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ADIPOSE TISSUE HORMONES – LEPTIN AND ADIPONECTIN IN A PATIENT OF NAFLD AND CONCOMITANT COPD

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Abstract. *Introduction*. COPD and NAFLD have common pathophysiological mechanisms, such as decreased physical activity, oxidative stress, low-intensity inflammation, and metabolic syndrome.

The aim of the study was to investigate adiponectin and leptin levels in patients with NAFLD with different frequency of COPD exacerbations. The study involved 142 patients, who, depending on the nosology and frequency of exacerbations of COPD were divided into several groups: 1a gr. (n = 22) - patients with NAFLD + COPD II gr B, 1b gr. (n = 30) - patients with NAFLD + COPD II gr C, 2a gr. (n = 46) - patients with COPD II gr B, 2b gr - (n = 44) - patients with COPD II gr C and group 3 - patients with NAFLD. Determination of leptin and adiponectin was performed by ELISA, hepatic steatosis was established using the Fibromax method and statistical methods were used.

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 gr - 3.9 times, serum adiponectin level was reduced 3.1 times and 2.3 times in patients 1b and 1a groups, respectively. 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. There was a positive correlation of adiponectin with total cholesterol and HDL ($r = 0.49$; $r = 0.43$; $p < 0.05$). 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, an imbalance of adipose tissue hormones has been registered in the form of a decrease in adiponectin content and an increase in leptin content, which changes in direct proportion to the increase in the frequency of COPD exacerbations. In patients with NAFLD with a high frequency of COPD exacerbations, there is a significant decrease in the ratio of adiponectin / leptin, which correlates with impaired lipid metabolism and a higher degree of hepatic steatosis.

Key words: NAFLD, COPD, hepatic steatosis, adiponectin, leptin, exacerbation.

Гормони жирової тканини - лептин та адипонектин у хворих на НАЖХП із супутньою ХОЗЛ
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Резюме. *Вступ.* ХОЗЛ та НАЖБП мають спільні патофізіологічні механізми, такі як зниження фізичної активності, окислювальний стрес, запалення низької інтенсивності та метаболічний синдром.

Мета роботи - дослідити рівні адипонектину та лептину у хворих на НАЖХП з різною частотою загострень ХОЗЛ.

Матеріали та методи. У дослідженні взяли участь 142 хворих, які в залежності від нозології та частоти загострень ХОЗЛ були розділені на декілька груп: 1а гр. (n=22) – хворі на НАЖХП+ ХОЗЛ II гр В, 1б гр. (n=30) – хворі на НАЖХП+ ХОЗЛ II гр С, 2а гр.(n=46) – пацієнти з ХОЗЛ II гр В, 2б гр – (n=44) – пацієнти з ХОЗЛ II гр С та 3 група – хворі на НАЖХП . Визначення лептину та адипонектину проводили методом ІФА, стеатоз печінки встановлювали за допомогою методу Фібромакс та використовували статистичні методи.

*Отримані результати та їх обговорення***.** У результаті проведеного аналізу встановлено, що у всіх хворих на НАЖХП та НАЖХП + ХОЗЛ зареєстровано достовірно знижені рівні адипонектину та підвищені рівні лептину. Найвиразніші зміни зареєстровані у хворих на НАЖХП, які за минулий рік мали більше як 2 загострення ХОЗЛ з госпіталізацією та належали до GOLD II. Середній показник загострень у

ції групі склав 2,52±0,25. Концентрація лептину в сироватці крові хворих на НАЖХП +ХОЗЛ корелювала з частотою загострень ХОЗЛ. У хворих 1б групи концентрація лептину була підвищена у 4,5 раз, а у 1а гр – у 3,9 разів, сироватковий рівень адипонектину був знижений у 3,1 раз та у 2,3 раза у хворих 1б та 1а груп відповідно. У пацієнтів із частими загостреннями спостерігалася значна позитивна кореляція між рівнями лептину та фактора TNF-a, що може бути пов'язано із збільшенням загального запалення. Виявлено позитивну кореляцію адипонектину із загальним холестерином і ЛПВЩ (r=0,49; r=0,43; p<0,05). Взаємозв'язок адипонектина із тригліцеридами (r=-0,54; p<0,05) і коефіцієнта адипонектин/лептин із ЛПНЩ (r= -0,43; p<0,05) носив зворотній характер.

