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EC GASTROENTEROLOGY AND DIGESTIVE SYSTEM

Research Article

Association of Nonalcoholic Fatty Liver Disease with Heart Failure Preserved Ejection Fraction

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Received: January 31, 2018; **Published:** March 01, 2018

Abstract

Metabolic disorders in metabolic syndrome (MS) lead to a change in the structure and function of the myocardium, the vascular wall, the risk and severity increase of arterial hypertension, coronary heart disease, heart failure.

Currently, the non-alcoholic fatty liver disease (NAFLD) as a hepatic component of the metabolic syndrome is considered. NAFLD is an independent factor of cardiovascular risk. Increased visceral adipose tissue may reflect epicardial adipose tissue (EAT) deposition. EAT - a new marker of cardio-vascular diseases, is associated with the severity and severity of the NAFLD. We tested the correlation between epicardial fat, alterations in cardiac geometry and function, evaluated fatty liver index, NAFLD fibrosis score in patients with heart failure preserved ejection fraction and metabolic syndrome.

Keywords: *Epicardial Adipose Tissue; Fatty Liver Index; Metabolic Syndrome; Non-Alcoholic Fatty Liver Disease; NAFLD Fibrosis Score; N-Terminal Pro-Peptide of Type III Collagen*

Abbreviations

EAT: Epicardial Adipose Tissue; HF-pEF: Heart Failure Preserved Ejection Fraction; MS: Metabolic Syndrome; NAFLD: Non-Alcoholic Fatty Liver Disease

Introduction

Data of the World Health Organization and numerous clinical studies have shown a steady increase in the prevalence of metabolic syndrome (MS) in the world [1]. Special attention is necessary for patients with overweight in the primary prevention of chronic non-communicable diseases, such as cardiovascular disease and type 2 diabetes. Therapy aimed at addressing the risk factors of adverse outcomes is rational, if the patient has a disease associated with MS.

Metabolic disorders in MS lead to a change in the structure and function of the myocardium, the vascular wall, the risk and severity increase of arterial hypertension, coronary heart disease, heart failure.

Currently, the non-alcoholic fatty liver disease (NAFLD) as a hepatic component of the metabolic syndrome is considered. NAFLD is one of the most prevalent chronic liver disorders and is characterized by excessive fat accumulation in the liver (steatosis) [2]. Up to 30% of patients with NAFLD develop non-alcoholic steatohepatits (NASH), in which steatosis by liver-cell injury, inflammation, fibrosis and cirrhosis is accompanied [3].

In the DIREG-2 study, the rate NAFLD was 37,3%. The main trend for non-cirrhotic non-alcoholic fatty liver disease prevalence was the progressive increase along with age from 2,90% in 12 - 17 y.o. patients to 42,96% in 60 - 69 y.o. patients. The highest prevalence of non-alcoholic steatosis was 34,26% in patients aged 70 - 80. Non-alcoholic steatohepatitis was most frequent in patients aged 50 - 59 (10,95%) [4].

NAFLD is an independent factor of cardiovascular risk. Insulin resistance, endothelial dysfunction, oxidative stress, systemic inflammation as the main causes of cardiovascular risk (CVR) in the NAFLD are considered [5-9]. NAFLD often accompanies the main components of the metabolic syndrome. Increased amount of adipose tissue around the liver and heart leads to an increased CVR [10-12]. Steatosis of the liver and myocardial steatosis coexist and interact [13].

Materials and Methods

The study included 77 patients heart failure with preserved ejection fraction (HF-pEF). the diagnosis of HF-pEF was confirmed by quality measuring of NT-proBNP. 39 patients with with HF-pEF and MS made up the first group, the second - 38 patients patients with HF-pEF, without the metabolic syndrome. The presence of metabolic syndrome was defined by using the 2001 National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATPIII) criteria, which requires the presence of at least three of the five features [14].

Exclusion criteria: alcoholic liver damage, viral hepatitis, cirrhosis.

All patients measured the thickness of epicardial fat. The level of triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, total cholesterol, serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (GGT) and fasting glucose was assessed. Diabetes mellitus was diagnosed based on the American Association of Diabetes criteria [15].

Transthoracic mode echocardiogram using commercially available equipment (Siemens Sequoia 512 with a sector probe 3V2Cs) was performed. Standard parasternal and apical views in the left lateral decubitus position. The thickness of the epicardial fat was measured with the technique by Iacobellis [13].

