Fundamental researches

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TNF-ALPHA AND SERUM GALECTIN-3 IN NON DIABETIC PATIENTS WITH HEART FAILURE WITH PRESERVED LEFT VENTRICULAR EJECTION FRACTION

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Insulin resistance (IR) leads to structural abnormalities in the heart. Purpose of the study is to investigate the levels of serum Gal-3 levels (sGal3), THF-alpha (TNF-a), Nt-proBNP, HOMA index and insulin and their relationships in non-diabetic patients with heart failure with preserved left ventricular ejection fraction (HFpEF). Forty five non-diabetic patients (27 males and 18 females; mean age 60.4.1±9.7 years) with HFpEF were examined. Patients with diabetes mellitus were excluded. The serum sGal3, TNF-alpha, Nt-proBNP and insulin levels measured in serum by ELISA, according to manufacturer's instructions. Homeostasis Model Assessment (HOMA) index was calculated as a measure of IR at fasting state (IR=fasting glucose × fasting insulin/22.5).The echocardiographic parameters were measured with M- and B-mode and calculated following the American Guidelines of Echocardiography Society. Continuous variables are expressed as median (25th, 75th percentile). For nonparametric Spearman's correlation analysis and Mann-Whitney U test were used. All statistical tests were 2-tailed, and $p < 0.05$ was considered statistically significant.

It was found, that IR often occurs in non-diabetic patients with HFpEF. The sGal3, TNF-alpha and insulin are significantly increased in HFpEF patients with IR and without T2DM our study shows an association of the IR, TNF-alpha and sGal3 with echocardiographic parameters in the non diabetic with HFpEF. This fact may indicate the influence of IR on fibrogenesis process and thus facilitate the processes of myocardial remodeling.

KEY WORDS: insulin resistance, tumor necrosis factor alpha, galectin -3, fibrosis, heart failure with preserved ejection function

ФНП-АЛЬФА ТА РІВЕНЬ СИРОВАТКОВОГО ГАЛЕКТИНУ-3 У ХВОРИХ З СЕРЦЕВОЮ НЕДОСТАТНОСТЮ ЗІ ЗБЕРЕЖЕНОЮ СИСТОЛІЧНОЮ ФУНКЦІЄЮ ЛІВОГО ШЛУНОЧКА БЕЗ ЦУКРОВОГО ДІАБЕТУ

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Інсулінорезистентність (ІР) призводить до структурних порушень серця. Мета дослідження: Вивчити рівні сироваткового галектіну-3 (сГал-3), ФНП-альфа, Nt-proBNP, інсуліну та індексу HOMA та їхнього взаємозв'язку у пацієнтів з серцевою недостатністю зі збереженою фракцією викиду (СН-зФВ) без цукрового діабету.

Обстежено 45 пацієнтів (27 чоловіків і 18 жінок, середній вік - 60,4 ± 9,7 року) з СН-зФВ. Пацієнти з цукровим діабетом були виключені. Сироваткові концентрації сГал-3, ФНП-альфа, Nt-proBNP та інсуліну визначалася з використанням набору реактивів «ELISA» відповідно до інструкції виробника. Гомеостатичний індекс ІР (HOMA-IR) розраховували за формулою: HOMA-IR = глюкоза натще (ммоль / л) х інсулін натще (мкЕД / мл) / 22,5). Ехокардіографічні параметри вимірювалися в М- і В-режимах і розраховувалися згідно з рекомендаціями Американського ехокардіографічного товариства. Отримані дані представлені у вигляді медіани і інтерквартільного розмаху (25-й і 75-й процентилі). При порівнянні вибірок використовували непараметричний критерій U тест Манна -Уітні. Для встановлення взаємозв'язку кількісних ознак вибіркових даних застосовували ранговий коефіцієнт кореляції Спірмена (rs). Статистично значущими вважалися відмінності даних і кореляція між даними при $p < 0,05$.

Було встановлено, що ІР досить часто зустрічається у пацієнтів з СН-зФВ навіть без наявності цукрового діабету 2 типу. У ході нашого дослідження виявлено достовірна асоціація ІР, рівнів ФНП-альфа, галектіну-3 і ехокардіографічних параметрів серця у пацієнтів з СН-зФВ без порушень

вуглеводного обміну. Це може свідчити про вплив ІР на процеси фиброгенезу і таким чином сприяти процесам ремоделювання міокарда.

