Risk Factors For The Progression Of Non-Alcoholic Fatty Liver Disease And The State Of Intestinal Microflora In Overweight And Obese Patients

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ABSTRACT

Recently, the growth of non-alcoholic fatty liver disease has been actively discussed in domestic and foreign literature. In Uzbekistan, the incidence of non-alcoholic fatty liver disease increased from 27.0% in 2007 to 37.1% in 2014 and ranked first among liver diseases.

KEY WORDS: non-alcoholic fatty liver disease, non-alcoholic fatty hepatosis and non-alcoholic steatohepatitis, BMI, intestinal microflora.

1. INTRODUCTION

The concept of non-alcoholic fatty liver disease includes two morphological forms of the disease with different prognosis: non-alcoholic fatty hepatosis and non-alcoholic steatohepatitis [18,5,6]. The severity of non-alcoholic steatohepatitis is highly variable, including fibrosis, cirrhosis, and hepatocellular carcinoma [1.18]. Non-alcoholic fatty liver disease is 20–86 cases per 1000 person-years according to the level of liver feces and / or ultrasound (ultrasound) data and 34 cases per 1000 cases per year according to PMR [14], according to other sources. The prevalence of non-alcoholic fatty liver disease among the adult population ranges from 17 to 46% [3.17].

According to the Russian study DIREG 2, non-alcoholic fatty liver disease was diagnosed in 37.3% (n = 50 145 people): USA - in 75.6% of patients, non-alcoholic steatohepatitis - in 24.4%, while 80.5% of patients had BMI. > 27 kg / m2, abdominal obesity (AO) - 67.2% [2.8]. According to a pooled meta-analysis (based on 21 cohort studies), obesity is associated with a 3.5-fold increase in the risk of non-alcoholic fatty liver disease [3,4,20]. In recent years, there has been an alarming trend towards an increase in non-alcoholic fatty liver disease among children [19], in about 3% of the entire child population and in 53% of obese children [9]. To clarify the classification of children with and without non-alcoholic steatohepatitis, a special histological scale has been developed for non-

alcoholic fatty liver disease in children - Pediatric NAFLD Histological Score, PNHS [18,11].

We decided to consider the relationship between intestinal microbiocenosis and non-alcoholic fatty liver disease, since disorders of human intestinal microbiocenosis occupy the third place in the structure of gastroenterological pathology [20]. Normal intestinal microflora supports all physiological functions of the host [12], with a beneficial effect on its health. At the same time, changes in the composition of the intestinal microflora (dysbiosis) can contribute to the development of diseases such as obesity, type 2 diabetes mellitus, inflammatory bowel diseases, and cardiovascular diseases [7]. To date, the results of controlled trials for the treatment of non-alcoholic fatty liver disease are not fully understood. There are no treatment standards, the recommendations are flexible and can be individual in each case [5], which prompted the study of the intestinal microflora in patients with non-alcoholic fatty liver disease, since the treatment includes the elimination of risk factors [5], 10,18] drugs that do not affect on the intestinal microflora.

Purpose - to conduct a comparative analysis of the lipid sector and intestinal microflora in patients with non-alcoholic fatty liver disease.

2. MATERIALS AND METHODS

The study was conducted at the Republican Specialized Scientific and Practical Medical Center for therapy and medical rehabilitation.

The study is based on data from 60 patients, of which 30 patients (group 1) with non-alcoholic fatty liver disease without diabetes mellitus, 30 patients (group 2) with type 2 diabetes mellitus and 20 healthy individuals (control group) without clinical and instrumental diagnostic signs of non-alcoholic fatty liver disease.

The age gradation of patients varied from 29 to 77 years, of which 18 were men and 42 were women.

Table 1. Patient distribution according to age and gender

Age	Patients with non-alcoholic fatty liver disease			
	Men	%	Women	%
31-40	3	5	5	8,3
41-50	2	3,3	8	13,3
over 51	13	21,7	29	48
Total	18	30	42	70

The peak incidence of non-alcoholic fatty liver disease occurs in the age period over 50 (69.7%), that is, at an older age.

