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BIOMARKERS OF CARDIOVASCULAR RISK IN PATIENTS WITH NON-ALCOHOLIC FATTY LIVER DISEASE

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Background. Non-alcoholic fatty liver disease (NAFLD) is the hepatic manifestation of metabolic syndrome (MetS), but its influence on the risk of developing cardiovascular diseases (CVD) is not fully clarified at present. The obesity growth in all economically developed countries is connected with NAFLD, which is found in 20-40% of adults and is also associated with increasing CVD risk.

The objective is to study the pathophysiological mechanism of NAFLD in connection with increased CVD risk and intensity of the liver fibrosis.

Material and methods. A total of 129 patients with obesity and MetS aged from 27 to 59 years old were investigated and the correlation of fibrosis intensity (according to the METAVIR scoring system) with glucose metabolism parameters and pro-inflammatory cytokines in plasma was estimated.

Results. It has been found a positive correlation between the intensity of liver fibrosis and concentration of pro-inflammatory cytokines in plasma. The levels of TNF-α, IL-6 and PAI-1 in plasma of patients with F3-4 were significantly higher not only compared to F0– patients ($p<0.05$) and F1 – patients ($p<0.05$), but to F2 – patients ($p<0.05$) as well.

Conclusion. NAFLD is a disease with an elevated level of inflammation markers such as tumor necrosis factor-α (TNF-α), interleukine-6 (IL-6) and plasminogen activator inhibitor-1 (PAI-1) in plasma, and this makes the risk of developing CVD much higher than in the healthy population.

Keywords: *obesity, MetS, pro-inflammatory cytokines, insulin resistance, liver fibrosis, NAFLD.*

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Introduction

Nowadays Non-alcoholic fatty liver disease (NAFLD) is the liver disease that leads to worsened quality of life, disability and increasing of mortality and is considered as a hepatic manifestation of metabolic syndrome (MetS). NAFLD is associated with high risk of development and progression of the cardiovascular diseases (CVD), non-alcohol steatohepatitis, liver insufficiency and hepatocellular carcinoma [1, 2, 3]. NAFLD is the most common metabolic liver disease, with a prevalence as high as 30% in developed countries [1]. Prevalence of NAFLD in general population is 20-40%, in patients with type 2 diabetes mellitus (T2DM) up to 70-90% [4, 5]. Early diagnosis of NAFLD is very important because developing of atherosclerosis [6, 7, 8, 9] and also significantly increasing of the CVD risk [8], especially among those with diabetes mellitus.

The recent studies have demonstrated that patients with NAFLD have altered cardiac function and structure, which may predispose to heart failure and atrial fibrillation [10, 11]. Several investigations indicate that NAFLD is an independent risk of CVD [8, 9, 12]. Atherosclerosis represents the most common pathological substrate of coronary heart disease and the characteristics of the disease as a chronic low-grade inflammatory condition is now largely accepted.

It has been also demonstrated that MetS is a biochemical basis for CVD and their complications [6, 13, 14, 15] though liver and intestines disorders triggering its pathogenic mechanisms but it has not been taken into account in clinical practice until now. In Russia, according to epidemiology research DIREG 2, NAFLD is found in 37.3%, including fatty hepatosis – 80.3%, steatohepatitis – 16.8%, cirrhosis – 2.9% [5]. These findings indicate the necessity of more detailed investigation on the role of inflammation biomarkers for the CVD risk in patients with NAFLD and MetS. The main goal of this investigation is to study plasma inflammation markers such as PAI-1, CRP-hs, TNF- α and IL-6, and glucose metabolism in patients with NAFLD and MetS and to clarify whether biomarkers of inflammation might be the potential markers the CVD risk in these patients.

Material and methods

It has been investigated 129 patients with NAFLD aged from 29 to 59 with NAFLD; the stage of disease was diagnosed according to the anamnesis data, laboratory and ultrasonography investigation, blood test (AST, ALT, ALP, GGTP). All patients had central obesity and MetS. They were recruited from Tyumen Medical University Clinic and Consultative Diagnostic Center during 2010-2012 years. Among them there were 42 males and 87 females. This study was performed according to human research Ethical Committee standards

following all claims of Helsinki declaration. This investigation has been approved by the Ethical Committee of the Tyumen State Medical University. Every patient gave his written consent for all data to be scientifically processed.