КЛЮЧОВІ СЛОВА: інсулінорезистентність, фактор некрозу пухлин альфа, галектін-3, фіброз, серцева недостатність із збереженою систолічною функцією лівого шлуночка

ФНО-АЛЬФА И УРОВЕНЬ СЫВОРОТОЧНОГО ГАЛЕКТИНА-3 У ПАЦИЕНТОВ С СЕРДЕЧНОЙ НЕДОСТАТОЧНОСТЬЮ С СОХРАНЕННОЙ ФРАКЦИЕЙ ВЫБРОСА БЕЗ САХАРНОГО ДИАБЕТА

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Инсулинорезистентность (ИР) приводит к структурным нарушениям сердца. Цель исследования: Изучить уровни сывороточного галектина-3 (сГал-3), ФНО-альфа, Nt-proBNP, инсулина и индекса HOMA и их взаимосвязи у пациентов с сердечной недостаточностью с сохраненной фракцией выброса (СН-СФВ) без сахарного диабета.

Обследовано 45 пациентов (27 мужчины и 18 женщин, средний возраст – 60,4 ± 9,7 года) с СН-СФВ. Пациенты с сахарным диабетом были исключены. Сывороточные концентрации сГал-3, ФНО-альфа, Nt-proBNP и инсулина, определялась с использованием набора реактивов «ELISA» в соответствии с инструкцией производителя. Гомеостатический индекс ИР (HOMA-IR) рассчитывали по формуле: HOMA-IR = глюкоза натощак (ммоль/л) х инсулин натощак (мкЕд/мл) /22,5). Эхокардиографические параметры измерялись в М - и В-режимах и рассчитывались согласно рекомендациям Американского эхокардиографического общества. Полученные данные представлены в виде медианы и интерквартильного размаха (25-й и 75-й процентили). При сравнении выборок использовали непараметрический критерий U тест Манна - Уитни. Для установления взаимосвязи количественных признаков выборочных данных применяли ранговый коэффициент корреляции Спирмена (rs). Статистически значимыми считались различия данных и корреляция между данными при $p < 0,05$.

Установлено, что ИР довольно часто встречается у пациентов с СН-СФВ даже без наличия сахарного диабета 2 типа. В ходе нашего исследования выявлена достоверная ассоциация ИР, уровней ФНО-альфа, галектина-3 и эхокардиографических параметров сердца у пациентов с СН-СФВ без нарушений углеводного обмена. Это может свидетельствовать о влиянии ИР на процессы фиброгенеза и таким образом способствовать процессам ремоделирования миокарда.

КЛЮЧЕВЫЕ СЛОВА: инсулинорезистентность, фактор некроза опухолей альфа, галектин-3, фиброз, сердечная недостаточность с сохраненной систолической функцией левого желудочка

INTRODUCTION

Heart failure (HF) is still a leading cause of both morbidity and mortality in Western society with increasing health care costs. Treatment of these patients requires considerable resources, part of which are spending on hospital care, and given the demographic trend in Ukraine to increase the proportion of the population in older age groups, the issues of the new methods development for prevention of progression, early diagnosis and treatment of heart failure is becoming very important [1]. It is known that diabetes mellitus (DM) aggravates the clinical course and prognosis of heart failure, particularly due to coronary heart disease (CHD). In recent years, the number of diabetic patients, mainly the type 2, in Ukraine has been increased considerably, and number of diabetic patients is about 1.1 million. It is expected that by 2025 the number of these patients reached the level of 5 %, [2], and globally the prevalence of diabetes is likely to increase from 371 million persons in 2013 to 552 million in 2030 [3]. This epidemic mainly refers to type 2 diabetes mellitus (T2DM), which is about 90-95 % of all cases. Modern lifestyle, environment and genetic factors, especially the interaction of the latter two, which influence the development of such an epidemic of diabetes, are closely associated with increased development and prevalence of obesity. Insulin resistance (IR) is a characteristic feature of obesity and type 2 diabetes mellitus and impacts the heart in various ways.

