NON-ALCOHOLIC STEATOHEPATITIS IN PATIENTS WITH OBESITY: INTERCONNECTION BETWEEN BODY MASS, CHANGES OF LIPID METABOLISM AND CONCOMITANT PATHOLOGY OF BILIARY TRACT

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Abstract

Aim. To study the main indices of lipid blood spectrum, which changes lead to DL formation, depending on body mass index (BMI) and concomitant pathology of biliary tract in patients with NASH and obesity.

Materials and methods. There were examined 100 patients with NASH in combination with obesity and BT pathology, in which during sonographic or morphological study of biopat of the liver were revealed the signs of hepatic steatosis. Among patients were 40 men and 60 women. The mean age of patients – (54,68±1,15) years old. The control group included 20 practically healthy persons (PHP).

BMI was determined by Quetelet formula. Depending of the degree of BMI increase all patients with NASH and obesity were divided into three groups: 1 group – with BMI 25–29,9 kg/m$^2$ – EBM; 2 group – with BMI 30–34,9 kg/m$^2$ – obesity of I degree; 3 group – with BMI 35–39,9 kg/m$^2$ – obesity of II degree. All examined patients had concomitant pathology from BT side. Depending on BT pathology all patients were also divided into 3 groups: NASH with chronic non-calculous cholecystitis (CNC); NASH with chronic calculous cholecystitis (CCC); NASH in patients after laparoscopic cholecystectomy (LCE) with concomitant postcholecystectomical syndrome (PCES). For characteristic of lipid exchange were determined the general cholesterol (GCS), general lipids (GL), triglycerides (TG), lipoproteins of the low density (LDL), lipoproteins of the high density (HDL). DL phenotype was determined by D. S. Fredrickson classification with modern additions.

Results. Analysis of lipid changes in patients with NASH demonstrated the reliable increase of GCS with parallel rise of TG, GL, LDL, fixed at increase of BMI relative to PHP (р<0,05, р<0,001) and to patients of other groups (р<0,05). Maximal values of GCS, TG, GL and also LDL were determined in 2 and 3 groups of observation at obesity of I and II degrees. There was registered the reliable decrease of HDL content in most patients of 3 group relative to the ones of 2 group, (р<0,01) and of 1 one.

The level of GCS, TG, GL and LDL was almost equally increased in all groups of observation of NASH: with concomitant CNC, CCC and in patients with PCES relative to PSP, (р<0,001). HDL indices were equally decreased at concomitant CNC and CCC relative to the patients with PCES background with HDL level within physiological norm (р<0,001, р$^F_=0,009$).

There are separated two main phenotypes of DL: IIa and IIb that were typical for patients with NASH and obesity with BT pathology. It was established, that IIb phenotype of dyslipidemia was most often observed in patients with BMI 30–34,9 kg/m$^2$ and 35–39,9 kg/m$^2$. Discussion. There were determined the features of changes of lipid blood spectrum of in this category of patients that are manifested by variability of disorders from hypercholesterolemia and hypertriglyceridemia on the background of increase of GCS, TG, GL, LDL and decrease of HDL. The progression of lipid disorders in patients with NASH in combination with obesity and BT pathology depends on increase of BMI parameters.

The concomitant pathology from BT side partially influenced the indices of lipid blood spectrum. Thus, the low level of HDL in patients with NASH in combination with obesity and concomitant CNC and CCC can be explained by the intense inflammatory processes in BT, attended with disorder of indices of lipid profile with decrease of HDL and increase of GCS, TG, GL, LDL.

Conclusion. Progression of intensity of lipid disorders in patients with NASH in combination with obesity and BT pathology depends on increase of BMI parameters.

The concomitant BT pathology partially influences the parameters of lipid blood spectrum. HDL was equally decreased in all patients with NASH at CNC and CCC relative to patients with concomitant PCES and HDL level within physiological norm. At NASH in combination with obesity at increase of BMI the DL phenomena more often appear in patients. There are separated two main phenotypes of dyslipidemias: IIa and IIb.

Keywords: non-alcoholic steatohepatits, obesity, biliary tract, lipid metabolism, body mass index.

