ORIGINAL ARTICLE

ANALYSIS THE METABOLIC STATUS OF PATIENTS WITH CORONARY ARTERY DISEASE AND NONALCOHOLIC FATTY LIVER DISEASE DEPENDING ON BODY MASS INDEX

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ABSTRACT

The aim: To analyze the metabolic status of patients with coronary artery disease and nonalcoholic fatty liver disease depending on body mass index.

Materials and methods: The cohort of patients included 107 people with coronary artery disease (CAD), nonalcoholic fatty liver disease (NAFLD) and overweight (n=56) or obesity (n=51). In all patients glucose, insulin, HbA1c, HOMA-IR, hsCRP, transaminases, creatinine, urea, uric acid, lipid profile, anthropometric parameters and ultrasound elastography were measured.

Results: During the analysis of serum lipid spectrum in patients with obesity: lower levels of HDL and higher TG concentration compared with patients who had overweight. The insulin level was almost twice as high as in patients with overweight and the HOMA-IR index was 3.49 (2.13;5.78), where as in patients with overweight it was 1.85 (1.28;3,01), $p<0.01$. In patients with coronary artery disease and overweight, the of hsCRP was 1.92 (1.18;2.98) mg/l and was significantly different from the hsCRP level in obese patients, which was 3.15 (2.64;3.66) mg/l, p=0,004.

Conclusions: In patients with coronary artery disease, non-alcoholic fatty liver disease and obesity, the metabolic profile was characterized by a more unfavorable lipid spectrum: lower levels of HDL and higher triglicerid concentration. Carbohydrate metabolism in obese patients included disorders such us impared glucose tolerance, hyperinsulinemia and insulin resistance. There was also a correlation between body mass index with insulin and glycated hemoglobin. Higher concentration hsCRP in obese compared with patients with overweight was observed. This confirms the role of obesity in the patogenesis of coronary artery disease, non-alcoholic fatty liver disease and systemic inflammation.

KEY WORDS: insulin resistance, body mass index, nonalcoholic fatty liver disease, coronary artery disease, high sensitivity C-reactive protein

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INTRODUCTION

Rapid globalization, urbanization, an aging society, and an increasing number of chronic diseases are posing new challenges for today's health care and economy. The progressive increase in the number of people with overweight or obesity makes it possible to speak of it as a pandemic of non-communicable origin. However, the number of patients with type 2 diabetes mellitus (T2DM) is increasing, which should be considered not only as an endocrine disease but also as a disease affecting the heart and blood vessels. Leading rolls in the pathogenesis of cardiometabolic complications are played by hyperglycemia, hyperinsulinemia and insulin resistance (IR), which lead to oxidative stress, endothelial dysfunction, activation of systemic inflammation and dyslipidemia [1].

Non-alcoholic fatty liver disease (NAFLD) is increasing globally and is the leading cause of chronic liver disease in developed countries. NAFLD often leads to poor quality of life, disability and death due to progression of steatosis, non-alcoholic steatohepatitis, fibrosis, cirrhosis, liver failure, and hepatocellular carcinoma. The prevalence of NAFLD in different countries ranges from 14-40 %. NAFLD is an integral part of the metabolic syndrome because the risk factors for it are dyslipidemia, IR or T2DM and obesity [2]. Moreover, it is the abdominal type of distribution of adipose tissue that often leads to the formation of NAFLD. NAFLD can be considered as a predictor of the development of an atherosclerotic process with which it has a common pathogenetic mechanisms - endothelial dysfunction, IR, oxidative stress. The pathogenesis of NAFLD is based on a change in the profile of hormones-regulators of fat metabolism of leptin and adiponectin. As a results, IR decreases the sensitivity of muscle and adipose tissue to insulin, leading to hyperglycemia or hyperinsulinemia. The latter increases lipolysis in adipose tissue, increases the level of free fatty acids (FFA) and slows down the rate of their β-oxidation in the mitochondria. The acceleration of the transport of FFA and their insufficient oxidation

leads to the accumulation of excess Triglycerides in the cytoplasm of hepatocytes and their secretion of a large number of very low density lipoproteins, which causes liver steatosis. Excessive FFA on the background of steatosis increases lipid peroxidation, promotes oxidative stress, increases the synthesis of TNF-α, IL-6,high sensitivity C-reative protein (hsCRP). These factors contribute to the activation of the inflammatory process, apoptosis, cytolysis, dystrophy and liver fibrosis, that is, the development of nonalcoholic steatohepatitis [3].