The problem of IR is extremely urgent today. IR is decrease sensitivity or response-veness to metabolic actions of insulin. Impaired insulin-mediated glucose uptake is a uniformly observed characteristic of the heart in these

states, although changes in upstream kinase signaling are variable and dependent on the severity and duration of the associated obesity or diabetes mellitus. The understanding of the physiological and pathophysiological role of insulin resistance in the heart is evolving.

An important role in the IR syndrome pathogenesis plays cytokines activation [4], and imbalance of these factors (increasing of interleukin (IL) -6, tumour necrosis factor (TNF) -α and decreasing of IL-10, IL-4) are considered as predictor of vascular complications. Proinflammatory cytokines are capable to modify cardiovascular function through a number of mechanisms that result in hypertrophy, dilation of the left ventricle (LV) of the heart, myocardial dysfunction, endothelial dysfunction, cardiomyopathy and fibrosis [5]. Because of this, in recent years, studies of pathophysiological role of cytokines in the pathogenesis of cardiovascular diseases which are not traditionally associated with inflammation, particularly HF various etiologies, are paid great attention [6].

To maintain high energy demands, the heart is capable of using many metabolic substrates. Although insulin signaling may directly regulate cardiac metabolism, its main role is likely the regulation of substrate delivery from the periphery to the heart, excess lipid accumulation in visceral adipose tissue. This actually causes acquisition of diabetogenic properties. In turn, visceral adipose tissue accumulates macrophages that release inflammatory cytokines, which can impair insulin sensitivity.

Thus, TNF-α increases the genes expression involved in the *de novo* synthesis of free fatty acids, which are responsible for insulin resistance and DM further formation [7]. Clinical studies confirm the connection between DM and LV dysfunction, which occurs regardless of hypertension or coronary artery disease presence. This coincides with the conclusions of the authors, who have demonstrated the relationship between the levels of proinflammatory cytokines and the degree of LV remodelling in patients with underlying metabolic disorders, including diabetes. [6].

Thus, changes in the myocardium in heart failure and presence of T2DM are morphologically characterized by hypertrophy of cardiomyocites and myocardial fibrosis due to a large number of extracellular matrixes in the interstitium of ventricular wall [8].

Recently in the literature a large number of myocardial fibrosis markers were described, - but special attention has been paid in patients with heart failure new biomarkers fibrosis - galectin-3. Galectin-3 is a 26 kDa chimaera-type galectin which is unique in that it is the only member of the galectin family [9] with an extended N-terminal domain constituted of tandem repeats of short amino acid segments (about 130 amino acids) linked to a single C-terminal carbohydrate-recognition domain. Whereas the C-terminal domain is responsible for lectin activity, the presence of the N-terminal domain is necessary for the full biological activity of galectin-3 [10, 11].

Galectin-3 is found in a wide range of species and tissues. Similar to other galectins, galectin-3 lacks a secretion signal peptide for classical vesicle-mediated exocytosis, so it is localized primarily in the cytoplasm, in the nucleus and mitochondria. When secreted into the extracellular space (via a non-classical secretory pathway that circumvents the endoplasmic reticulum and Golgi complex. Galectin-3 is involved in numerous pathological processes such as growth, proliferation, endogen inflammation and myocardial fibrosis. [12-14].

OBJECTIVE

Purpose the study is to investigate the levels of serum Gal-3 levels (sGal3), THF-alpha (TNF-a), Nt-proBNP, HOMA index and insulin and their relationships in non-diabetic patients with heart failure with preserved left ventricular ejection fraction (HFpEF).

MATERIALS AND METHODS

Forty five patients (27 males and 18 females; mean age 60.4.1 ± 9.7 years) with HFpEF, I-III NYHA functional classes with EF > 45 % of ischemic genesis without concomitant diabetes mellitus type 2 (T2DM) were examined. All patients were divided into two groups: 32 (71.17 %) patients with HFpEF and IR and 13 (28.9 %) patients with HFpEF and without IR. In control group were included 10 patients without HF, DM and IR (mean age 47.1 ± 9.5 years).