DOI: 10.21303/2504-5679.2016.00115 © Aleksandra Filippova
1. Introduction

Liver plays an important role for development of lipid metabolism with formation of dyslipidemia (DL). According to the literature data, DL (hypertriglyceridemia, hypercholesterolemia or their combination) are often observed at fatty disease of liver – in 20–81% of cases [1]. Today the term “dyslipidemia” is connected with diverse changes of lipid spectrum in blood plasma – rise, lowering or even complete absence of separate fractions, appearance of unusual or pathological phenotypes [2]. DL is a proved risk of development of NAFDL [3], obesity [4] and cardiovascular pathology [5–7].

The changes of lipid metabolism begin at the level of hepatocyte [8]. Chronic diffuse disease of the liver (CDDL) and namely non-alcoholic fatty disease of the liver (NAFDL) is a specific model of disorder of many mechanisms of lipid metabolism regulation. According to the literature data, the disorders of lipid metabolism are based on disorders of the functional state of liver [9].

It is typical, that in patients with NAFDL at hypertriglyceridemia non-alcoholic steatohepatitis (NASH) develops more often that at hypercholesterolemia [1].

Analysis of literature demonstrates that at excessive body mass (EBM) or obesity is usually observed the certain degree of disorder of lipid, carbohydrate and other metabolisms [10]. Obesity is associated with DL, including the intense hypertriglyceridemia, increase of the content of lipoproteins of very low density, decrease of formation of lipoproteins of the high density (HDL) [11].

At the modern stage the data about disorders of lipid exchange, collected in literature, can form hypothesis, according to which, as a result of human evolution as biological specie was created the specific type of lipid metabolism, at which even the middle (normal) level of cholesterol (CS) is potentially dangerous in the aspect of DL development [3] and, as a consequence, NAFDH [2], cholesterosis of gall bladder, cholelithiasis or adipigenous pancreatitis [12]. It is possible, that the special “tension” of the human lipid metabolism can be the retribution for the way of life: features of nutrition, insufficient physical and intense intellectual activity, non-season hormonal activity [3].

The other important proposition is that the hypercholesterolemia it is not a single factor of disorder of lipid exchange and the risk of NAFDL and obesity development [2].

According to our researchers, the lipids of the blood serum, measured in the different periods of development of hepatobiliary pathology can be the weak reflection of the true DL in the critical time of gallstones creation [1]. The proof of this statement is the following facts: after cholecystectomy the decrease of lipids of blood serum is registered and at exacerbation of chronic calculous cholecystitis, especially, at appearance and increase of concrements the lipids level in blood reliably raises [12].

Thus, for adequate analysis of disorders of lipid metabolism at NAFDL it is important to evaluate not only the level of general cholesterol (GCS) in blood but also the level of lipoproteins of the low density (LDL), HDL, general lipids (GL) and also obligatory the level of triglycerides (TG).

2. Aim of the work

To study the main indices of lipid spectrum of blood, which changes lead to the DL formation, depending on body mass index (BMI) and concomitant pathology of biliary tract (BT) in patients with NASH in combination with obesity.

3. Materials and methods

There were examined 100 patients with NASH in combination with obesity and BT pathology, who were on stationary treatment in clinic of SI “Institute of gastroenterology, NAMS of Ukraine”, in which were detected the sigs of hepatic steatosis during sonographic or morphological study of biotpat of the liver. Among patients were 40 men and 60 women. The mean age of patients – (54,68±1,15) years old. The control group included 20 practically healthy persons (PHP). All patients signed the informed consent to participation in the research.

