	3.81±0.25**##'	2.41±0.12**#	20.62±0.64**##'
	p _F between groups	0.066	0.013	0.180	0.016

Notes: * – p<0.05; ** – p<0.001 compared to AHP; # – p<0.05; ## – p<0.001 compared to the group of patients with the BMI of 25-29.9 kg/m²; ' – p<0.05 compared to the group of patients with the BMI of 30-34.9 kg/m²; p_F – level of significance of difference in the indices between groups with different BMI in total according to univariate disperse analysis ANOVA

BT pathology. It was confirmed by the results of the correlation analysis. In particular, in patients with NAHS and NASH, an increase in the BMI resulted in elevated levels of IgA ($r_s=0.323$, $p<0.001$ and $r_s=0.20$, $p<0.05$), IgM ($r_s=0.325$, $p<0.001$ and $r_s=0.189$, $p<0.05$), IgG ($r_s=0.262$, $p<0.01$ and $r_s=0.191$, $p<0.05$) and CIC ($r_s=0.321$, $p<0.001$ and $r_s=0.223$, $p<0.05$), respectively.

Subsequently, we investigated the relationship between the parameters of humoral immunity in patients with NAFL, concomitant OB and BT comorbidity using the comparative analysis (Table 3).

Table 3. Comparative characteristics of humoral immunity indicators in patients with non-alcoholic fatty liver disease and concomitant obesity depending on co-existent biliary tract pathology (M±M)

Group	CIC, optical density units	IgA, g/l	IgM, g/l	IgG, g/l	
AHP (n=30)	3.33±0.27	1.73±0.20	1.56±0.12	13.03±0.47	
NAHS	Subgroup 1a, CNC (n=34)	6.01±0.64**	2.57±0.21*	1.76±0.11	14.54±0.94
	Subgroup 1b, CCC (n=33)	5.53±0.31**	2.95±0.17**	2.0±0.09*	17.13±0.86*#
	Subgroup 1c, PCS (n=33)	4.61±0.32**'	2.60±0.17**	1.63±0.10''	13.47±0.92''
	p _F between groups	0.093	0.279	0.033	0.017
NASH	Subgroup 2a, CNC (n=35)	6.95±0.64**	3.36±0.19**	2.35±0.12**	18.52±0.69*#
	Subgroup 2b, CCC (n=30)	7.02±0.67**	3.33±0.19**	2.16±0.11**	19.49±0.69*#
	Subgroup 2c, PCS (n=35)	5.32±0.31**##'	3.08±0.17**	2.15±0.12**	16.84±0.94*#'
	p _F between groups	0.052	0.494	0.412	0.066

Notes: * – p<0.05; ** – p<0.001 compared to AHP; # – p<0.05; ## – p<0.001 compared to the group of patients with CNC; ' – p<0.05 compared to the group of patients with CCC; p_F – level of significance of difference in the indices between groups with different pathologies of the biliary tract in total according to univariate disperse analysis ANOVA

Among patients with NAHS, the level of IgA increased by 1.5 times in subgroup 1a ($p<0.05$) and subgroup 1c ($p<0.001$) as related to AHP. The highest level of IgA was observed in subgroup 1b. There was an increase by 1.7 times as related to AHP ($p<0.001$).

The indicators of IgM and IgG in patients of subgroup 1a and subgroup 1b were statistically compared to the group of AHP ($p>0.05$ for all comparisons). In case of CCC, the levels of immunoglobulin M and G exceeded those in AHP by 1.3 times ($p<0.05$ and $p<0.001$, respectively); in patients of subgroup 1c, they exceeded the levels by 1.2 and 1.3 times ($p<0.05$).

CIC indicators were the highest in subgroup 1a and subgroup 1b with an increase by 1.8 and 1.7 times compared to AHP ($p<0.001$). Intergroup comparison showed that the lowest intergroup level of immune complexes was observed in subgroup 1c being higher than the normal one by 1.4 times only ($p<0.05$) and significantly different from the values of patients of subgroup 1b ($p<0.05$).

Similar but more significant changes were observed in patients with NASH. Thus, in almost all groups of patients with NASH, IgA levels increased approximately twofold compared to AHP ($p<0.001$ for all comparisons). Almost similar increase in the indicators of IgM (from 1.4 to 1.5 times compared to normal values) was found in all groups of the observation ($p<0.001$ for all comparisons).

The dependence from BT comorbidity was observed when studying intergroup indices of IgG. The highest level was seen in subgroup 2a and subgroup 2b with an increase by 1.4 and 1.5 times compared to AHP ($p<0.001$), while the lowest level was seen in subgroup 2c with an increase by 1.3 times compared to AHP ($p<0.001$) and by 1.2 times compared to patients of subgroup 2b ($p<0.05$).