The traditional concept that positions adipose tissue as an energy depot was refuted when scientists demonstrated the link between pro-inflammatory cytokines and obesity. In obesity, the balance of pro- and anti-inflammatory adipokines changes towards the pro-inflammatory due to the increase in the volume of visceral adipose tissue and changes in its metabolism. Visceral fat is much more active in the endocrine plane than the subcutaneous, it is the secretion of factors that systematically affect the body's immune, metabolic and endocrine processes and cause damage to the endothelium, activation of leukocytes, impaired blood clotting, and the involvement of the coagulation system and impact on the complement system. An additional mechanism that contributes to inflammation associated with obesity is changes in the gut microbiota and increased intestinal wall permeability, which facilitates the passage of lipopolysaccharide complexes into the bloodstream, which leads to the development of chronic endotoxemia and increase the production of inflammatory factors. Components of metabolic syndrom generate chronic systemic low-grade inflammation, "metaflamation", which interferes with adipose tissue homeostasis [4, 5].

THE AIM

The aim of article is analyze the metabolic status of patients with coronary artery disease and nonalcoholic fatty liver disease depending on body mass index.

MATERIALS AND METHODS

Clinical trial was conducted with accorandce to the Declaration of Helsinki, The Convention for the Protection of Human Rights and Biomedicine, Legislation of Ukraine and agreed by commission on ethics of research, experimental development and scientific works of Danylo Halytsky Lviv National Medical University: Protocol No. 3 of March 25, 2019. All patients signed an informed consent before the study.

The patients enrolled in this study had coronary artery disease (CAD), NAFLD and overweight or obesity. The cohort of patients included 107 people (women – 26 (24,3 %), men – (81 (75,7 %). The average patients age was 60,3 (58,8;61,7) years. All patients were divided in two groups depending on BMI: 1stgroup 25-29.9 kg/m^2 (26,9 (25.5;28.0) kg/m^2), 2nd group >30kg/m^2(33.3 (31.9;35.9 kg/m^2). The degree and type of obesity were determined by WHO criteria and IDF (2015). Diagnosis of CAD was considered verified by the results of coronarography and/or the presence of myocardial infarction (MI) in anamnesis more than three months before. 102 (95,3%) patients had a history of MI and/or myocardial revascularization procedures. Treatment of patients with CAD was administered according to unified clinical protocol "Stable coronary artery disease" approved by the Ministry of Health of Ukraine № 152,dated 02.03.2016 (with amendments 23.09.2016 № 994) and Guidelines for the Management of Dyslipidaemias (ESC/EAS 2016).

Physical examination and anthropometric parameters was also conducted. Fasting glucose and serum glucose at 2 hours after drinking the glucose solution, insulin, glycated hemoglobin (HbA1c), HOMA-IR, lipids, hsCRP, ALT, AST, ALP, GGTP, creatinine, urea, uric acid were measured for all patients. The level of $HbA1_C$ in the whole blood was determined by turbidimetric assay method, using test system «HemoglobinA1c-direct» BioSystems (Spain). Insulin and hsCRP in serum was determined on chemiluminescent immunoassay analyzer «Immulite 2000» (Siemens, Germany) using a proper reagent (Immulite2000Insulin and Immulite 2000hsCRP, USA). Biochemical indices and lipids were performed by generally accepted methods on automatic analyzer «BioSystems» (Spain) using original set of reagents.