Diagnosis of NASH and BT pathology was set according to standardized protocols of diagnostics and treatment of diseases of digestive organs in correspondence with order of MHP of Ukraine № 271 of 13.06.2005 year and № 826 of 06.08.2014 [13, 14], ICD-10, on the base of the data of anamnesis, clinical and instrumental (ultrasound of organs of abdominal cavity, intraop-
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4. Results

Analysis of lipid changes in patients with NASH (Table 1) demonstrated the reliable increase of GCS with parallel increase of TG, GL, LDL, fixed at the growth of BMI, relative to PHP (from \( p<0.05 \) to \( p<0.001 \)) and patients of other groups \( p<0.05 \)). GCS in patients with NASH was 8.69±0.55 in 3 group and 7.77±0.36 mmol/l in 2 group, with increase by 35.6 % and 21.2 % respectively relative to the patients of 1 group (6.41±0.49 mmol/l; \( p<0.05 \)) and with increase in 1.7 and 1.5 times as to PHP (\( p<0.001 \) at all comparisons). The maximal values of TG were also detected in 3 and 2 groups of observation (2.60±0.16 mmol/l and 2.47±0.17 mmol/l, respectively) with increase by 38.3 % and 31.4 % comparing with 1 group with TG level 1.88±0.15 mmol/l (\( p<0.05 \)).
and with decrease in 2.3 and 2.2 times as to PHP (p<0.001 at all comparisons). The level of GL maximally changed in patients of 3 group (9.54±0.31 g/l), exceeding the respective values in PHP in 1.8 times (p<0.001), in patients of 1 group (7.31±0.33 g/l) by 30.5 % (p<0.001), indices in 2 group (8.41±0.26 g/l) – by 13.4 % (p<0.01).

Table 1
Comparative characteristic of indices of lipid metabolism in patients with non-alcoholic steatohepatitis in combination with obesity and biliary tract pathology depending on BMI (M±m)

<table>
<thead>
<tr>
<th>Index</th>
<th>PHP, n=20</th>
<th>1 group, BMI (25–29.9 kg/m²), n=40</th>
<th>2 group, BMI (30–34.9 kg/m²), n=37</th>
<th>3 group, BMI (35–39.9 kg/m²), n=23</th>
<th>pₓ between groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>GCS, mmol/l</td>
<td>5.23±0.17</td>
<td>6.41±0.49*</td>
<td>7.77±0.36**#</td>
<td>8.69±0.55**#</td>
<td>0.005</td>
</tr>
<tr>
<td>TG, mmol/l</td>
<td>1.14±0.09</td>
<td>1.88±0.15**</td>
<td>2.47±0.17**#</td>
<td>2.60±0.16**#</td>
<td>0.005</td>
</tr>
<tr>
<td>GL, g/l</td>
<td>5.18±0.30</td>
<td>7.31±0.33**</td>
<td>8.41±0.26**#</td>
<td>9.54±0.31**#</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL, unit</td>
<td>38.5±2.2</td>
<td>63.6±5.9**</td>
<td>83.6±7.1**#</td>
<td>96.2±10.0**#</td>
<td>0.010</td>
</tr>
<tr>
<td>HDL, mmol/l</td>
<td>1.62±0.05</td>
<td>1.66±0.14</td>
<td>1.15±0.07**#</td>
<td>1.05±0.08**#</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Note: * – p<0.05; ** – p<0.001 comparing with PHP group; # – p<0.05 comparing with correspondent group of patients with BMI 25–29.9 kg/m²; ” – p<0.05 comparing with correspondent group of patients with BMI 30–34.9 kg/m²; pₓ – level of significances of differences of indices between groups with different BMI in whole by ANOVA univariate disperse analysis

There was a significant increase of fractions of atherogenic LDL that was also fixed in 3 and 2 groups and reached maximal values (96.2±10.0 units and 83.6±7.1 units respectively) with increase in 1.5 and 1.3 times comparing with patients of 1 group and LDL level – 63.6±5.9 units (p<0.05 at all comparisons) and with increase in 2.5 and 2.2 times as to PHP (p<0.001 at all comparisons). In patients with NASH, who had BMI 30–34.9 kg/m² and 35–39.9 kg/m², concentration of antiatherogenic HDL fraction in blood serum was lower (1.15±0.07 mmol/l and 1.05±0.08 mmol/l, respectively) comparing with BMI 25–29.9 kg/m² (p<0.01) and PHP (p<0.001). At that HDL level in patients with BMI 25–29.9 kg/m² did not differ from PHP values (p>0.05).