Fatty Liver Index (FLI) [16]:

$$e^{0,953 \times \log e (TG) + 0,139 \times BMI + 0,718 \times \log e (GGT) + 0,053 \times WC - 15,745} /1+(e0,953 \times \log e (TG) + 0,139 \times BMI + 0,718 \times \log e (GGT) + 0,053 \times WC - 15,745) \times 100$$

NAFLD Fibrosis Score (NFS) [17]:

$$-1,675 + 0,037 \times A + 0,094 \times BMI + 1,13 \times IFG/\text{ diabetes (yes = 1, no = 0)} +0,99 \times AST/ALT - 0,013 \times PL - 0,66 \times Al$$

TG: Triglycerides, g/l; BMI: Body Mass Index kg/m^2; GGT: Gamma-Glutamyl-Transferase, IU/L; WC: Waist Circumference, sm; A: Age, Years; AST: Aspartate Aminotransferase, IU/L; PL: Platelets, 109/l; ALT: Alanine Aminotransferase, IU/L; Al: Albumin, g/dl.

In this group of patients we measured markers of collagen synthesis - N- terminal propeptide of collagen type III (PIIINP) to assess the process of fibrosis and the contribution of this process to the development of heart failure by means of immunoassay («USCN Life Science», China).

Statistical processing of the results out using the program Statistica 6 (StatSoft, USA) was carried.

Results

Characteristics of patients

Of the 77 patients - 25 (32%) males. The median age was 63,9 ± 10,3 years. The majority of patients in both groups were women (57% and 53%, respectively). The duration of heart failure in both groups was an average of 8 years. The differences in the duration of heart failure anamnesis in the two groups was not revealed (Table 1).

Variables	All patients n = 77	HF-pEF and MS n = 39	HF-pEF no MS n = 38	P
Age (yrs) (**μ ± σ**)	63,9 ± 10,3	63,0 ± 11,0	64,8 ± 9,5	0,6
Male, n (%)	25 (32)	17 (43)	18 (47)	1,0
Waist circumference (cm) (**μ ± σ**)	95,0 ± 6,6	107,9 ± 13,0	82,5 ± 7,9	0,00001
Waist-to-hip ratio (**μ ± σ**)	0,91 ± 0,75	0,94 ± 0,07	0,89 ± 0,06	0,00001
Body mass index; (Kg/m^2)	29,0 ± 5,80	33,1 ± 5,4	24,8 ± 1,9	0,00001
Duration of heart failure, years	8,3 ± 6,3	9,6 ± 7	7 ± 5,2	p = 0,07
Arterial hypertension n, (%)	72 (95)	39 (100)	33 (86)	0,03
Duration arterial hypertension, years	11,5 ± 9,25 10,0 (5,0 - 20,0)	13,9 ± 10,3 10,0 (5,0 - 20,0)	9,1 ± 7,4 8,5 (5,0 - 10,0)	0,03
Coronary heart disease, n (%)	49 (65)	25 (64)	24 (63)	0,52
Duration coronary heart disease, years	6,3 ± 6,1 7,0 (0,0 - 10,0)	6,5 ± 6,35 7,0 (0,0-10,0)	6,1 ± 5,3 6,0 (0,0 - 10,0)	1,0
I NYHA, n (%)	10 (13)	4 (10)	6 (16)	0,77
II NYHA, n (%)	32 (42)	16 (41)	16 (42)	
III NYHA, n (%)	30 (39)	17 (44)	13 (34)	
IV NYHA, n (%)	5 (6)	2 (5)	3 (8)	
Myocardial infarction/ acute coronary syndrome, n (%)	21 (27)	11 (28)	10 (26)	0,85
Stroke, n (%)	4 (5)	2 (5)	2 (5)	0,97
Violation of rhythm and conduction, n (%)	47 (61)	21 (54)	26 (68)	0,28
Diabetes n, (%)	18 (16)	18 (46)	0 (0)	0,0003
Hyperglycemia, n (%)	12 (23)	11 (28)	1 (3)	0,0003
cholelithiasis, n (%)	17 (22)	12 (31)	5 (13)	0,077
biliary sludge, n (%)	30 (39)	17 (43)	13 (34)	
Cholesterosis gallbladder, n (%)	5 (6)	3 (8)	2 (5)	
Ultrasonographic steatosis n, (%)	50 (64)	35 (89)	15 (39)	0,00015
Obesity, n (%)	26 (34)	26 (34)	0	0,00001
Overweight, n (%)	15 (19)	12 (31)	3 (7)	0,00001

Table 1: *Characteristics of 77 patients with HF-pEF both MS (group one) and no MS (group two).*

Was found ultrasound-measured liver steatosis in 89% of patients in the group one (GO) vs 39% in the group two (GT) (p = 0,00015).

