FREQUENCY OF EXACERBATIONS IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE AS ONE OF THE FACTORS OF PROGRESSION OF NON-ALCOHOLIC FATTY LIVER DISEASE

Abstract. This article presents the results of studies obtained by observing patients with non-alcoholic fatty liver disease (NAFLD) on the background of chronic obstructive pulmonary disease (COPD). As a result of the analysis it was found that the frequency of exacerbations of COPD with hospitalization in overweight patients in the presence of NAFLD leads to increased imbalance of adipose tissue hormones in the form of decreased adiponectin and increased leptin, and correlates with impaired lipid metabolism and severe grade of hepatic steatosis. In patients with frequent exacerbations, there is a significant positive correlation between leptin levels and TNF-α factor, which may be associated with an increase in overall inflammation. The revealed imbalance of adiponectin and leptin content in patients with COPD with overweight is a factor in the progression of NAFLD.

Keywords: NAFLD, COPD, hepatic steatosis, adiponectin, leptin, exacerbation.

Introduction. According to GOLD, patients with chronic obstructive pulmonary disease (COPD) often have a common metabolic syndrome. It is 23%-53% and depends on the stage and degree of inflammation. These patients have a higher cardiovascular risk [1,2]. Today, there is growing evidence that adipose tissue is an endocrine organ, and inflammatory visceral fat contributes to systemic
inflammation and is associated with COPD-dependent cardiometabolic comorbid conditions [3]. COPD and nonalcoholic fatty liver disease (NAFLD) have common pathophysiological mechanisms, such as decreased physical activity, oxidative stress, low-intensity inflammation, and metabolic syndrome. The severity of COPD is recognized as an independent risk factor for NAFLD [4]. Insufficient determination of the factors of unity of pathogenetic mechanisms of NAFLD progression on the background of COPD and the lack of uniform recommendations for the treatment of patients with comorbid pathology has led to the relevance of our studies.

**The aim of the study** was to investigate the dependence of adiponectin and leptin levels in patients with NAFLD on the frequency of COPD exacerbations and to establish their relationship with the grade of hepatic steatosis.

**Materials and methods.** The study involved 142 patients who were hospitalized at the pulmonology department of the Transcarpathian Regional Clinical Hospital named after Andrei Novak during 2018-2020 with a diagnosis of COPD II group B and C. Among the subjects were 60.5% (86) men and 39.5% (56) women. The average age was 57.8 ± 1.5 years.

The studies were performed with the informed consent of patients, and their methodology was in line with the 1975 Declaration of Helsinki and its 1983 revision and approved by the Uzhhorod National University Local Bioethics Commission (Minutes № 1 of 10.01.2020).

The criteria for inclusion in the study confirmed the diagnosis of chronic obstructive pulmonary disease (GOLD II) and age over 40 years and less than 70 years and / or NAFLD. Criteria for inclusion in the study confirmed the diagnosis of chronic obstructive pulmonary disease (GOLD II) and age over 40 and less than 70 years and / or NAFLD. Exclusion criteria were the presence of markers of viral hepatitis B and C, markers of autoimmune hepatitis / cross syndrome (anti-LKM-1, anti-SLA and anti-LC-1) and HIV infection, alcohol consumption, toxic liver damage and patient rejection from research.

The diagnosis of COPD was made according to the International Classification of Diseases-10 revision and confirmed by spirometry, which recorded a decrease in the ratio of FEV1 / FJEL <0.7 (70%) after taking a bronchodilator. The duration of
the disease, the frequency of exacerbations of COPD during the last year was determined by retrospective study of the anamnesis (order of the Ministry of Health of Ukraine № 555 from 27.06.13).

The diagnosis of NAFLD was established according to the unified clinical protocol "Non-alcoholic steatohepatitis" (2014) and the adapted clinical guideline based on the evidence "Non-alcoholic fatty liver disease" (2012), according to the recommendations of the European Liver Study Association (EASL).

To assess the trophological status of patients, height, weight, waist circumference, and body mass index (BMI) were determined, which was calculated according to the generally accepted formula. The BMI of 18.5-24.9 kg / m2 was considered the norm. Patients in groups 1 and 3 were overweight (PMT), and group 2 included patients with COPD who had normal body weight.