The direct dependence of indices of lipid profile from BMI is demonstrated by the results of correlative analysis: BMI increase led to the growth of the levels of GCS (rₛ=0.454, p<0.001), TG in plasma (rₛ=0.417, p<0.001), LDL (rₛ=0.393, p<0.001), GL (rₛ=0.465, p<0.001) and reliable lowering of HDL (rₛ=–0.356, p<0.001).

Analysis of distribution of changes of indices of lipid metabolism comparing with norm (Fig. 1) demonstrated that GCS level was increased in 35 (94.6 %) patients of 2 group, in all patients of 3 group (n=23–100 %) and only in 25 (62.5 %) patients from 1 group (p<0.01), that shows an expressed dependence of lipid blood spectrum parameters from BMI indices. Analogous reliable data were observed also relative to the indices of TG, GL and LDL. Maximal number of increased data of TG was in 2 group – 34 (91.9 %) and 3 group – 23 (100 %) against 24 (60 %) cases in 1 group (p<0.01).

GL increase was typical for 22 (95.7 %) patients from 3 group, for 25 (67.5 %) ones from 2 group that reliably (p<0.01) increased the correspondent indices in patients of 1 group (n=13–32.5 %). GL value within physiological norm was observed only in 1 (4.3 %) patient from 3 group relative to 12 (32.4 %) from 2 group, p<0.01 and 27 (67.5 %) from 1 group, (p<0.001).

LDL level was increased in all patients 23 (100 %) from 3 group, in 31 (83.8 %) from 2 group comparing with only 15 (37.5 %) patients from 1 group (p<0.01). LDL normal values were observed in 2 group only in 5 (13.5 %) against 19 (47.5 %) from 1 group (p<0.01). The opposite tendency of changes was established at analysis of index of HDL content in the blood of patients with NASH in all groups of comparison. Especially, there was registered the reliable decrease of HDL content in most patients from 3 group – in 15 (65.2 %) relative to 16 (43.2 %) patients from 2 group and only to 5 (12.5 %) from 1 group (p<0.01).
Fig. 1. Distribution of changes of the lipid metabolism parameters comparing with norm in patients with non-alcoholic steatohepatitis in combination with obesity depending of BMI: * – p<0,05; ** – p<0,01 comparing with correspondent group of patients with BMI 25–29,9 kg/m²; # – p<0,05 comparing with correspondent group of patients with BMI 30–34,9 kg/m²

At detail consideration of lipid profile indices in patients with NASH in combination with obesity depending on concomitant BT pathology (Table 2) analogical tendencies were revealed and they were expressed by all indices of lipid spectrum. Thus, GCS content – 7,18±0,38 mmol/l exceeded PHP value by 37,3 % in patients with concomitant CNC, by 49,7 % in patients with CCC and by 40,7 % at PCES (р<0,001 at all comparisons). TG indices also were almost equally increased in all groups of observation with maximal increase in 2,1 times as to PHP in patients with PCES, and in 1,9 times in patients with concomitant CNC and CCC (р<0,001 at all comparisons).

Table 2
Comparative characteristic of indices of lipid metabolism in patients with non-alcoholic steatohepatitis in combination with obesity depending on concomitant pathology of biliary tract (M±m)

<table>
<thead>
<tr>
<th>Index</th>
<th>PHP, n=20</th>
<th>With CNC, n=35</th>
<th>With CCC, n=30</th>
<th>With PCES, n=35</th>
<th>pF between groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>GCS, mmol/l</td>
<td>5,23±0,17</td>
<td>7,18±0,38*</td>
<td>7,83±0,55*</td>
<td>7,36±0,54*</td>
<td>0,639</td>
</tr>
<tr>
<td>TG, mmol/l</td>
<td>1,14±0,09</td>
<td>2,15±0,19*</td>
<td>2,21±0,16*</td>
<td>2,42±0,16*</td>
<td>0,486</td>
</tr>
<tr>
<td>GL, g/l</td>
<td>5,18±0,30</td>
<td>8,09±0,29*</td>
<td>8,04±0,43*</td>
<td>8,53±0,32*</td>
<td>0,540</td>
</tr>
<tr>
<td>LDL, unit</td>
<td>38,5±2,2</td>
<td>80,2±7,3*</td>
<td>83,6±9,6*</td>
<td>72,4±6,0*</td>
<td>0,565</td>
</tr>
<tr>
<td>HDL, mmol/l</td>
<td>1,62±0,05</td>
<td>1,16±0,08#</td>
<td>1,19±0,10#</td>
<td>1,02±0,16</td>
<td>0,009</td>
</tr>
</tbody>
</table>