Functional status was determined using the NYHA-FC and the 6 min walk distance. Body weight was recorded in kilograms. Serum concentrations of Gal-3, TNF-alpha, insulin and Nt-proBNP were measured using an enzyme-linked immunosorbent assay with mono- and polyclonal antibodies according to manufacturer's instructions. Optical density measure-

ments were performed on a semiautomatic ELISA analyzer «Immunochem-2100». Serum concentrations of glucose were measured by glucose oxidase test according to manufacturer's instructions. Optical density measurements were performed on a semiautomatic biochemical analyzer CHEM-7. The sGal3 and insulin were measured in serum by ELISA. Homeostasis Model Assessment (HOMA) index was calculated as a measure of IR at fasting state (IR=fasting glucose × fasting insulin/22.5). The upper limit of the HOMA-IR was 2.77 [Wallace, 2004].

The echocardiographic parameters (left ventricular end-diastolic and systolic volume (LVEDV and LVESV), inter ventricular septum fractional thickening (IVSFT), inter ventricular septum fractional thickening (IVSFT), left ventricle posterior wall fraction thickening (LVPWFS), left ventricular ejection fraction (LVEF), E/A ratio) were measured with M- and B-mode echocardiography using Ultrasound's Vivid Three with a 2.5-MHz probe (Japan) and calculated following the American Guidelines of Echocardiography Society.

All of the statistical analyses were performed with the Microsoft Excel 7.0 and SPSS 21.0 Inc. software package. The distribu-tion of variables was analyzed with Kolmogorov-Smirnov test. Nonparametric variables were analyzed with Kruskal-Wallis test. To established the relationship between quantities parametric variables was used one-way analysis of variance (ANOVA) and Spearman's correlation analysis. Other differences were determined by one-way ANOVA. All statistical tests were 2-tailed, and $p < 0.05$ was considered statistically significant.

RESULTS AND DISCUSSION

All enrolled patients provided written informed consent. The exclusion criteria in the study were: heart failure with reduced ejection fraction < 45 %; type 1 and 2 DM, valvular heart disease; recent (up to 10 days) episodes of acute heart failure; acute coronary syndrome within the previous 3 months; inflammatory diseases in the acute stage; increase of thyroid function; cancer. The study protocol was approved by ethical committee of Government Iinstitution «L.T. Malaya Therapy National Institute of the National Academy of Medical Sciences of Ukraine». The baseline clinical characteristics of examined patients are displayed in table 1.

No statistical differences were detected in age, sex, systolic and diastolic blood pressure levels, heart rate, body mass index, 6-Minute walk distance, ejection fraction of LV and index E/A in Performance status scale scores and the distribution of NYHA class between groups (tab. 1).

Table 1

Baseline Demographic and Clinical Characteristics of the Study Population (Me [LQ; UQ]) (n=45)

Index	Group 1 - Patients with HFpEF and without IR (n=13)	Group 2 - patients with HFpEF and IR (n=32)	Control Group (n = 10)
Sex (male / female). n (%)	8 (61.5 %)/5 (38.5 %)	19 (59.4%)/13 (40.6 %)	13 (38.7 %)/18 (58.1 %)
Age. years	64.0 [57.0; 66.0]	60.50 [54.25; 65.0]	50,5 [37,8; 55,3]
Duration of HF. years	4.0 [2.5; 12.5] ♦	5.0 [2.0; 8.5] ■	0
Systolic blood pressure. mm Hg	160.0 [144.0; 170.0] ♦	170.0 [160.0; 179.0] ■	117,5 [110.5; 131,5
Diastolic blood pressure. mm Hg	100.0 [90.0; 100.0] ♦	100.0 [90.0; 100.0] ■	78.0 [71.0; 80.0]
Heart rate. bpm	77.0 [61.0; 82.0]	73.50 [66.50; 84.75]	68.0 [64.3; 71,5]
Body mass index. kg/m2	29.86 [28.91; 31.18] ♦	30.68 [29.14; 34.03] ■	25,8 [24,3; 27,0]
6-Minute walk distance. m	348.0 [272.0; 387.0] ♦	355.00 [298.50; 388.0] ■	582,5 [563,3; 600,3]
Performance status scale. score	2.0 [2.0; 3.0] ♦	3.0 [2.0; 3.0] ■	0 [0; 0]
NYHA class: II III	7 (53.8%) 6 (46.2%)♦	24 (75.0%) 8 (25.0%)■	0 [0;0]
Ejection fraction of LV. %	58.0 [57.0; 60.5] ♦	61.5 [57.25; 63.75] ■	65.5 [64,3; 68.5]
E/A	0.8 [0.8; 0.94] ♦	0.8 [0.8; 0.90] ■	1.6 [1.5; 1.6]