Patients with metabolic syndrome have the highest risk of developing non-alcoholic fatty liver disease [5, 6].

Based on this, we examined the anthropometric parameters: body weight, height, waist, hips, BMI calculation and waist / hip ratio.

Table 2. BMI of examined patients with non-alcoholic fatty liver disease, (M ± m)

Parameters	BMI	Abdominal obesity
1 – group (p- 30)	29,5±1,26	106,3±4,2
2 - group (p- 30)	33,7±1,22*	110,5±1,7

Note: * - the difference is significant compared with SG (p <0.05)

The study did not include: patients with hepatitis of viral, alcoholic and drug etiology, cumulative diseases, cardiac liver fibrosis, liver cirrhosis, chronic renal failure, stage II, III circulatory failure, organic colon disease.

Verification of the diagnosis of hypertension was based on ultrasound parameters characteristic of fatty hepatosis, in the absence of other causes of changes in the sound conduction of the liver with normal or moderately elevated levels of ALT, bilirubin, alkaline phosphatase and GGTP. In the presence of ultrasound liver changes characteristic of fatty hepatosis and an increase in cytolysis (more than 2N), bilirubin, alkaline phosphatase and GGTP, the diagnosis of non-alcoholic steatohepatitis was established. The diagnosis of diabetes mellitus was established after consulting an endocrinologist with confirmed laboratory tests (blood glucose, impaired glucose and glycohemoglobin tolerance).

Examination of patients with non-alcoholic fatty liver disease included clinical, laboratory, instrumental, physicochemical and immunological methods. The general plan of the patient's examination for the diagnosis of non-alcoholic fatty liver disease included: a general blood test, a biochemical blood test (ALT, ASAT, GGTP, ALP, total bilirubin), a study of the lipid profile (cholesterol, TG, LDL, HDL), microbiological examination.

Sowing feces to consider the microflora of the colon was performed 2 times. The fabric for the study was fecal tests collected instantly after the act of defecation.

Ultrasound examination of the stomach organs was performed for all patients utilizing the ALOCA device (Japan) employing a sensor with a recurrence of 3.5 MG in genuine mode. Specific attention was paid to the state of the hepatobiliary framework. The sizes of the liver, echogenicity of the liver parenchyma, and the perceivability of the vascular design were assessed.

3. RESULTS

The nearness of an increment within the echogenicity of the changed parenchyma of the liver, accompanied by the acoustic impact of attenuation of ultrasound within the profound layers of the parenchyma, was too echosonographic. The structure of the liver parenchyma remained homogeneous. In this case, the shape of the organ was not abused, the forms remained smooth, the edge was sharp. In patients with non-alcoholic greasy liver illness, the foremost common diffuse shape of fatty infiltration was 37 individuals (61.7% of cases), in which there was a uniform increment in echogenicity over the whole surface of the liver, a central shape was recognized in as it were 7 patients (11.7%) and nearby shape in 16 people (26.7%).

In this way, in patients with non-alcoholic greasy liver illness, the nearness of greasy infiltration, presented most frequently within the shape of a diffuse shape, is famous. Too, in most patients, hypomotor-type gallbladder dyskinesia was watched, went with by a feeling of largeness within the right hypochondrium of changing degrees of concentrated, as well as the nearness of dyspeptic signs and abdominal-pain syndromes, showed by throbbing torment or distress within the right hypochondrium without a clear connection with nourishment

admissions. In expansion, the endless lion's share of patients appeared expanded weakness and asthenic disorder.

Ponders of biochemical parameters of blood serum characterizing the state of cytolytic and cholestatic pointers of hepatocytes, we conducted independently in bunches 1 and 2. Ponders have shown that, in patients, there was an increment within the markers of "cytolysis" of AlAT (cytoplasmic enzyme, present in huge amounts within the liver) by 2.8 and 3, 3 times ($p < 0.05$) and AcAT (mitochondrial enzyme present in expansive sums within the heart, liver, skeletal muscles and kidneys) 2.9 and 3.8 times, respectively ($p < 0.05$). In spite of the reality that AlAT could be a more particular marker of hepatocyte harm than AcAT due to its predominant localization within the liver parenchyma, a unmistakable highlight of patients with nonalcoholic greasy liver infection is an increment within the AST / ALT coefficient..