Note * – p<0,001 comparing with PHP group; # – p<0,05 comparing with correspondent group of patients with PCES; pF – level of significance of difference of indices between groups with NASH in whole by ANOVA univariate disperse analysis

GL content was also increased in all patients with NASH, in 1,6 times at CNC and CCC and in 1,7 times in patients with concomitant PCES (р<0,001 at all comparisons). LDL values were increased in 1,9 times at concomitant PCES and in 2,1 and 2,2 times respectively in patients with concomitant CNC and CCC (р<0,001 at all comparisons). HDL was equally decreased in groups with concomitant CNC and CCC in 1,4 times (р<0,001) and did not differ from PHP indices in patients with concomitant PCES that indicates to the less inflammatory activity in BT after LCE. This point of view is proved also by the less intergroup increase of LDL in patients with concomitant PCES.
Revelation of deviations of the lipid metabolism indices depending on the limit of physiological norm in patients with NASH in combination with obesity taking into account BT pathology is presented on the Fig. 2. According to the data of Fig. 2, the raise of FCS, TG, GL and LDL was observed with equal frequency in all groups of observation. The reliably significant changes of HDL level at the expense of their decrease were typical for patients with concomitant PCES and were observed in 8 (22,9 %) against 17 (48,6 %) in patients with concomitant CNC (p<0,05).

Table 3
Frequency of revelation of the main dyslipidemia phenotypes among patients with non-alcoholic steatohepatitis in combination with obesity and pathology of biliary tract depending on BMI

<table>
<thead>
<tr>
<th>Groups</th>
<th>DL presence/absence</th>
<th>BMI phenotypes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Absence of DL</td>
<td>IIA</td>
</tr>
<tr>
<td>NASH, n=100</td>
<td>BMI-1.2 (25–29,9 kg/m²), n=40</td>
<td>25 (62,5 %)</td>
</tr>
<tr>
<td></td>
<td>BMI-2.2 (30–34,9 kg/m²), n=37</td>
<td>6 (16,2 %)*</td>
</tr>
<tr>
<td></td>
<td>BMI-3.2 (35–39,9 kg/m²), n=23</td>
<td>*</td>
</tr>
<tr>
<td>p&lt;, between groups</td>
<td>&lt;0,001</td>
<td>0,431</td>
</tr>
</tbody>
</table>

Note: * – p<0,001 comparing with correspondent group of patients with BMI 25–29,9 kg/m²; p<, – level of significance of differences between groups with different BMI in whole by χ² criterion

According to the table data, at NASH reliable changes were detected relative to the patients with BMI 25–29,9 kg/m² (p<0,001). Thus, IIB phenotype was observed in 26 (70,3 %) patients with BMI 30–34,9 kg/m² and in 18 (78,3 %) with BMI 35–39,9 kg/m² against 11 (27,5 %) at BMI 25–29,9 kg/m² (p<0,001). The absence of DL was fixed only in 6 (16,2 %) patients with BMI 30–34,9 kg/m² and was not observed at all at BMI 35–39,9 kg/m² relative to patients with BMI 25–29,9 kg/m² – in 25 (62,5 %) (p<0,001).
5. Discussion

In patients with NASH in combination with obesity and BT pathology the disorders of lipid metabolism play one of the main roles in the formation of metabolic status. There were established the features of changes of the lipid blood spectrum in this category of patients that are manifested in variability of disorders from hypercholesterolemia to hypertriglyceridemia on the background of increase of LDL and decrease of HDL. The received data of comparative evaluation of lipid parameters of patients with NASH in combination with obesity and BT pathology testify that TG play an important role in formation of lipoproteins, increase of GL and LDL content in patients with NASH.