Similar changes were observed when studying the indicators of CIC. Thus, the highest intergroup level of immune complexes was observed in subgroup 2a and subgroup 2b with an increase by 2.1 times ($p<0.001$) and in subgroup 2c the increase was by 1.6 times only compared to AHP ($p<0.001$) and by 1.3 times as related to subgroup 2a and subgroup 2b ($p<0.05$ for all comparisons).

The comparative intergroup analysis showed that the presence of BT comorbidity resulted in some changes in the immune status of patients with comorbid NAFLD and OB. In the presence of severe inflammatory BT changes during the exacerbation of the pathology, more significant changes in humoral indices were observed in patients with CNC and CCC compared to patients who underwent cholecystectomy on the background of PCS aggravation.

The aforementioned trends concerning the dependence of the degree of changes in the parameters of humoral immunity from concomitant BT pathology in patients with NAHS and NASH were confirmed by the results of the correlation analysis. Particularly, the presence of CNC or CCC in patients with NAHS was found to lead to more increased levels of CIC, immunoglobulin M and immunoglobulin G, rather than the state after laparoscopic cholecystectomy: for CIC ($r_s=0.206$, $p<0.05$), for IgG ($r_s=0.221$, $p<0.05$), for IgM ($r_s=0.201$, $p<0.05$). In patients with NASH: for CIC ($r_s=0.243$, $p<0.05$), for IgG ($r_s=0.218$, $p<0.05$).

Conclusions

Thus, the obtained data indicated that one of the elements in the pathogenesis of NAFLD with concomitant OB and BT pathology is a significant

change in the indicators of humoral immunity, namely the increase in the levels of Ig (A, M, G) and CIC which depend on the clinical form (non-alcoholic hepatic steatosis or non-alcoholic steatohepatitis), increase in the BMI and the presence of BT comorbidity. Changes in the indicators of humoral immunity shows the development of immune deficiency in patients with comorbid NAFLD.

Prospects for further research

The study of the characteristics of T-cell immunity depending on the body weight and BT pathology in patients with comorbid NAFLD, concomitant OB and BT pathology is promising.

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СТАН МІСЦЕВОГО ІМУНІТЕТУ РОТОВОЇ РІДИНИ У ДІТЕЙ ДОШКІЛЬНОГО ВІКУ Череп'юк О.М.

Івано-Франківський національний медичний університет, Івано-Франківськ, Україна

СОСТОЯНИЕ МЕСТНОГО ИММУНИТЕТА РОТОВОЙ ЖИДКОСТИ У ДЕТЕЙ ДОШКОЛЬНОГО ВОЗРАСТА Черепюк Е.Н.

Івано-Франківський національний медичний університет, Івано-Франківськ, Україна

STATE OF LOCAL IMMUNITY OF THE ORAL FLUID IN PRESCHOOL CHILDREN E. N. Cherepiuk

Department of Pediatric Dentistry

Ivano-Frankivsk National Medical University, Ivano-Frankivsk, Ukraine

Резюме. Вміст секреторного імуноглобуліну А та лізоциму визначали у 83 дітей дошкільного віку з різним рівнем інтенсивності карієсу. Встановлено, вміст секреторного імуноглобуліну А та лізоциму в ротовій рідині дітей дошкільного віку з віком збільшується. У дітей у різні вікові періоди з високим рівнем інтенсивності карієсу, концентрація секреторного імуноглобуліну А та лізоциму в ротовій рідині значно нижча, по відношенню до дітей з низьким рівнем інтенсивності карієсу.

Ключові слова: діти, карієс тимчасових зубів, рівень інтенсивності карієсу, імуноглобулін А, лізоцим.

Резюме. Содержание секреторного иммуноглобулина А и лизоцима определяли у 83 детей дошкольного возраста с различным уровнем интенсивности кариеса. Установлено, содержание секреторного иммуноглобулина А и лизоцима в ротовой жидкости дошкольников с возрастом увеличивается. У детей в различные возрастные периоды с высоким уровнем интенсивности кариеса концентрация секреторного иммуноглобулина А и лизоцима в ротовой жидкости значительно ниже, по отношению к детям с низким уровнем интенсивности кариеса.

Ключевые слова: дети, кариес временных зубов, уровень интенсивности кариеса, иммуноглобулин А, лизоцим.

Abstract. The concentration of secretory immunoglobulin А and lysozyme was determined in 83 preschool children with different levels of dental caries intensity. The obtained results indicated the increase in the levels of secretory immunoglobulin А and lysozyme in the oral fluid of preschool children with age. In children with a high level of dental caries intensity, the concentration of secretory immunoglobulin А and lysozyme in the oral fluid was significantly lower compared to children with a low level of dental caries intensity.

Keywords: children; dental caries of deciduous teeth; the level of dental caries intensity; immunoglobulin А; lysozyme.