Blood tests

In GO levels of ALT(p = 0,0064), GGT (p = 0,003) was higher (Table 2). The indices do not exceed the normal values, but in the group of patients with CHF and the metastatic syndrome of these indicators is higher. The following results were obtained in the GO: higher uric acid (p = 0.00003) and this increased with the arterial hypertension stage; the glucose was 6.6 ± 1.7 mmol/l; glucose significantly correlated with BMI (r = 0.52, p = 0.0001); glucose significantly correlated with waist circumference (r = 0.52, p = 0.0001); glycosylated hemoglobin was significantly (p = 0.0014) higher and was 5.8 ± 1.8%; HbA correlated with GGT (r = 0.69, p = 0.04 Lipid abnormalities were detected in both groups, and their frequency was not statistically different.

Variables (μ ± σ)	All patients n = 77	HF-pEF and MS n = 39	HF-pEF no MS n = 38	p
ALT ((U/L)	23,4 ± 17,00	26,1 ± 17,3	20,6 ± 16,7	0,0064
AST (U/L)	24,1 ± 14,3	26,1 ± 15,0	22,1 ± 13,4	0,065
GGT (U/L)	25,1 ± 20,8	30,7 ± 19,2	19,3 ± 7,2	0,003
Uric acid (μmol/l)	306,8 ± 133,9	370,5 ± 104,0	241,6 ± 126,4	0,00003
Fasting glucose (μmol/l)	5,9 ± 1,5	6,6 ± 1,7	5,1 ± 0,6	0,0001
HbA, %	5,2 ± 1,8	5,8 ± 1,8	3,9 ± 0,9	0,0014
Total cholesterol (mmol/l)	5,8 ± 1,4	5,5 ± 1,4	6,2 ± 1,4	0,032
Triglyceride (mmol/l)	1,7 ± 1,2	1,7 ± 1,0	1,6 ± 1,4	0,3
LDL-C (mmol/l)	4,1 ± 2,5	4,2 ± 3,2	3,9 ± 1,6	0,68
HDL-C (mmol/l)	1,3 ± 0,4	1,2 ± 0,4	1,3 ± 0,5	0,75

Table 2: *Laboratory ccharacteristics of 77 patients with HF-pEF both MS (group one) and no MS (group two). ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; GGT: Gamma-Glutamyl-Transferase; HbA: Glycosylated Hemoglobin; HDL-C: High-Density Lipoprotein Cholesterol; LDL-C: Low-Density Lipoprotein Cholesterol*

Echocardiography

The GO LV myocardial mass is greater 202.6 ± 64.4 g vs 163,4 ± 42,7 (p = 0.0032). The size of the heart chambers is larger than in the group two: ESD 3.55 ± 0.69 cm vs 3,24 ± 0,61 (p = 0.005); ESV 51.5 ± 23.3 ml vs 45,6 ± 22,0 (p = 0.012); RV 2,85 ± 0.50 cm vs 2,6 ± 0,32 (p = 0.005); RA 4.0 ± 0.62 cm vs 3,62 ± 0,69 (p = 0.011); LA 3.87 ± 0.69 cm vs 3,57 ± 0,72 (p = 0.016); IVST 1.14 ± 0.16 cm vs1,03 ± 0,11 (p = 0.004); LVPWth 1.12 ± 0.13 cm vs 1,03 ± 0,11 (p = 0.023). Thus, in patients with CHF and MS, the thickness of the walls and the size of the heart chambers is greater than in patients with CHF without MS (Table 3).