After screening, which included anthropometry, tonometry, blood biochemical test, glucose metabolism disorders detection, abdominal organs ultrasound investigation, all patients were divided into 4 groups. 1-st group included central obese patients (waist circumference >80 cm for women and >94 for men) (n=35). 2-nd group included patients with MetS (n=33) (central obesity plus one of the following: arterial hypertension, BP > 130/85 mm hg; increased level of triglycerides in plasma (TG>1.7 mmol/l); decreased high density lipoproteins plasma level (HDLP < 1.0 mmol/l for men and < 1.2 mmol/l for women) or increased level of low density lipoproteins in plasma (LDL > 3.0 mmol/l). 3-d group included patients with MetS and impaired glucose metabolism (n=30): fasting glucose (fasting plasma glucose >5.6-6.1 mmol/l) and/or impaired glucose tolerance (plasma glucose > 7.8 and < 11.1 mmol/l in 2 hours after 75-g glucose tolerance test). 4-th group included patients with MetS and firstly diagnosed type 2 diabetes mellitus (n=31) (fasting glucose plasma level >6.1 mmol/l and/or >11.1 mmol/l in 2 hours after 75-g glucose tolerance test. Control group included 32 healthy volunteers adjusted by age and gender with body mass index (BMI) 18.5-24.9 kg/m^2.

Exclusion criteria were: age more than 60; viral hepatitis in anamnesis; toxic, drug-induced, congenital metabolic liver diseases; rapid weight loss, parenteral nutrition more than 2 weeks; malabsorbtion; opistorchis invasion; refusal to participate.

After the groups were formed, obesity and liver damage prevalence were estimated in relation to impaired glucose metabolism. Special investigation included system inflammation plasma level detection: CRP-hs, TNF- α, IL-6, PAI-1. These tests were performed by enzyme-linked immunosorbent assay (ELISA) using Bender Med Systems reagents. Plasma insulin quantitative analysis was done by ELISA using DRG reagents. HOMA index (homeostasis model assessment – insulin resistance), showing liver insulin resistance (IR) was calculated with Matthews D.R. et al. formula. HOMA = fasting plasma insulin (mkU/ml)*fasting plasma glucose (mmol/l)/22.5.

Ultrasound steatosis (Accuvix V20 Prestige) criteria were: increased hepatic echogenicity, hyper-attenuation of the beam, mild or absent positive mass effect geographic borders, no distortion of vessels. Fibrosis intensity stage was detected according to «METAVIR» system (elastometry - Fibroscan Echosens France): F0 – no fibrosis, F2 – portal fibrosis with singular septa, F3 – portal fibrosis with plural septa without false lobules, F4-liver cirrhosis. Final step of our research was to describe the correlation of metabolic parameters, system inflammation markers and fibrinolysis inhibitor with elastomeric intensity stage of NAFLD.

Besides, we defined liver fibrosis prognostic value to pro-inflammatory cytokines high plasma levels. The variables are presented as median and 25-75 percentile – Me (interquartile range). Data statistically processed with Mann-Whitney test, χ^2 test and Spearman's rank correlation coefficient. Results were considered statistically significant if p-value was found to be less than 0,05.

Results and discussion

It has not been found a correlation of BMI with impaired glucose metabolism in patients with MetS, while maximal waist/hip ratio was found in patients with metabolic syndrome and T2DM. Plasma transaminases blood test has shown that centrally obese patients had significantly higher AST, ALT, ALP, GGTP plasma levels compared to the controls ($p<0.05$), although medians of these parameters were within normal range. Patients with MetS had AST, ALT, ALP, GGTP plasma levels significantly higher than in the control group ($p<0.05$) and in patients with central obesity ($p<0.05$) (table 1).

In the 1-st group 18% of patients had transaminase increase more than 2-fold, in the 2-nd group – 36.7%, in the 3-d – 38.7% and about 50% in the 4-th. NAFLD ultrasound features were found in 95.4% of patients (figure).