The decrease of intensity of reverse transport of GCS from tissues to liver as a result of insufficient synthesis of HDL and essential level of hypercholesterolemia in LDL content and hypertriglyceridemia create conditions not only for development and progression of NAFDL but also for the vascular disorders, especially, atherosclerotic injury of the main vessels and the ones of liver and create conditions for formation of the vascular component of NAFDL pathogenesis and its progression.

The received data testify that progression of intensity of lipid disorders in patients with NASH in combination with obesity and BT pathology depend on increase of BMI parameters. Analysis of lipid changes in patients with NASH demonstrated the reliable increase of GCS with parallel raise of TG, GL, LDL, fixed at growth of BMI relative to PHP (from p<0.05 to p<0.001) and patients of the other groups (p<0.05). The highest indices of GCS, TG, GL, LDL were in patients with NASH and obesity of I degree (p<0.001) and obesity of II degree (p<0.001), and the least heightened parameters of the lipid blood spectrum, relative to PHP, at BMI (p<0.05; p<0.001). Analogous changes but with decrease of HDL were also fixed at obesity of I and II degree in patients of groups of NASH relative to PHP (p<0.05). Along with it, at EBM HDL content did not differ from PHP values (p<0.05). It is possible to assume that BMI changes on the background of its growth act as independent additional factor of progression of NASH in combination with obesity and also favor the development and progression of other metabolic disorders.

On the background of received data, depending on concomitant BT pathology is obvious that the lipid metabolism disorders were observed in all groups of patients with NASH in combination with obesity, were characterized with hypertriglyceridemia and disorder of metabolism and transport of CS, that were more intense in patients with NASH and concomitant CNC and CCC at the lowered HDL level. The presence of concomitant pathology from BT side partially influenced the indices of lipid blood spectrum. Thus, the low level of HDL in patients with NASH in combination with obesity and concomitant CNC anc CCC can be explained by the intense inflammatory processes in biliary tract, attended with disorders of indices of lipid profile with decrease of HDL and increase of CS, TG, GL and LDL.

The received data testify that at NASH with increased BMI the DL phenomena take place more and more often. There were separated two main phenotypes of dyslipidemia: IIа та IIb, which
comparing with nosology and stage of disease of patients allowed consider them as the main phenotypes, typical for the studied comorbid pathology. The second phenotype of dyslipidemia is manifested as a complex of biological defects of lipid metabolism as moderate hyperlipidemia and is typical for patients with NASH.

In further works it is planned to study the lipid-phospholipid disorders, depending on BMI and reveal their influence on progression of the main disease in patients with comorbid course of non-alcoholic fatty disease of liver and obesity on the background of concomitant pathology of biliary tract.

6. Conclusions

1. Progression of intensity of lipid disorders in patients with NASH in combination with obesity and BT pathology depends on increase of BMI parameters. The most indices of GCS, TG, GL, LDL were in patients with NASH at obesity of I degree (p<0,001) and obesity of II degree (p<0,001), and the lowest parameters of lipid blood spectrum, relative to PHP, at EBM (p<0,05, p<0,001).

2. Concomitant pathology from BT side partially influenced the indices of lipid blood spectrum. Thus, HDL were equally decreased in patients with NASH at concomitant CNC and CCC relative to the norm (p>0,001) and HDL level within physiological norm in patients with concomitant PCES (p>0,05).

3. At NASH in combination with obesity with BMI increase the DL phenomena appear in patients more often. There were two main phenotypes of dyslipidemia: IIa та IIb. Is was established, that IIb phenotype of dyslipidemia was most often observed in patients with BMI 30–34,9 kg/m^2 and 35–39,9 kg/m^2 as to patients with BMI 25–29,9 kg/m^2 (p<0,001).

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[14] Order of HM from Ukraine 06.08.2014 N 826. Unified clinical protocols of primary, secondary (specialized) medical care “Nonalcoholic steatohepatitis”.