Insulin resistance index was calculated by the formula:

HOMA-IR=fasting insulin (μIU/ml)*fasting serum glucose (mmol/l)/22.5.

Patients with HOMA-IR>2.77 was insulin resistance (IR).

Elastography is used as an alternative to liver biopsy to assess liver stiffness owing to its accuracy, non-invasiveness and easy acceptance among patients. With the increasing prevalence of NAFLD worldwide, elastography is the most appropriate non invasive to assess fibrosis, NASH, and non-NASH NAFLD. A Toshiba Aplio 300 ultrasound device was used (Toshiba Medical Systems, Tokyo, Japan) .

The results are given as mean values with statistical error. The values with normal distribution are presented as confidence interval (95 %); and the values, where distribution significantly differ from normal, are presented as interval of 25 % and 75 % percentiles. Comparison of groups was performed by means of Mann-Whitney U-test. Categorical data were presented as proportions and analyzed using the Chi-square test. Spearman's rho correlation tests were used to report the associations between variables. The results were considered statistically reliable at $p<0.05$.

Table I. Data of lipid, glucose metabolism and liver and kidney function in patients with CAD, NAFLD and overweight (1stgroup) and patients with CAD, NAFLD and obesity (2nd group)

Baseline Characteristic	1st group, n=56	2nd group, n=51	P
HDL, mmol/l	1,25 (1,00;1,45)[2]	1,16 (1,08;1,24)[2]	0,04
LDL, mmol/l	2,73 (2,47;2,99)[1]	2,44 (1,96;3,26)[2]	0,07
Cholesterol, mmol/l	4,88 (4,54;5,22)[2]	4,31 (3,78;5,39)[2]	0,16
Triglycerides, mmol/l	1,37 (1,00;2,21)[2]	1,71 (1,43;1,99)[1]	0,01
ALT, U/l	24,65 (15,13;35,55)[2]	23,50 (15,80;42,15)[2]	0,28
AST, U/l	28,74 (26,19;31,29)[1]	25,20 (20,35;31,35)[2]	0,21
ALP, U/l	87,65(79,44;95,86) [1]	78,73 (78,22;84,52)[2]	0,14
GGTP, U/l	36,50(24,45;59,08)[2]	44,90 (27,70;64,75)[2]	0,09
Creatinine, mcmol/l	87,27 (83,09;91,45)[1]	89,91(89,40;93,44)[2]	0,11
Urea, mmol/l	5,71 (5,27;6,15)[1]	5,48 (4,97;5,86)[2]	0,19
Uric Acid, mcmol/l	379,17 (352,60;405,74)[1]	385,00 (308,50;456,00)[2]	0,34
Glucose, mmol/l	6,00 (5,50;6,42)[2]	6,11 (5,65;6,70)[2]	0,06
Glucose 2 ,mmol/l	7,52 (7,18;7,78)[2]	8,09 (7,71;8,47)[1]	0,03
HbA1, %	5,08 (4,90;5,26)[1]	5,30 (4,70;5,90)[1]	0,11
Insulin, μIU/ml	7,14 (4,56;11,33)[2]	13,00 (7,78;20,15)[2]	< 0,01
HOMA-IR	1,85 (1,28;3,01)[2]	3,49 (2,13;5,78)[2]	< 0,01

[1] – values with normal distribution, M (M-CI;M+CI).

[2] – values, where distribution significantly differ from normal, Me (25%;75%).