Table 1. – Comparison of patients with metabolic syndrome and impaired glucose tolerance (25-75 percentile)

Parameter	Controls (n=32)	1-st group (n=35)	2-nd group (n=33)	3-d group (n=30)	4-th group (n=31)
BMI kg/m^2	21.9 (21.5-24.1)	32.8 * (29.7-35.7)	34.4 * (33.2-37.6)	34.6 * (32.4-38.4)	35.8 * (32.6-38.9)
Waist/Hip ratio	0.79 (0.74-0.8)	1.10 *(1.05-1.16)	1.11 *(1.07-1.18)	1.08 *(1.02-1.16)	1.21* (1.17-1.28) p_{1-4}<0.05. p_{2-4}<0.05. p_{3-4}<0.05
AST U/l	18 (12.5-26)	26 * (17.4-30)	36* (27.5-47.5) p_{1-2}<0.05	38 * (34-50) p_{1-3}<0.05	48.5 * (42-58) p_{1-4}<0.05 p_{2-4}<0.05. p_{3-4}<0.05
ALT E/l	17.5 (13-24)	25 * (18-27)	42.5 * (20-57) p_{1-2}<0.05	42 * (25-52.5) p_{1-3}<0.05	49 * (34-60) p_{1-4}<0.05
ALP U/l	150 (123-167)	201 * (186-240)*	236 * (198-261)	315 * (257-387) p_{1-3}<0.05. p_{2-3}<0.05	320 (286-400) *.**.***
GGTP U/l	23 (18-26)	38 * (23-43)	42 * (28-51)	67* (39-75) p_{1-3}<0.05. p_{2-3}<0.05	59 * (40-70) p_{1-4}<0.05. p_{2-4}<0.05

** - p<0,05 compared to controls; p1-2 , p1-3 p1-4 – compared to the 1-st group; p2-3, p2-4 - compared to with the 2-nd group; p3-4 - compared to the 3-d group. Analysis performed by Mann-Whitney U - test.*

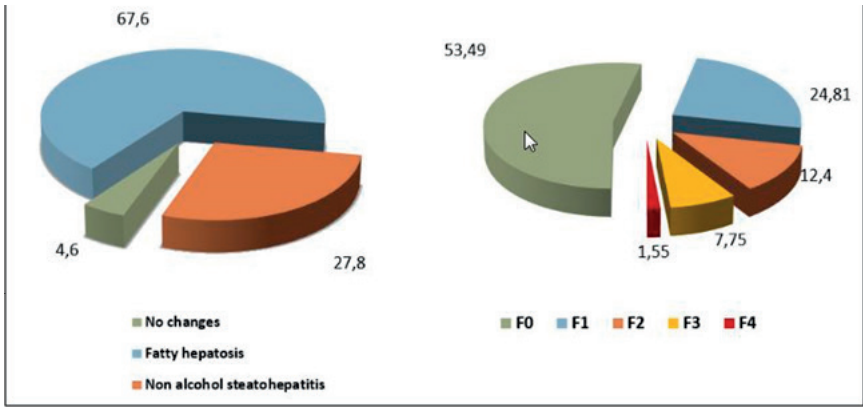

Figure – Liver damage incidence and fibrosis intensity («METAVIR») in patients with obesity and metabolic syndrome

Intergroup analysis showed that in patients with T2DM and GMD these features were found in 100% of cases, in patients with central obesity – in 88.7% of cases and in patients without glucose metabolism disorders – in 93.9%. Within NAFLD liver hepatosis was prevalent, non-alcohol steatohepatitis (transaminase plasma level increase more than 2-fold than recommended) was present in about 27.8%. Minimal amount of these patients was found in the 1-st group – 11.4%, in the 2-nd group they made up 24.2%, 33.3% if MS accompanied with GMD, and almost a half, 45.2%, in patients with firstly diagnosed T2DM. Despite the ultrasound features of NAFLD, elastometry has shown no fibrosis signs in 53.5% of patients. In the obesity group, it was true for 71.4% of cases, MS-group – for 60.6%, GMD-group – 46.7%, and for MetS and newly diagnosed type 2-DM-group – 32.6%.