Variables	All patients n = 77	HF-pEF and MS n = 39	HF-pEF no MS n = 38	p
Epicardial fat , mm	2,46 ± 1,75	3,39 ± 1,82	1,51 ± 1,03	0,00001
E/A	0,88 ± 0,40	0,85 ± 0,34	0,91 ± 0,45	0,58
E/e'	5,44 ± 2,30	5,60 ± 2,25	5,26 ± 2,39	0,35
EDD, cm	4,91 ± 0,57	5,0 ± 0,54	4,82 ± 0,59	0,12
ESD,cm	3,40 ± 0,67	3,55 ± 0,69	3,24 ± 0,61	0,005
EDVI, ml	116,6 ± 32,8	120,5 ± 33,9	112,6 ± 32,6	0,173
ESV, ml	48,6 ± 22,7	51,5 ± 23,3	45,6 ± 22,0	0,012
LVM, g	184,1 ± 58,3	202,6 ± 64,4	163,4 ± 42,7	0,0032
EF (%)	59,1 ± 8,2	57,2 ± 6,73	59,4 ± 7,07	0,1
IVST, cm	1,09 ± 0,15	1,14 ± 0,16	1,03 ± 0,11	0,004
LVPWth, cm	1,07 ± 0,13	1,12 ± 0,13	1,03 ± 0,11	0,023
RV,cm	2,75 ± 0,43	2,85 ± 0,50	2,6 ± 0,32	0,036
RA, cm	3,81 ± 0,68	4,0 ± 0,62	3,62 ± 0,69	0,011
Left Atrial, cm	3,71 ± 0,72	3,87 ± 0,69	3,57 ± 0,72	0,016

Table 3: *Echocardiographic characteristics of 77 patients with HF-pEF both MS (group one) and no MS (group two). E/A: E to A ratio; E/e': E to e' ratio: EDD: End-Diastolic Dimension; ESD: End-Systolic Dimension; EDVI: End-Diastolic Volume; ESV: End-Systolic Volume; LVM: Left Ventricular Mass; EF: Ejection Fraction; IVST: Interventricular Septum Thickness; LVPWth: Thickness of Left Ventricular Posterior Wall; RV: Right Ventricular; LV: Left Ventricular; LA: Left Atrial.*

The epicardial fat thickness (EAT) in GO is 3.39 ± 1.82 mm vs 1,51 ± 1,03 (p = 0.00001). In GO EFT correlated with FLI (r = 0,52; p = 0,004); NFS (r = 0,29; p = 0,002); glycosylated hemoglobin (r = 0,41; p = 0,016); BMI (r = 0,29; p = 0,003).

FLI and NFS

FLI in GO 73.3 ± 20.1 vs 27.5 ± 18.8 (p = 0.00001) (Table 4). FLI correlated with glucose (r = 0,42; p = 0,009); glycosylated hemoglobin (r = 0,41; p = 0,011); LV myocardial mass (r = 0,48; p = 0,0001); EAT (r = 0,52; p = 0,004); LVPWth (r = 0,34; p = 0,004).

FLI	**All patients n = 77**	**HF-pEF and MS n = 39**	**HF-pEF no MS n = 38**	P
< 30, n (%)	26 (34)	0 (0)	26 (66)	0,001
30-59, n (%)	20 (26)	9 (23)	11(29)	0,55
≥ 60, n (%)	31 (40)	30 (77)	1 (3)	0,029
NFS	**All patients n = 77**	**HF-pEF and MS n = 39**	**HF-pEF no MS n = 38**	P
<-1,455, n (%)	7 (9)	2 (5)	5 (13)	0,0008
-1,455 - 0,675, n (%)	51 (65)	22 (56)	29 (76)	0,68
> 0,675, n (%)	19 (26)	15 (39)	4 (11)	0,006

Table 4: *Value FLI and NFS of 77 patients with HF-pEF both MS (group one) and no MS (group two).*

NFS in GO 0,45 ± 1,1, vs -0,46 ± 0,7 (p = 0,00001). Tabl.4. NFS correlated with glucose (r = 0,54; p = 0,001); glycosylated hemoglobin (r = 0,51; p = 0,002); total cholesterol (r = -0,43; p = 0,008); EAT (r = 0,29; p = 0,014); EDD (r = 0,27; p = 0,02); ESD (r = 0,27; p = 0,02); EDVI (r = 0,25; p = 0,02); ESV (r = 0,28; p = 0,02); LVM (r = 0,51; p = 0,005); AA (r = 0,45; p = 0,013); LA (r = 0,41; p = 0,023).

N- terminal Propeptide of Collagen Type III (PIIINP)

The level of PIIINP in the first group was 3.3 ± 1.5 μg / l against - 2.3 ± 1.3 μg / l in GT (p = 0.00046).In GO PIIINP was significantly higher in patients with III stage AH (p = 0,007 Kruskal-Wallis test); patients with abdominal obesity had significantly higher PIIINP (p = 0,0009 U-Mann-Whitney test), and is 3,3 ± 1,5 μg/l; the presence of hepatic steatosis, disorders of carbohydrate and lipid metabolism in the main group significantly affect the level of PIIINP (Table 5).