Depending on the nosology and frequency of exacerbations of COPD were divided into several groups: 1a group (n = 22) - patients with NAFLD + COPD II group B, 1b gr. (n = 30) - patients with NAFLD + COPD II group C, 2a group (n = 46) - patients with COPD II group B, 2b group - (n = 44) - patients with COPD II group C and group 3 - patients with NAFLD.

Enzyme-Immuno-Sorbent-Assay (ELISA) was used to determine the levels of C-reactive protein (CRP), leptin, adiponectin, as well as serum TNF-a concentrations on the automatic enzyme-linked immunosorbent assay "STATFAX" according to the instructions attached to the Diagnostics Biochem Canada and DRG (US) reagent kits. To determine the grade of steatosis and stage of liver fibrosis used a non-invasive method of diagnosis - FibroMax, which includes: FibroTest, ActiTest, SteatoTest, AshTest, NashTest. Analysis and processing of results was performed using Microsoft Windows 10 and STATISTICA application packages.

**Results and discussion.** As a result of the analysis, it was found that all patients with NAFLD and NAFLD + COPD had significantly reduced levels of adiponectin and elevated levels of leptin. The most pronounced changes were registered in patients with NAFLD, who last year had more than 2 exacerbations of COPD with hospitalization and belonged to GOLD II. The average exacerbation in this group was 2.52 ± 0.25. The concentration of leptin in the serum of patients with NAFLD
COPD correlated with the frequency of exacerbations of COPD. In patients of group 1b the concentration of leptin was increased 4.5 times, and in 1a group - 3.9 times, serum adiponectin level was reduced 3.1 times and 2.3 times in patients 1b and 1a groups, respectively. An increase in blood leptin levels is associated with leptin resistance. Therefore, leptin resistance (ratio of leptin to triglycerides) was additionally calculated. In the examined patients with NAFLD + COPD, the leptin resistance index was 25.35 ± 2.43 and was twice as high as in patients with NAFLD without COPD - 12.4 ± 1.32.

Decreased adiponectin content in patients with NAFLD who had frequent exacerbations of COPD correlated with the degree of hepatic steatosis (r = 0.47; p <0.05), and increased leptin levels (29.5 ± 1.71 ng / ml against 7.03 ± 0.52 ng / ml; p <0.05).

Furthermore in these patients there was a positive correlation between leptin values (r = 0.48; p <0.05) with the grade of fatty infiltration of the liver, while a similar relationship between adiponectin / leptin was negative (r = -0.34; p <0.05). With increasing leptin levels in the blood and decreasing adiponectin / leptin ratio, the grade of hepatic steatosis increased according to FibroMax. Thus, in group 1b 63.3% (19 of 30) patients had severe liver steatosis (S ≥2.0), while in group 1a such patients had 36.4% (8 of 22), and in Group 3 - 26.6% (8 out of 30), which is significantly lower (p <0.05).

In patients with frequent exacerbations, there was a significant positive correlation between leptin levels and TNF-a factor, which may be associated with an increase in overall inflammation. Our data coincide with the results obtained in a meta-analysis of the literature where it is noted that a positive correlation between the concentration of leptin and TNF-a was detected only in exacerbations. Most studies have shown that leptin concentrations in stable patients with COPD did not differ significantly from those in the control group, but increased with exacerbations, although slightly [5]. In patients with COPD II group B without NAFLD, with a small number of exacerbations, leptin levels did not differ from the control group.

A positive correlation of adiponectin with total cholesterol and HDL was
detected ($r = 0.49$; $r = 0.43$; $p <0.05$). The relationship between adiponectin and triglycerides ($r = -0.54$; $p <0.05$) and the adiponectin / leptin ratio to LDL ($r = -0.43$; $p <0.05$) was inverse.

**Conclusions.** 1. In patients with NAFLD + COPD with overweight, an increase in the imbalance of adipose tissue hormones in the form of a decrease in adiponectin and an increase in leptin, which is directly proportional to the increase in the frequency of COPD exacerbations.

2. In patients with NAFLD with a high frequency of exacerbations of COPD in the presence of increased body weight, a decrease in the ratio of adiponectin / leptin significantly reigns with a violation of lipid metabolism and a higher grade of hepatic steatosis.

3. Significant imbalance in the content of adiponectin and leptin in patients with COPD with overweight is a factor in the progression of NAFLD.

**References**