Having analyzed CRP-hs plasma level we have found that its concentration in patients with central obesity is almost 3-fold higher ($p<0.05$) compared to healthy controls. In patients with MetS CRP-hs plasma level was higher not only compared to controls, but also to patients with central obesity ($p1\text{-}2<0.05$). This parameter was found on maximal level in patients with impaired glucose metabolism. Comparison of TNF-α and IL-6 plasma levels showed the same tendency, but in patients with MetS these cytokines levels were significantly higher than in controls ($p<0.05$), and also they were higher in patients with central obesity ($p1\text{-}2<0.05$). PAI-1 plasma level in patients with central obesity and metabolic syndrome, independently to accompanying impaired glucose metabolism, was significantly higher ($p<0.05$) compared to healthy controls (68.8 (61.5-87.4) ng/ml) (table 2).

The level of inflammation markers in plasma was investigated in dependence of intensity of liver fibrosis according to elastometry; in patients without fibrosis these parameters were minimal. While fibrosis intensity grew worse, we found that almost every inflammation marker (except CRP-hs) and PAI-1 plasma levels increased. Thus, in patients with F1 CRP, pro-inflammatory cytokines TNF-α and IL-6 and PAI-1 plasma levels were significantly higher than in patients without fibrosis. The level of inflammatory markers in patients with central obesity, MetS and F-2 liver fibrosis stage, every investigated parameter was significantly higher not only than in patients without liver fibrosis features, but also than in patients with portal fibrosis without septa ($p<0.05$) (table 3).

Table 2. – Inflammation markers plasma levels and glucose metabolism parameters in patients with obesity, metabolic syndrome, early glucose metabolism disorders and type 2 DM (25-75 percentile)

Parameter	Controls (n=32)	1-st group (n=35)	2-nd group (n=33)	3-d group (n=30)	4-th group (n=31)
CRP-hs mg/ml	0.64 (0.32-0.73)	1.89* (1.32-3.0)	3.1* (2.65-4.23) p1-2<0.05	4.57* (3.2-5.8) p1-3<0.05. p2-3<0.05	4.86* (3.1-5.56) p1-4<0.05. p2-4<0.05
TNF-α pg/ml	19.3 (14.7-56.4)	113.5* (95.6-240)	218.6* (123.8-302.1) p1-2<0.05	328.5* (174.7-396.7) p1-3<0.05	391.4* (256.8-414.7) p1-4<0.05
IL-6 pg/ml	0.89 (0.65-1.65)	3.21* (1.82-4.76)	4.78* (3.23-7.54) p1-2<0.05	6.75* (2.43-9.54) p1-3<0.05. p2-3<0.05	18.1* (6.56-22.5) p1-4<0.05. p2-4<0.05. p3-4<0.05
PAI-1 ng/ml	68.8 (61.5-87.4)	105.4* (91.5-123.6)	118.9 * (105.5-140.6)	187.6 *(134.5-235.6) p1-3<0.05. p2-3<0.05	199.7 (154.5-265.8) p1-4<0.05. p2-4<0.05.
Glucose mmol/l	4.44 (4.2-4.85)	4.7 (4.22-5.1)	5.23* (4.63-5.4)	5.63* (5.6-6.27) p_{1-3}<0.05	6.5* (5.9-7) p_{1-4}<0.05. p_{2-4}<0.05. p_{3-4}<0.05
HbA1c, %	4.67 (4.37-4.9)	5.1 (4.74-5.51)	5.22 (4.8-5.78)	6.1* (5.7-6.36) p_{1-3}<0.05	7.6* 6.81-7.9) p_{1-4}<0.05. p_{2-4}<0.05. p_{3-4}<0.05
Index HOMA IR	1.41 (1.2-1.78)	2.23* (1.6-2.67)	3.85* (2.58-4.3) p_{1-2}<0.05	5.73* (3.5-6.8) p_{1-3}<0.05. p_{2-3}<0.05	5.92* (4.7-6.9) p_{1-4}<0.05. p_{2-4}<0.05

** - p<0,05 compared to controls; p1-2 , p1-3 p1-4 - compared to the 1-st group, p2-3, p2-4 - compared to the 2-nd group, p3-4 compared to group, Mann-Whitney U test*

Maximal CRP – plasma concentration was found in patients with F3-4 fibrosis stage and it significantly differed from CRP – plasma level of F-0 ($p<0.05$) and F1 ($p<0.05$) patients. Difference in CRP – plasma concentration between patients with F3-4 and F2 liver fibrosis stage was not significant. The highest TNF-α, IL-6 and PAI-1 plasma level was also found in patients with F3-4 liver fibrosis stage, and it significantly exceeded the same parameters in patients not only with F0 ($p<0.05$), F1 ($p<0.05$), but also F2 liver fibrosis stage ($p<0.05$). We have to report that «METAVIR» investigation showed no relation of liver fibrosis stage to insulin plasma level and insulin resistance index. While inflammation markers plasma level was increased TNF-α – $r=0.5$; $p<0.001$ and IL-6 – $r=0.65$; $p<0.001$ and PAI-1 $r=0.69$; $p<0.001$ is related also with intensity of liver fibrosis. The prognostic value of liver fibrosis for high CVD risk markers estimated by relative probability (RP), and odds ratio (OR) is presented in table 4.