Висновки. 1.У хворих на НАЖХП+ ХОЗЛ зареєстровано дисбаланс гормонів жирової тканини у вигляді зниження вмісту адипонектину та підвищення вмісту лептину, який прямо пропорційно змінюється з підвищенням частоти загострень ХОЗЛ. У хворих на НАЖХП з високою частотою загострень ХОЗЛ відмічається достовірне зниження співвідношення адипонектин/лептин, що корелює із порушенням ліпідного обміну та вищим ступенем стеатозу печінки.

Ключові слова: НАЖХП, ХОЗЛ, стеатоз печінки, адипонектин, лептин, загострення.

Introduction

Non-alcoholic fatty liver disease (NAFLD) is the most common liver pathology, occurring in developed countries in 20–30% of the adult population, and non-alcoholic steatohepatitis (NASH) is reported in 2–3% of the general population [1]. According to a number of authors, at the initial examination in 30–40% of patients with NASH liver fibrosis is detected, which in 5–10 years in 20–25% of cases progresses to liver cirrhosis, and 30–40% of these patients die from complications [2, 3]. NASH is currently considered to be one of the most common causes of elevated liver tests without clinical symptoms [4].

There is a two-way relationship between NAFLD and metabolic syndrome, when NAFLD can be the cause or outcome of metabolic syndrome [5]. NAFLD doubles the risk of metabolic syndrome over the next few years, and is a new independent cardiovascular risk factor [6,7].

According to GOLD, patients with chronic obstructive pulmonary disease (COPD) have a common metabolic syndrome. It is 23% -53% and depends on the stage and degree of inflammation. These patients have a higher risk of coronary heart disease, cardiac arrhythmias or heart failure [8,9].

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 [10]. In 1995, the protein adiponectin was discovered, which is secreted by white adipose tissue and has anti-inflammatory and antioxidant properties [11]. The opposite property is leptin. In a healthy person, leptin suppresses appetite [12]. Obesity produces an increased amount of leptin in the body, and due to its binding to C-reactive protein, the level of which is also high, leptin is inactivated. In addition, leptin is a pleiotropic cytokine and plays an important role in the induction and maintenance of systemic inflammation along with other proinflammatory cytokines (TNF-α, IL-IL-6, IL-8) [12].

COPD and NAFLD have common risk factors and 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 [13]. Insufficient determination of the pathogenetic mechanisms of NAFLD progression in patients with COPD and the lack of uniform recommendations for the treatment of patients with combined 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 degree of hepatic steatosis.

Materials and methods

Under observation were 142 patients who were hospitalized in the pulmonology department of the Transcarpathian Regional Clinical Hospital named after Andrew 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 mean age was 57.8 ± 1.5 years.

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

10.01. 2020). 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 refusal of the patient from researches.

The diagnosis of COPD was distinguished according to the International Classification of Diseases-10 revision and confirmed by spirometry, which recorded a decrease in the ratio of FEV1/FVC <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). based on the evidence of "Non-alcoholic fatty liver disease" (2012), according to the recommendations of the European Association for the Study of the Liver (EASL)

Enzyme-linked immunosorbent assay 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 included in the Diagnostics Biochem Canada and DRG reagent kits (USA). Leptin resistance was determined by the formula:

LR = leptin (ng / ml) / triglycerides (TG)

All clinical, biochemical and immunological studies were performed in the certified laboratory of the Transcarpathian Regional Clinical Hospital named after Andriy Novak and private laboratories ("Dila" and "Synevo").