The entire bilirubin was expanded, but it was not statistically noteworthy. The GGTP record was increased within the 1st bunch of patients by 100% ($p < 0.05$), and within the 2nd bunch 2.4 times ($p < 0.05$). The alkaline phosphatase record (a marker of cholestasis) was expanded in patients with non-alcoholic fatty liver illness in both bunches 4.0 and 4.0 times, separately, compared with sound individuals, significantly.

Table 3. Indicators of biochemical parameters of blood serum of patients with non-alcoholic fatty liver disease (M ± m)

Indicators	**AlAT, U / L**	**AsAT, U / L**	**Bilirubin, µmol / l**	**ShF, Unit / l**	**GGTP, Unit / l**
Healthy	19,3± 3,3	15, 2± 4,4	9, 2± 0,51	79 ,7± 10,2	39,73± 7,3
1 group	55, 8± 6,62*	44, 0± 6,98*	21,02± 1,17*	317,9± 25,34*	79,78± 16,18*
2 group	62,7± 7,86*	58, 4± 9,05*	22, 04± 2,62*	377, 1± 31, 46*	95, 95± 19, 08*

Note: * - the difference is significant compared with healthy individuals ($p < 0.05$)

Table 4. Lipid spectrum of blood serum of patients with non-alcoholic fatty liver disease

Parameters	**Healthy**	**1 group**	**2 group**
Total cholesterol, mmol / l	5,97 ± 0	5,82±0,24	6,13±0,41
triglycerides, mmol / l	3,01 ± 0,32	2,74±0,34	3,26±0,32
HDL, mmol / l	1,02 ± 0,12	1,17±0,12*	0,86±0,04*
LDL, mmol / l	3,33 ± 0,23	3,41±0,30	3,19±0,16
VLDL, mmol / l	0,63 ± 0,04	0,62±0,10*	0,94±0,05*
Atherogenic index	5,24 ± 0,58	4,72±0,27*	5,76±0,37*

Note: * - the difference is statistically significant compared between 1 and 2 gr. ($p < 0.05$-0.001)

HDL *- high density lipoprotein cholesterol,* ***LDL*** *- low density lipoprotein cholesterol,* ***VLDL*** *- very low density lipoprotein cholesterol*

In this way, the considers conducted in this area appeared that the course of non-

alcoholic greasy liver disease is went with by impeded serum lipid range, which is communicated by a diminish in HDL and an increment in LDL and TG. The awkwardness of the lipid range was corresponding to the severity of the infection and was altogether higher in patients. Non-alcoholic greasy liver illness with the presence of T2DM. Within the 2nd bunch, the values were somewhat higher: the level of TG was significantly higher, but no significant differences were found within the level of HDL cholesterol diminished to diagnostically noteworthy deviations characteristic of non-alcoholic fatty liver malady. All patients showed a 1.5–2-fold increment within the cholesterol of cholesterol, which is ordinary for hypertriglyceridemia. The most articulated deviations of this pointer were watched in patients of the 2nd gather. LDL cholesterol was more reliable with the target level overwhelmingly. The atherogenicity index significantly surpassed the reasonable values in all inspected, but basically ($p < 0.01$) in patients of the 2nd gather.

The nearness and degree of dysbiotic changes within the huge digestive system in patients Non-alcoholic fatty liver disease was analyzed taking into consideration the information of clinical and microbiological studies. Studies appeared that of all 60 patients inspected with non-alcoholic greasy liver malady, dysbiosis was watched in 57 (95%) patients. So, dysbiosis of the 1st degree was recognized in 15%, patients of the 2nd degree - in 36.6% of patients, 3 degrees - in 40% and 4 degrees in 5%.