	HF-pEF and MS n = 39			p
Hepatic steatosis	No	Yes		0,025
	2,07 ± 0,8 μg/l	3,3 ± 1,5 μg/l		
Disorders of lipid metabolism	2,2 ± 1,0 μg/l	3,1 ± 1,5 μg/l		0,015
Disorders of carbohydrate	Normal	Hyperglycemia	Diabetes	p
	2,8 ± 0,8 μg/l	3,3 ± 1,6 μg/l	3,6 ± 1,6 μg/l	0,01

Table 5: *Factors affecting the level of PIIINP in patients with HF-pEF and MS (group one).*

The statistical analysis revealed significant correlations between laboratory data and PIIINP: uric acid (r = 0,37; p = 0,001); glucose (r = 0,29; p = 0,011); glomerular filtration rate (r = -0,37; p = 0,002); FLI (r = 0,47; p = 0,001); NFS (r = 0,31; p = 0,007).

Discussion

The statistical analysis revealed significant correlations between laboratory data and PIIINP: uric acid (r = 0,37; p = 0,001); glucose (r = 0,29; p = 0,011); glomerular filtration rate (r = -0,37; p = 0,002); FLI (r = 0,47; p = 0,001); NFS (r = 0,31; p = 0,007).

The obtained correlation of FLI, NFS with glucose level and glycosylated hemoglobin most likely reflect the process of steatosis and liver fibrosis with the progression of carbohydrate metabolism disorders in patients with MS and CHF. Also, based on the data obtained, we can assume the contribution of liver steatosis to the development of insulin resistance and the development of diabetes. D.E.S.I.R study revealed similar results. The study demonstrated that the risk of developing diabetes grew in were obtained in the general population when the value of FLI increased [19].

Visceral adipose tissue is an important indicator the fat content in the liver. Visceral adipose tissue is a self-endocrine organ, secreting adipocytokines and hormones that affect inflammation, insulin resistance and accumulation of fat in the liver. Some researchers hold the view that it is hepatic fat and not visceral adipose tissue is the main predictor of insulin resistance regardless of obesity, visceral adipose tissue and plasma adipocytokine levels. NAFLD is considered a highly sensitive marker of adipose tissue dysfunction [20].

Increased visceral adipose tissue may reflect epicardial adipose tissue (EAT) deposition. EAT - a new marker of cardio-vascular diseases [21] is associated with the severity and severity of the NAFLD [22]. Thickness of epicardial fat plays an important role in the development of the HF-pEF [23,24]. It is possible that EAT which secretes vasoactive molecules that regulate coronary arterial tone, and modulate inflammation [23], interferes with the autonomic nervous system determining both cardiovascular and liver damage [24].

In the majority of studies on the EAT, patients with AH, CHD, MS, AF, but without CHF were studied. In such studies, EAT was more than 5 mm. In one of the small works, where was studied the EAT in patients with CHF and AF, a lower EAT was revealed than in studies without CHF [25]. The results of our work 3.39 ± 1.82 mm vs 1.51 ± 1.03 mm also confirm this hypothesis. In our study, the relationship between EAT and FLI ($r = 0.52$, $p = 0.004$) NFS ($r = 0.29$, $p = 0.002$) was found.

Increased PIIINP predictor of decompensated HF, repeated hospitalization and mortality from the CVD. In addition, the PIIINP marker is a lesion of the liver. A number of studies in patients with HF-pEF and metabolic disorders marked by a higher level of this marker. In our work it was revealed that its level is significantly higher in the group of patients with MS and HF-pEF (3.3 ± 1.5 μg/L, $p = 0.00046$). Disorders of lipid and carbohydrate metabolism, hepatic steatosis is associated with an increase in PIIINP in patients with HF-pEF and MS. A number of studies have obtained data on the correlation PIIINP with the histological picture of NAFLD [26-28]. In our work similar results were obtained. In the group one, an increase in the value of FLI ($r = 0.47$, $p = 0.001$) and NFS ($r = 0.31$; $p = 0.007$) is accompanied by an increase in PIIINP.

Conclusion

The use of non-invasive methods for diagnostic steatosis and liver fibrosis, the determination of EAT in patients with HF-pEF and MS will identify patients at high risk, provide them with the necessary treatment and prevent worsening of CHF.

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Volume 5 Issue 4 April 2018