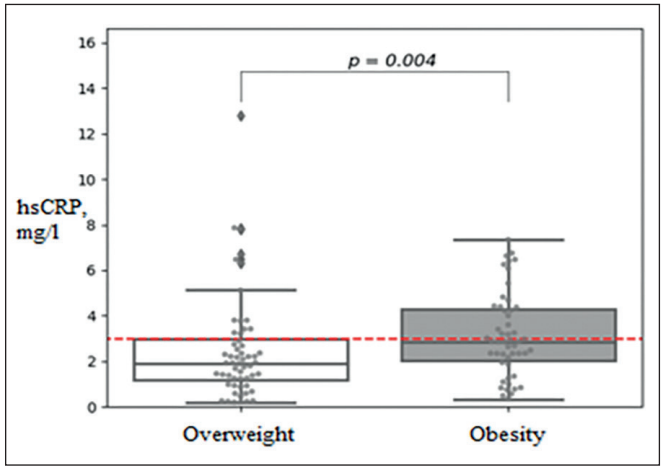

Fig. 1. Concentration of hsCRP in patients with CAD and NAFLD depending on the presence of obesity, p =0.004

RESULTS

During the analysis of serum lipid spectrum in patients with obesity: lower levels of HDL (1.16 (1.08;1.24) mmol/l versus 1.25 (1.00;1.45)) mmol/l, p<0.05) and higher TG concentration (1.71 (1.43;1.99) mmol/l vs 1.37 (1.00;2.21) mmol/l, p<0.05) compared with patients who had overweight. LDL levels were not significantly different between the groups, as they were more dependent on the statin dose taken by patients to correct dyslipidemia. The levels of liver enzymes, creatinine, urea, and uric acid were not significantly different between the groups.

Indicators of the carbohydrate spectrum also had great features in patients with coronary artery disease and obesity, the level of glycemia 2 hours after loading was significantly higher than in patients with overweight (8.09 (7.71; 8.47) mmol/l vs 7.52 (7.18; 7.78) mmol/l, p=0.03), the insulin level was almost twice as high as in patients with overweight (13.00 (7.78;20.15) μIU/ml versus 7.14 (4.56;11.33) μIU/ml, p<0.01), and the HOMA-IR index was 3.49 (2.13;5.78), where as in patients with overweight it was 1.85 (1.28;3,01), p < 0.01. Fasting glucose and HbA1c concentrations did not differ significantly between these groups. The proportion of patients with impaired glucose tolerance among patients with CAD, NAFLD and overweight was 21.4 % (12 patients), among patients with CAD, NAFLD and obesity - 33.3 % (17 patients), with no significant difference between the groups also (p=0.17). Among patients with coronary artery disease with obesity, the proportion of patients with hyperinsulinemia was significantly higher than among patients with BMI and was 52.9 % (27 people) versus 21.4 % (12 people) (p<0.01). The proportion of patients with HOMA-IR-confirmed IR was 58.8 % of patients with obesity (39 patients) and 30.4 % of patients with overweight (17 patients) and differed significantly between groups (p<0.01) (Table I).

In order to evaluate systemic inflammation, which is considered one of the pathogenetic mechanisms of atherosclerosis and cardiovascular risk factor, the concentration of hsCRP in the serum of patients was determined. The

proportion of persons with this marker increased in the BMI group was 25.0 %, where as in the obese group it was 43.1 %, p<0.05. The median and 25 % and 75 % percentiles of hsCRP in patients with CAD and overweight were 1.98 (1.18;2.98) mg/l, respectively, while in obese patients with CAD - 3,15 (2.64; 3.66) mg/l, the difference between the medians was statistically reliable (p<0.01). The clinical significance of hsCRP as a cardiovascular risk factor has a cut-off of 3.0 mg/l, and the upper quartile in the group with overweight was within this range. In contrast, for obese patients, the upper quartile exceeded the cut-off (Fig. 1).

We carried out a study to determine the value of liver stiffness measurement based on ultrasound elastography, in patients with NAFLD. In the first group the stage of fibrosis was F0- 93%, F1- 7%, in the second group the value was F0- 71%, F1,F2 - 29%.

In the study of correlations between BMI and lipid, carbohydrate metabolism, and hsCRP levels, there were significant associations with insulin levels (r=0.35, p<0.05), glycated hemoglobin levels (r=0.22, p<0.05) and hsCRP level (r=0.41, p<0.05). The lack of association with the lipid spectrum is evidently due to the effects of statin therapy in these patients.