Multiple inflammatory markers are strongly correlated to the obesity stage and with insulin resistance markers are reliable prognostic criteria of CVD risk [8, 10, 16]. Pro-inflammatory cytokines play an important role in the implementation of blood hypercoagulation processes, impaired regulation of vascular tone, development of acute coronary syndromes, induction of metabolic processes in skeletal muscles and the progression of muscular dystrophy (development of cardiac cachexia syndrome) [17]. Thus, TNF-α having the highest prognostic value for insulin resistance onset in lipid tissue, depresses expression of genes, which are responsible for glucose metabolism, fatty acids oxidation and stimulates the genes that are responsible for de novo cholesterol and fatty acids synthesis [18].

IL-6 is thought to be a «hepatocyte activating factor» [19, 20]. This cytokine can induce synthesis of many acute phase proteins, such as fibrinogen and CRP-hs which are also well known as markers of CVD risk [8]. IL-6 itself is known to be strongly associated with CVD, including chronic heart failure, high grades of stable angina and atrial fibrillation [10, 16, 17, 21]. Results of our investigation showed that the plasma level of pro-inflammatory cytokines TNF-α and IL-6 in patients with NAFLD and MetS accompanied with T2DM almost 2-fold higher than in control group, and the role of IL-6 in liver pathology remains not clear at present. It activates several cells, such as immune system cells, hepatocytes and osteoclasts. Besides this IL-6 has a wide range of biological functions, including inflammation and cancerogenesis, it also regulates immune response and sustains haemopoiesis [16, 22, 23]. Maximal plasma level of IL-6 was found in patients with T2DM.

Several studies also have shown increased gene expression of PAI-1 in patients with obesity [18, 23, 24]. It has been found positive correlation between PAI-1 and MetS – especially with fasting glucose and insulin, TG, BMI and visceral adipose tissue mass [18, 23]. Our results clearly demonstrated that the PAI-1 plasma level in patients with MetS and glucose metabolism disorders is significantly higher than in patients with obesity and impaired glucose metabolism. PAI-1 plasma level higher 80 ng/ml is considered to be the upper limit; over limit in obese patients is considered to be a cardiovascular risk factor [22, 24].

Normally PAI-1 is mainly synthesized in endothelium cells, hepatocytes, thrombocytes and smooth muscle cells. In patients with obesity, the main PAI-1 producer becomes adipose tissue. In our

Table 3. – Inflammation marker plasma levels in patients with obesity and MS in dependence of liver fibrosis stage («METAVIR») (25-75 percentile)

Parameter	F 0 (n=69)	F 1 (n=32)	F 2 (n=16)	F 3-4 (n=12)
CRP-hs, mg/l	2,98 (1,56-3,59)	3,68* (2,9-4,23)	4,6*, ** (3,5-5,65)	4,9*, ** (3,9-5,4)
TNF-α, pg/ml	137,5 (99,4-247,6)	287,3* (145,6-343,4)	356,5*,** (201,5-399,3)	414,4*,**,*** (396,7-419)
IL-6, pg/ml	4,21 (3,1-6,7)	7,8* (4,5-10,2)	14,8*,** (10,4-19,6)	21,2*,**,*** (15,4-24,1)
PAI-1, pg/ml	110,6 (75,7-140,5)	140,2* (90,5-190,6)	190,5*,** (154,6-240,4)	235,5*,**,*** 189,3-270)

** - p<0,05 compared to F 0, ** - p<0,05 compared to F 1, *** - p<0,05 compared to F 2, Mann-Whitney U test*

Table 4. – Liver fibrosis prognostic value in diagnosis of elevated cardiovascular risk markers