All patients were performed ultrasound examination of the abdominal cavity according to the conventional method, by Philips HDI-1500 with a scanning sensor with a frequency of 3.5 MHz. Depending on the ultrasound picture of fatty infiltration of the liver and the inflammatory process in all patients, steatosis was assessed as minimal, moderate and severe. To determine the degree of steatosis and liver fibrosis used a non-invasive diagnostic method - FibroMax, which includes: FibroTest, ActiTest, SteatoTest, AshTest, NashTest. The study is based on a comprehensive analysis of 10 biochemical parameters: α-2-macroglobulin, Haptoglobin, Apolipoprotein A1, GGT, total bilirubin, ALT, AST, blood glucose, TG, total cholesterol.

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

Depending on the nosology, patients were divided into several groups: group 1 (main n = 52) - NAFLD + COPD and two comparison groups - group 2 (n = 90) - patients with COPD II and 3 group (n = 30) - patients with NAFLD. Taking into account the frequency of exacerbations of COPD groups 1 and 2 in turn were divided into: 1a gr. (n = 22) - patients with NAFLD + COPD II gr B and 1b gr. (n = 30) - patients with NAFLD + COPD II gr C and 2a gr. (n = 46) - patients with COPD II gr B and 2b gr - (n = 44) - patients with COPD II gr C. Average exacerbation in group B - 1.02 ± 0.22 and in group C - 2.52 ± 0.25. The groups were representative by age, sex and severity of the disease. The control group consisted of 30 healthy individuals (mean age 35.3±1.4 years). Patients were prescribed basic therapy for COPD in accordance with the order of the Ministry of Health of Ukraine №555 from 27.06.13 (fenoterol / ipratropium bromide 50/20 in one dose after 8 hours).

For statistical processing of the obtained data, parametric and nonparametric methods (Kraskel-Wallis analysis, Mann-Whitney test; Pearson rectilinear correlation method, Student's test) were used in the SPSS 11.5 package environment.

Results and discussion

We determined the levels of adiponectin and leptin in all patients with COPD, NAFLD and NAFLD combined with COPD depending on the frequency of exacerbations and the severity of COPD according to the GOLD classification. As a result of the analysis, it was found that in all patients with NAFLD and NAFLD associated with COPD, significantly reduced levels of adiponectin and increased levels of leptin were registered in comparison with the control group (Fig. 1).