DISCUSSION

Pandemic of obesity has led to an increase in research in this area. Accordingly, there is a new understanding of the mechanisms of development of CAD, NAFLD in obesity. In patients with cardiovascular pathology, widespread atherosclerosis, dyslipoproteinemia in 90% of cases fatty infiltration of the liver with elements of fibrosis occurs, which, according to the authors, is a pre-stage of steatohepatitis [1]. NAFLD is one of the most common chronic diseases associated with the accumulation of intrahepatic triglycerides.

Many scientific studies indicate that insulin resistance is characteristic of NAFLD, even without obesity. However, NAFLD alone cannot be considered a cause of insulin resistance, but rather a consequence.

A common pathogenetic mechanism of coronary heart disease and NAFLD is atherogenic dyslipidemia, which is found in 20-80%. A high correlation between total calcium index and lipid metabolism in patients with stable angina with NAFLD has been established. This indicates the direct involvement of disorders of lipid metabolism and systemic inflammation in the processes of atherogenesis of patients with NAFLD [5, 6].

Patient's age and long-term disease lead to deepening of lipid metabolism disorders in patients with comorbid pathology. The main cause of death of such patients are cardiovascular diseases [3]. "Non-lipid" risk factors for atherosclerosis include arterial hypertension, impaired carbohydrate metabolism, obesity, hypodynamia, smoking, and the like. Therefore, prevention should be aimed at correcting these risk factors as well.

Today, the issue of digestive organ dysfunction, in particular the liver and intestines, plays an important role in the development of dyslipidemia. Qualitative and quantitative changes of blood lipids are associated with inhibition of the activity of the reticuloendothelial system of the liver, enterohepatic circulation of bile acids, and impaired co-operation in the system. In the formation of insulin resistance in obesity plays an important role adipose tissue synthesizing, the effects of which affect the formation of dysmetabolic processes, oxidative stress, leading to disorders of the cardiovascular syste.

The Ajmal M.R. et al. study indicates that NAFLD is very common in patients with cardiovascular disease (69.2%) and is significantly associated with metabolic syndrome and its individual components. The levels of hsCRP and TNF-α were significantly higher in patients with NAFLD and showed an upward trend with increasing visceral fat [4, 7]. Kim J. et al. in retrospective study proved that the concomitant presence of NAFLD and systemic inflammation as assessed by hsCRP increases the risk of coronary artery calcification (non-invasive surrogate marker of atherosclerosis) development over four years [8].

Our study had some limitations: 1) the patients who participated in the study at the time of the examination received atorvastatin, β-blockers and diuretics at different doses for cardiovascular pathology, which could affect the metabolic profile; 2) the study did not have a control group with normal body weight, which could affect the interpretation of the indicators.

CONCLUSIONS

In patients with coronary artery disease, non-alcoholic fatty liver disease and obesity, the metabolic profile was characterized by a more unfavorable lipid spectrum: lower levels of HDL and higher triglicerid concentration. Carbohydrate metabolism in obese patients included disorders such us impared glucose tolerance (postprandial glycemia 8,09 (7.71;8.47) mmol/l vs 7.52 (7.18;7.78) mmol/l, p=0.03), hyperinsulinemia (serum fasting insulin 13.00 (7.78;20.15) μIU/ml vs 7.14 (4.56;11.33) μIU/ml, p<0.01) and insulin resistance (HOMA-IR 3.49 (2.13;5.78) vs 7.14 (4.56;11.33) μIU/ml, p<0.01). There was also a correlation between body mass index with insulin and glycated hemoglobin. Higher concentration hsCRP in obese compared with patients with overweight was observed (hsCRP 3.15 (2.64; 3.66) mg/l vs 1.98 (1.18; 2.98) mg/l, p<0.01) and significant associations BMI with hsCRP (r=0.41, p<0.05). This confirms the role of obesity in the patogenesis of coronary artery disease, non-alcoholic fatty liver disease and systemic inflammation.

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The Authors declare no conflict of interest.

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