Parameter	RP	95% CV	OR	95% CV
TNF-α >200 pg/ml	2,4	1,6-3,6	5,7	2,6-12,2
TNF-α >300 pg/ml	4,6	2,1-9,7	7,7	3-19,7
IL-6 >4 pg/ml	1,39	1,1-1,7	3,9	1,5-9,5
IL-6 >6 pg/ml	2,4	1,6-3,5	8	3,5-18,3
PAI-1>80 ng/ml	1,2	1-1,44	2,3	0,96-5,5
PAI-1>160 ng/ml	3,1	1,6-6,3	4,7	2-11,3
PAI-1>240 ng/ml	8,6	2-36,2	11,1	2,4-51

RP - relative probability, OR – odds ratio, CV – confidence interval (Compared to patients with no fibrosis).

research patients groups were comparable in central obesity parameters, thus higher PAI-1 plasma level in patients with impaired glucose metabolism cannot be completely related to adipose tissue mass. Probably these results can be explained by system inflammation intensity being a step in central obesity progression. At first adipose tissue is a source of pro-inflammatory cytokines; than liver becomes additional independent pro-inflammatory cytokines producer. This hypothesis can be confirmed by the relation of system inflammation markers to the intensity liver damage; especially it concerns IL-6 and PAI-1 level increase, while insulin resistance is more associated with accompanying metabolic disorders and duration of obesity.

In patients with central obesity and MetS estimation of NAFDL stage progression prognostic value for inflammation markers and fibrinolysis inhibitor plasma level indication showed that liver fibrosis increases the probability of pro-inflammatory cytokines high plasma concentration detection, so they may be used as early prognostic and possibly diagnostic markers of developing CVD.

Conclusion

Results of this investigation have clearly demonstrated that the concentration of the inflammation markers TNF-α, IL-6, PAI-1 and CRP-hs in patients with NAFLD is much higher in comparison with healthy controls. The clinical implication of these findings is that patients with NAFLD need more care aiming at the early diagnosing of CVD and early treatment interventions for decreasing the risk of CVD development and its complications. In the near future the down-regulation of systemic inflammation may be a promising therapeutic strategy in the prevention and treatment of NAFLD and CVD.

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БИОМАРКЕРЫ РИСКА СЕРДЕЧНО-СОСУДИСТЫХ ЗАБОЛЕВАНИЙ У ПАЦИЕНТОВ С НЕАЛКОГОЛЬНОЙ ЖИРОВОЙ БОЛЕЗНЬЮ ПЕЧЕНИ

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Введение. Неалкогольная жировая болезнь печени (НАЖБП) – печеночное проявление метаболического синдрома, но ее влияние на риск развития сердечно-сосудистых заболеваний (ССЗ) в настоящее время полностью не выяснено. Рост ожирения во всех экономически развитых странах связан с НАЖБП, которая встречается у 20-40% взрослого населения, и также связана с повышением риска развития ССЗ.

Цель данного исследования – изучение патофизиологических механизмов НАЖБП в связи с повышенным риском ССЗ и интенсивностью фиброза печени.

Материал и методы. Обследованы 129 пациентов с ожирением и метаболическим синдромом в возрасте от 27 до 59 лет, произведена оценка корреляции интенсивности фиброза (по шкале METAVIR) с параметрами обмена глюкозы и уровнем провоспалительных цитокинов в плазме крови.

Результаты. Выявлена положительная корреляция между интенсивностью фиброза печени и концентрацией провоспалительных цитокинов в плазме. Уровни ФНО-α, ИЛ-6 и ИАП-1 в плазме у пациентов с F3-4 были значительно выше не только по сравнению с F0-пациентами ($p<0,05$) и F1-пациентами ($p<0,05$), но также с F2-пациентами ($p<0,05$).

Выводы. НАЖБП представляет собой заболевание с повышенным уровнем маркеров воспаления, таких как фактор некроза опухоли-α (ФНО-α), интерлейкин-6 (ИЛ-6), ингибитор активатора плазминогена-1 (ИАП-1) в плазме, и это провоцирует риск развития ССЗ гораздо выше, чем в здоровой популяции.

***Ключевые слова**: ожирение, метаболический синдром, провоспалительные цитокины, инсулинорезистентность, фиброз печени, НАЖБП.*

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