♦ - significant difference between the Group1 and Control Group ($p < 0,01$)
■ - significant difference between the Group2 and Control Group ($p < 0,01$)

IR was diagnosed in 32 (71.17 %) patients with HFpEF patients without a history of diabetes. In the group with HFpEF and IR the level of glucose, sGal3, TNF-alpha and insulin were significantly higher compared to the HFpEF patients without IR and controls ($p < 0.01$, $p < 0.05$, $p < 0.05$ and $p < 0.0001$ respectively) (tab. 2).

Table 2

Baseline Metabolic Profile of the Study Population (Me [LQ; UQ]) (n=45)

Index	Group 1 - Patients with HFpEF and without IR (n=13)	Group 2 - patients with HFpEF and IR (n=32)	Control Group (n = 10)
Glucose. mmol/l	4.75 [4.08; 5.17]	6.08 [5.37; 7.03] ✸	4,35 [3,66; 4,62] ■
Insulin. μIU/ml	7.99 [6.64; 10.29]	22.41 [15.79; 41.11] ✸	8,3 [5,5; 11.3] ■
HOMA-IR	1.56 [1.49; 2.18]	6.13 [4.07; 11.5] ✸	1,39 [1,05; 2,29] ■
Gal-3. ng/ml	3.04 [2.45; 3.17]	3.32 [2.82; 3.76] ✸	2.38 [2.25; 2.73] ■
TNF-alpha, pg/ml	3.21 [2.78; 4.44]	5.43 [3.69; 6.82] ✸	2,98 [2.46; 3.35] ■
Nt-pro-BNP, pg/ml	207.0 [125.54; 309.76] ♦	125.39 [110.93; 175.15]	125.09 [119,59; 262,82]

✸ - significant difference between the Group1 and Group 2 ($p < 0,05$)
♦ - significant difference between the Group1 and Control Group ($p < 0,01$)
■ - significant difference between the Group2 and Control Group ($p < 0,01$)

Glucose, insulin levels and index HOMA-IR was modestly correlated with left ventricular ejection fraction value ($r=0.371$; $p < 0.05$, $r=0.306$; $p < 0.05$ and $r=0.381$; $p < 0.01$, respectively) (tab. 3). BMI were modestly correlated with left ventricular ejection fraction value and IVSFT measures ($r=0.412$; $p < 0.01$ and $r=0.416$; $p < 0.01$, respectively) (tab. 3), also with serum TNF-alpha levels ($r = 0.345$, $p <0.05$); (tab. 4) in the general HF-patients population.

Table 3

Correlative relationship in HF-patients (n=45) (I)

Index	SBP	EF LV	IVSFT	LVPWFS	E/A
BMI		$r = 0.412$; $p < 0.01$	$r = 0.416$; $p < 0.01$		
Glucose	-	$r = 0.371$; $p < 0.05$	-	-	-
Insulin	-	$r = 0.306$; $p < 0.05$	-	-	-
Gal-3	$r = 0.359$; $p < 0.01$		-	-	$r = 0.316$; $p < 0.05$
HOMA-IR	-	$r = 0.381$; $p < 0.01$	-	-	-

Table 4

Correlative relationship in HF-patients (n=45) (II)

Index	Glucose	Insulin	HOMA-IR	TNF-alpha
BMI	-	-	-	$r = 0.345$; $p < 0.05$
Glucose	-	$r = 0.446$; $p < 0.05$	$r = 0.649$; $p < 0.0001$	$r = 0.399$; $p < 0.05$
Insulin	$r = 0.446$; $p < 0.05$	-	$r = 0.959$; $p < 0.0001$	-
Gal-3	-	-	-	$r = 0.548$; $p < 0.0001$

Serum galectin-3 levels were inversely correlated with the ratio of peak transmitral flow velocity (E/A) value ($r = -0.316$, $p < 0.05$); a directly correlated with SBP ($r = 0.359$, $p < 0.01$), serum TNF-alpha levels ($r = 0.548$, $p < 0.001$). Conversely, the serum TNF-alpha levels mildly correlated with glucose levels ($r = 0.399$, $p < 0.05$). The increasing of sGal3 levels associated with increasing TNFa levels ($\chi^2 = 7.379$, $p = < 0.05$) (tab. 4).