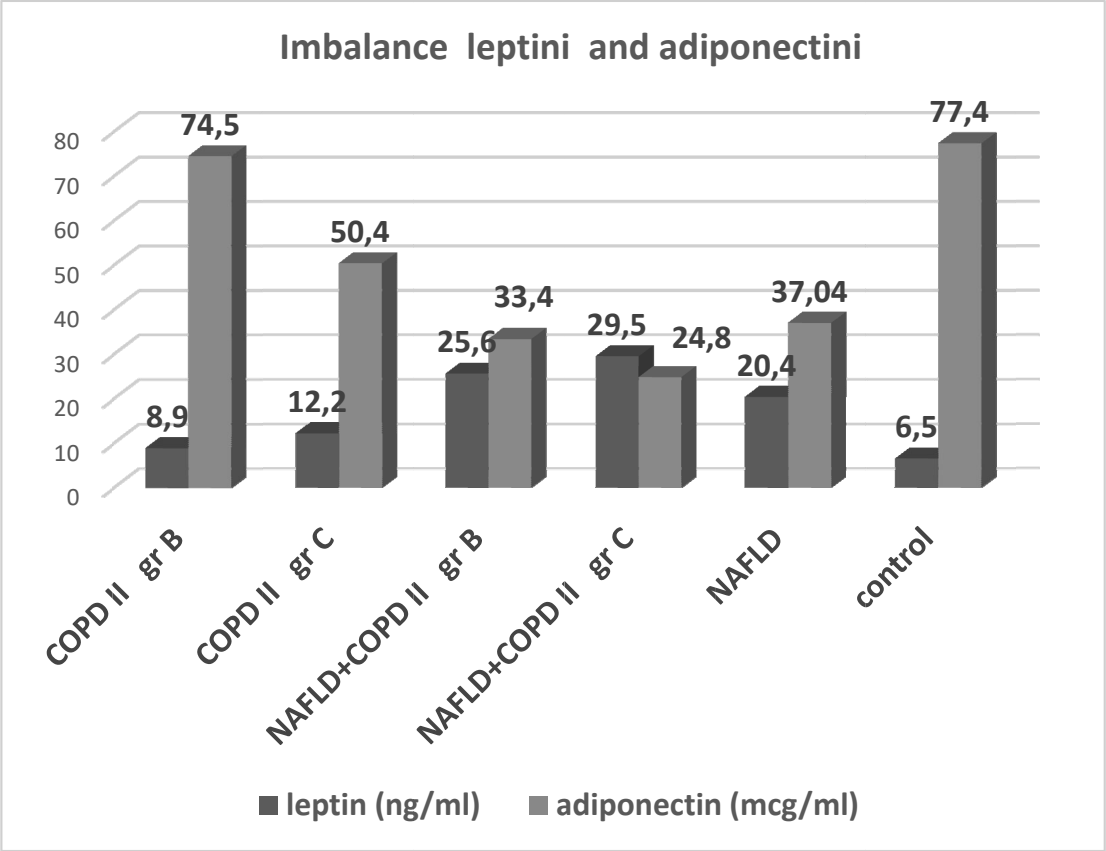

Fig. 1 Levels of leptin and adiponectini

The most significant 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. Thus, in patients of group 1b, the concentration of leptin was increased 4.5 times, and in group 1a - 3.9 times, compared with the control group. At the same time, the serum level of adiponectin was reduced by 3.1 times and 2.3 times in patients of groups 1b and 1a, respectively.

Adipocyte dysfunction was also reported in patients with NAFLD without COPD, where serum leptin concentrations were 3.1 times higher and adiponectin concentrations 2.1 times lower, which is substantial compared to the control group ($p < 0.05$).

In patients with COPD II gr C without NAFLD, was registered increase leptin levels in 1.9 times. This is apparently due to the involvement of this adipocytokine in chronic inflammation. In patients with frequent exacerbations, there was a significant positive correlation between leptin levels and tumor necrosis factor-α (TNF-a), which may be associated with an increase in overall inflammation.

Our data matches with the results obtained in the 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 [14]. In our study, in patients with COPD II gr B without NAFLD, with a small number of exacerbations, leptin levels did not differ from the control group. = 0.47; $p < 0.05$), and elevated leptin levels (29.5 ± 1.71 ng / ml versus 7.03 ± 0.52 ng / ml; $p < 0.05$).

Additionally, for these patients there was a positive correlation of leptin values ($r = 0.48$; $p < 0.05$) with the degree 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 degree of hepatic steatosis increased

according to FibroMax. Thus, in group 1b 63.3% (19 of 30) patients had severe stages of hepatic 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).

An increase in leptin levels in the blood is associated with leptin resistance. Therefore, leptin resistance (ratio of leptin to triglycerides) was additionally calculated. In the examined patients with COPD + COPD leptin resistance was 25.35 ± 2.43 and was twice as high as in patients with COPD without COPD - 12.4 ± 1.32.

For group 1b patients - there is a significant decrease in the ratio of adiponectin / leptin, which correlated with disorders of lipid metabolism. We found a positive correlation of adiponectin with total cholesterol and HDL (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. Negative linear correlations between adiponectin and total cholesterol and HDL were found in group 1a, (r = 0.29; r = 0.33; p> 0.05), which is inconsequential.

According the above, patients with NAFLD + COPD there is an imbalance of adipose tissue hormones in the form of a decrease in adiponectin and an increase in leptin, which rapidly forces with increasing exacerbations of COPD. Elevated serum leptin levels are directly proportional to the severity of liver disease and the stage of liver damage.

Conclusions

1. In patients of NAFLD + COPD, an imbalance of adipose tissue hormones has been registered in the form of a decrease in adiponectin content and an increase in leptin content, which changes in direct proportion to the increase in the frequency of COPD exacerbations.

2. In patients with NAFLD with a high frequency of COPD exacerbations, there is a significant decrease in the ratio of adiponectin / leptin, which correlates with impaired lipid metabolism and a higher degree of hepatic steatosis.

Conflict of interest. The authors declare no conflict of interest in the preparation of this article.

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