The table presents information on the recurrence of discovery of intestinal dysbiosis in patients. Nonalcoholic greasy liver infection of the gotten comes about is obvious, intestinal microflora clutters were more pronounced in patients of bunch 2 with the nearness of T2DM. In gather 1, there was predominantly dysbacteriosis of 2 degrees 13 (43.3%) additionally 1 degree 5 (16, 7%) 3 degrees 9 (30%) patients. In patients of gather 2, dysbiosis of 2 and 3 degrees 13 (43, 3%) and 11 (36.6%), separately, were predominantly watched. It ought to be famous that 2 (6.7%) patients had review 4 dysbiosis.

Table 5. The degree of dysbiosis in patients with non-alcoholic fatty liver disease

	Normal flora	**I**	**II**	**III**	**IV**
Group 1	3 (10%)	5 (16, 7%)	13 (43, 3%)	9 (30%)	-
Group 2	-	4 (13,3%)	13 (43,3%)	11 (36, 7%)	2 (6,7%)

A study of the composition of the intestinal microflora in patients with dysbacteriosis Non-alcoholic fatty liver illness appeared that the most prominent number of associations, both positive and negative, their strength and noteworthiness level with other microorganisms colonizing the colon, was characteristic of bacterioiods. So, there was a positive relationship between the concentration of bacteroids, on the one hand, and bifidobacteria ($r = 0.54$; $p < 0.01$) and lactobacilli ($r = 0.60$; $p < 0.01$), on the other, additionally between the substance of bifidobacteria and lactobacilli ($r = 0.34$; $p < 0.05$), which may be due to the presence of common components for controlling their numbers.

Hence, in all patients with non-alcoholic greasy liver malady, infringement of the intestinal microbiocenosis were identified overwhelmingly of the 2nd degree and 3rd degree. In expansion, the most pronounced intestinal microflora clutters were recorded in patients

with non-alcoholic greasy liver disease with the nearness of T2DM. A relationship investigation of the connections between the files of intestinal microbiocenosis in patients with non-alcoholic greasy liver illness uncovered that the greatest number of associations, their quality and importance level with other microorganisms colonizing the colon was characteristic of bacterioiods. In common, the combination of non-alcoholic greasy liver disease and 1 and 2 degrees of dysbiosis is characterized by torment within the right hypochondrium, for the 3rd and 4th degrees - torment within the umbilical locale, as well as a combination of torments of diverse localization. The recurrence of discovery of torment around the navel can be utilized to distinguish a more pronounced degree of dysbiosis.

4. CONCLUSION

Non-alcoholic greasy liver infection involves a noteworthy put within the structure of the incidence of the gastrointestinal tract. Non-alcoholic greasy liver infection is almost 20-40% agreeing to the literature [13]. In spite of certain propels in pharmacotherapy of this pathology, one of the most issues is the non-specificity of the clinical appearances of the introductory organize. Non-alcoholic greasy liver infection is the stage of hepatic steatosis, which can cause awkward treatment and infection progression.

According to considers, it was found that patients with non-alcoholic greasy liver infection noted the presence of greasy penetration, displayed most regularly within the frame of a diffuse frame. Moreover, the larger part of patients showed hypomotor-type dyskinesia of the gallbladder, went with by a feeling of heaviness in the proper hypochondrium of shifting degrees of concentrated.

When examining the biochemical parameters of blood serum, it was uncovered that in patients with non-alcoholic greasy liver infection, a noteworthy increment within the levels of "cytolysis" and "cholestasis" in the blood serum, as well as a infringement of the lipid range of the blood serum, which is communicated by a diminish in HDL and an increment within the LDL and TG pool . Biochemical awkwardness was proportional to the seriousness of the malady and was altogether higher in patients. Non-alcoholic fat liver disease with the nearness of T2DM.

Thinks about of the intestinal microflora appeared that in all patients with non-alcoholic greasy liver disease, infringement of the intestinal microbiocenosis were transcendently of the 2nd degree. In addition, the most articulated intestinal microflora disarranges were recorded in patients with non-alcoholic fatty liver infection with the nearness of T2DM.

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