Among the patients included in the 2nd group (heart failure in combination with insulin resistance) (tab. 5) left ventricular ejection fraction value had a direct correlation with the serum concentration of TNF-alpha ($r = 0.362$, $p < 0.05$), HOMA index ($r = 0.394$, $p < 0, 05$); glucose ($r = 0.401$, $p < 0.05$). As a total group, patients with heart failure and insulin resistance had a direct association between the TNF-alpha level and galectin-3 ($r = 0.522$, $p < 0.01$) (tab. 5).

Table 5

Correlative relationship in HF-patients with IR (n=32)

Index	DBP	EF LV	IVSFT	LVPWFS	Gal-3
BMI			r = 0.523; p < 0.01	r = 0.521; p < 0.01	
Glucose	r = 0.363; p < 0.05	r = 0.401; p < 0.05	-	-	-
HOMA-IR	-	r = 0.394; p < 0.05	-	-	-
TNF-alpha		r = 0.362; p < 0.05			r = 0.552; p < 0.01

In the 1st group of patients (heart failure without insulin resistance) a strong inverse correlation between galectin-3 levels and E/A ratio ($r = -0.899$; $p < 0.0001$) was found. Also elevated insulin levels were associated with higher SBP and DBP values, but galectin-3 levels and index HOMA score had positive correlation with IVSFT ($r = -0.721$; $p < 0.01$) ($r = -0.645$; $p < 0.05$) and LVPWFS ($r = -0.714$; $p < 0.01$) ($r = -0.640$; $p < 0.05$) (tab. 6).

Table 6

Correlative relationship in HF-patients without IR (n=13)

Index	SBP	DBP	IVSFT	LVPWFS	E/A
Insulin	r = 0.601; p < 0.05	r = 0.818; p < 0.05	-	-	-
HOMA-IR	-	-	r = 0.645; p < 0.05	r = 0.640; p < 0.05	-
Gal-3	-	-	r = 0.721; p < 0.01	r = 0.714; p < 0.01	r = 0.899; p < 0.0001

There are some changing in the heart muscle caused by remodelling of morphological and anatomical structures of the heart, and sympathoadrenal and renin-angiotensin-aldosterone systems hyperactivity in HF. In patients with heart failure to meet the increased metabolic demands, which are increased in cardiac output occurs due to stroke output increasing, which leads to the development of left ventricular eccentric hypertrophy.

Myocardial dysfunction due to diffuse, not ischemic fibrosis associated with obesity [15], hypertension [16], aging [17] and diabetes mellitus [18].

At present, there are insignificant data about myocardial energy and humoral supplying, disruption of the mechanisms of their interaction and regulation in heart failure. There are evidences of the relationship of functioning efficiency, coronary heart disease (CHD) and hyperinsulinemia in heart failure patients. The severity of the clinical manifestations in heart failure determined by the insulin sensitivity of the myocardium and peri-

pheral muscle and insulin content in the blood. In our study we demonstrated that increasing the serum glucose, insulin levels and index HOMA-IR was modestly correlated with left ventricular ejection fraction value.

This is consistent with the results of recent meta-analyzes, where association of increasing insulin and glucose levels with increased risk of cardiovascular disease in non-diabetic patients was demonstrated [19, 20]. Moreover, elevated of serum glucose and insulin levels have pro-atherogenic properties [21], which may be the prospect of further research.

Whereas increasing insulin and glucose levels are a direct result of insulin resistance. IR may facilitate to the development of atherosclerosis not only by increasing glucose and insulin levels, but also through mechanisms which include, dyslipidaemia, hypertension, and inflammation [21, 22]. It is known that IRS-1 is the main substrate cytoplasmic enzymatic activity of the insulin receptor [23]. Interaction between TNF-a receptor and IRS-1 probably may inhibit the insulin signal transduction pathway in a cell by decreasing the tyrosine kinase activity of the insulin receptor and phosphorylation of tyrosine. In our study, it was found that the levels of TNF-alpha are progressively increased. At the same in our study the significantly higher TNF-alpha levels were observed in HFpEF and IR patients group compared with those without IR and controls.

Hyperglycaemia, which leads to microangiopathy, reduces the number of capillaries per unit area of the myocardium that leads to ischemia, cardiomyocites apoptosis and activation of fibrogenesis. Wakasaki H et al. demonstrated that increased activity of β-type protein kinase-C (PKC-β), induced by hyperglycaemia, leads to myocyte necrosis and fibrosis, which can be prevented by inhibition of PKC-β [24].

In our study increasing galectin-3 levels (marker of fibrosis) were founded in those patients, whose insulin, TNF-a levels and index HOMA were increased. Moreover, serum galectin-3 levels was inversely correlated with the ratio of peak transmitral flow velocity (E/A) value and had positive correlation with SBP values.

Metabolic factors may also play a role in the development of myocardial dysfunction; hyperinsulinemia and insulin resistance, that can be consequence of proinflammatory cytokine activation, may all contribute to myocardial fibrosis and myocardial dysfunction. Moreover, the deposition of advanced glycation end products (AGEs) may result in increased left ventricular stiffness and consequently to diastolic dysfunction [25].

In addition, modest correlation serum galectin-3 and TNF-a level was found in general population of HF-patients and at the presence of carbohydrate metabolism abnormalities in HF-patients. This dependence increases with the progression of IR. That may be due to increase of fibrosis degree in enhanced inflammation and insulin resistance.

CONCLUSIONS

1. IR was diagnosed in 71.1 % HFpEF patients without a history of diabetes.
2. Serum galectin-3, TNF-alpha and insulin are significantly increased in HFpEF patients with IR and without T2DM.
3. Serum galectin-3 levels were directly correlated with SBP, and inversely correlated with diastolic left ventricular dysfunction. With increasing serum galectin-3 levels increases diastolic dysfunction of the left ventricular severity.
4. Our study shows an association of the IR, TNF-alpha and sGal3 with echocardiographic parameters in the non diabetic with HFpEF. This fact may indicate the influence of IR on fibrogenesis process and thus influence the processes of myocardial remodeling in HFpEF patients.

PROSPECTS FOR FUTURE STUDIES

The study and analysis of the relationships between changes in levels of immunological inflammation, galectin-3, an index of insulin resistance, parameters of intracardiac hemodynamics in patients with heart failure of different etiologies are promising.

REFERENCES

1. Rekomendatsiyi Asotsiatsiyi kardiolohiv Ukrayiny z likuvannya khronichnoyi sertsevoyi nedostatnosti u doroslykh (perehlyad 2011 roku).

2. Haydayev Yu.O. Stan endokrynolohichnoyi sluzhby Ukrayiny ta perspektyvy rozvytku medychnoyi dopomohy khvorym z endokrynnoyu patolohiyeyu / Yu.O. Haydayev // Mezhdunarodnyiy endokrinologicheskiy zhurnal. — 2009. — № 2 (4). — S. 9-14.
3. International Diabetes Federation. IDF Diabetes Atlas. - 6th edn. - 2013.
4. Fasshauer M. Regulation of adipocytokines and insulin resistance / M. Fasshauer, R. Paschke // Diabetologia. – 2012. – Vol. 46 (12). – P. 1594–1603.
5. Mehra V.C. Cytokines and cardiovascular disease / V.C. Mehra, V.S. Ramgolam, J.R. Bender // J. Leukoc. Biol. – 2005. – Vol. 78(4). – P. 805–818.
6. Strissel K. J. Adipocyte death, adipose tissue remodeling, and obesity complications / K. J. Strissel, Z. Stancheva, H. Miyoshi // Diabetes. – 2007. – Vol. 56 (12). – P. 2910–2918.
7. Ritchie S. A. The role of insulin and the adipocytokines in regulation of vascular endothelial function / S. A. Ritchie, M. N. Ewart, C. G. Perry [et al.] // Clinical Science. – 2004. – Vol. 107. – P. 519–532.
8. Poornima I.G. Diabetic cardio-myopathy / I.G. Poornima, P. Parikh, R.P. Shannon // Circulat. Res. – 2006. – Vol. 98. – P. 596.
9. Dumic J. Galectin-3: an open-ended story / J. Dumic, S. Dabelic, M. Flögel // Biochim Biophys Acta. – 2006. – Vol. 1760. – P. 616-35.
10. Tseluyko V.I. Effektivnost aliskirena u bolnyih s fibrillyatsiey predserdiy / V.I. Tseluyko, Z.S. Vashakidze, T.V. Motyilevskaya [i dr.] // Liky Ukrayiny. – 2011. - № 4 (8). – S. 32-35.
11. McAlister F. Meta-analysis Global Group in Chronic Heart Failure (MAGGIC). Survival patients with heart failure with preserved or reduced left ventricular ejection fraction: an individual patient data meta-analysis / F. McAlister, C. Berry, R.N. Doughty [et. al.] // Eur Heart J. - 2012. – Vol. 33. – P. 1750–1757.
12. Vizir V.A. Biomarkeryi pri serdechnoy nedostatochnosti — novyie orientiryi lechebnoy taktiki? / V.A. Vizir, V.V. Popov, N.P. Kopitsa [i dr.] // Sertse i sudyny. — 2011. – № 2. – P. 108–113.
13. Calvier L. Galectin-3 Mediates Aldosterone-Induced Vascular Fibrosis / L. Calvier, M. Miana, P. Reboul [et al.] // Arterioscler Thromb Vasc Biol. – 2013. – Vol. 33(1). – P. 67-75.
14. deFilippi C.R. Galectin-3 in heart failure-linking fibrosis, remodeling, and progression / C.R. deFilippi, G.M. Felker // US Cardiology. – 2010. - Vol. 7. - P. 67-70.
15. Wong C. Obesity cardiomyopathy: pathogenesis and pathophysiology / C. Wong, T.H. Marwick // Nat Clin Pract Cardiovasc Med. - 2007. – Vol. 4. – P. 436–443.
16. Diez J. Mechanisms of cardiac fibrosis in hypertension / J. Diez // J Clin Hypertens (Greenwich). - 2007. – Vol. 9. – P. 546–550.
17. Tabet J.Y. Inflammation, cytokines and anti-inflammatory therapies in heart failure / J.Y. Tabet, M.E. Lopes, S. Champagne [et al.] // Arch. Mal. Coeur. Vaiss. – 2002. – Vol. 95(3). – P. 204–212.
18. Jellis C. Association of Imaging Markers of Myocardial Fibrosis With Metabolic and Functional Disturbances in Early Diabetic Cardiomyopathy / C. Jellis, J. Wright, D. Kennedy [et al.] // Circulation: Cardiovascular Imaging. - 2011. – Vol. 4. – P. 693-702.
19. Sangaralingham S.J. The aging heart, myocardial fibrosis, and its relationship to circulating C-type natriuretic peptide / S.J. Sangaralingham, B.K. Huntley, F.L. Martin [et al.] // Hypertension. – 2011. – Vol. 57. – P. 201–207.
20. Sarwar N. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies / N. Sarwar, P. Gao, S.R. Seshasai [et al.] // Lancet. – 2010. – Vol. 375. – P. 2215–2222.
21. Giacco F. Oxidative stress and diabetic complications / F. Giacco, M. Brownlee // Circ Res. – 2010. – Vol. 107. – P. 1058–1070.
22. Zherd'ova N.M. Vplyv insulinorezystentnosti na sertsevo-sudynni zakhvoryuvannya u patsiyentiv iz tsukrovym diabetom 2-ho typu ta metody yiyi korektsiyi / N.M. Zherd'ova // UKR. MED. CHASOPYS. – XI/XII 2013. – Vyp. 6 (98). - S. 53-54.
23. Uilyamz G. Rukovodstvo po diabetu / G. Uilyamz, D. Pikap // M.: MEDpress-inform, - 2003. – 248 s.
24. Wakasaki H. Targeted overexpression of protein kinase C beta2 isoform in myocardium causes cardiomyopathy / H. Wakasaki, D. Koya, F.J. Schoen [et al.] // Proc Natl Acad Sci USA. – 1997. – Vol. 94. – P. 9320–9325.
25. Bauters C. Influence of diabetes mellitus on heart failure risk and outcome / C. Bauters, N. Lamblin, E.P. McFadden [et al.] // Cardiovasc Diabetol. – 2003. – Vol. 2. – P. 1–16.