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**ADVANCED GLYCATED END PRODUCTS,
GALECTIN-3, MATRIX
METALLOPROTEINASE-9 ACTIVITY
IN MEN WITH HEART FAILURE AND
CONCOMITANT BENIGN PROSTATIC
HYPERPLASIA WITH ANDROGEN DEFICIENCY**

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Ключевые слова: *сердечная недостаточность, сохраненная фракция выброса, дефицит тестостерона, конечные продукты гликации*

Abstract. Advanced glycation end products, galectin-3, matrix metalloproteinase-9 activity in men with heart failure and concomitant benign prostatic hyperplasia with androgen deficiency. Nedzvetsky V.S., Sirenko O.Yu., Tkachenko V.A., Kuryata O.V. The aim was to evaluate serum levels of matrix metalloproteinases-9 activity, advanced glycation end products, galectin-3, C-reactive protein in men with heart failure and benign prostatic hyperplasia with testosterone deficiency. The testosterone level was determined by immune-enzyme analysis. The content of advanced glycation end products in plasma were analysed by quantitative autofluorescence. The metalloproteinases-9 activity was estimated with fluorometry. The level of galectin-3, C-reactive protein was determined by immune-enzyme analysis. 1st group was made up by the men with heart failure and benign prostatic hyperplasia with testosterone deficiency; 2nd group – by the men without testosterone deficiency. The men with heart failure and benign prostatic hyperplasia with testosterone deficiency had a significantly higher level of advanced glycation end products, galectin-3, matrix metalloproteinases-9 activity in comparison with men with heart failure without testosterone deficiency ($p < 0.001$). Correlation relations between serum advanced glycation end products in patients of the main group with age, ejection fraction, testosterone level were determined – $r = 0.48$ ($p < 0.001$), $r = -0.62$ ($p < 0.001$), $r = -0.66$ ($p < 0.001$) respectively. Receiver operating characteristic analysis for predictive role in heart failure with preserved ejection fraction have shown high degree of sensitivity and specificity for advanced glycation end products in serum ($p < 0.001$). Middle-aged men with heart failure with preserved ejection fraction and benign prostatic hyperplasia with testosterone deficiency are characterised by increased serum advanced glycation end products, galectin-3, matrix metalloproteinases-9 activity, C-reactive protein. Serum advanced glycation end products are potential biomarkers of development of heart failure with phenotype of preserved ejection fraction in this cohort.

Реферат. Кінцеві продукти глікації, рівень галектину-3, активність матриксної металопротеїнази-9 у чоловіків із серцевою недостатністю і супутньою доброякісною гіперплазією передміхурової залози з андрогенним дефіцитом. Недзвєцький В.С., Сіренко О.Ю., Ткаченко В.А., Курята О.В. Метою було визначити рівень активності матриксної металопротеїнази-9, рівні кінцевих продуктів глікації, галектину-3, С-реактивного білка в чоловіків із серцевою недостатністю та доброякісною гіперплазією передміхурової залози з дефіцитом тестостерону. Рівень тестостерону визначали за допомогою імуноферментного аналізу. Кінцеві продукти глікації в плазмі аналізували за допомогою методу кількісної автофлуоресценції. Активність матриксної металопротеїнази-9 оцінювали денситометрично. Рівень галектину-3, С-реактивного білка визначали за допомогою імуноферментного аналізу. Першу групу склали чоловіки із серцевою недостатністю та доброякісною гіперплазією передміхурової залози з дефіцитом тестостерону; другу – чоловіки із серцевою недостатністю та доброякісною гіперплазією передміхурової залози без дефіциту тестостерону. Чоловіки із серцевою недостатністю та доброякісною гіперплазією передміхурової залози з дефіцитом тестостерону мали достовірно вищий рівень кінцевих продуктів глікації, галектину-3, активності матриксної металопротеїнази-9 порівняно з чоловіками із серцевою недостатністю із відсутністю дефіциту тестостерону ($p < 0,001$). Визначено кореляційні зв'язки між кінцевими продуктами глікації сироватки крові в пацієнтів основної групи з віком, фракцією викиду, рівнем тестостерону – $r = 0.48$ ($p < 0,001$), $r = -0.62$ ($p < 0,001$), $r = -0.66$ ($p < 0,001$) відповідно. Результати receiver operating characteristic аналізу щодо прогностичної значущості розвитку фенотипу серцевої недостатності із збереженою фракцією викиду продемонстрували високий рівень чутливості та специфічності для кінцевих продуктів глікації сироватки крові ($p < 0,001$). Чоловіки середнього віку із серцевою недостатністю зі збереженою фракцією викиду та доброякісною гіперплазією передміхурової залози з дефіцитом тестостерону характеризуються підвищеним рівнем кінцевих продуктів глікації сироватки крові, галектину-3, активності матриксної металопротеїнази-9, С-реактивного білка. Кінцеві продукти глікації в сироватці крові є потенційними біомаркерами розвитку серцевої недостатності за фенотипом збереженої фракції викиду в цій когорті пацієнтів.

Despite the progress in the treatment of patients with heart failure (HF), significant morbidity and mortality of these patients are still observed [9]. There is a growing interest to the hormonal disorders that accompany HF, thus deficiency of testosterone has been shown an independent marker for worse outcomes in patients with HF [5, 7]. Several studies have shown that low testosterone level is independent risk factor for poor prognosis in male with HF, which is associated with decreased survival in patients with coronary heart disease [10, 13].

The last decade benign prostatic hyperplasia (BPH) has positioned as new metabolic disease of the aging male with high prevalence of cardiovascular comorbidity [6]. Several data indicate that a low testosterone, more than a high testosterone, might have a negative impact on prostate metabolism. Well-known fact that serum testosterone has been shown to decrease in men with age by approximately 2%-3% annually [8]. In this way aging men have increased risk of developing the both disorders – cardiovascular diseases and BPH.

The role of testosterone in HF developing is presented in formation of preserved ejection fraction (EF) especially after myocardial infarction (MI), but this mechanism remains poorly understood. The results of numerous studies have shown decreased testosterone level which is associated with metabolic syndrome progress, diabetes type 2 and cardiovascular disease [8, 12]. Further, low testosterone level was associated with high serum levels of insulin resistance, advanced glycation end products (AGEs) in men without diabetes [4, 14]. It should also be noted that testosterone attenuates matrix metalloproteinases (MMPs) activity and the cellular processes of intima in vitro [12]. Thus increased level of MMPs activity caused by low testosterone level may lead to progression of vascular remodeling.

The development and progression of cardiac fibrosis are associated with low testosterone level and increased inflammatory biomarkers [8]. However, the specific role of testosterone in pathways of myocardial remodeling with the formation of HF phenotypes remains not entirely clear.

The aim of present study was to evaluate serum levels of matrix metalloproteinase -9 activity, AGEs, galectin-3, C-reactive protein (CRP) in men with HF and BPH with testosterone deficiency and theirs predictive characteristic as biomarkers of heart failure with preserved ejection fraction (HFpEF).

MATERIALS AND METHODS OF RESEARCH

The study was conducted with approval from the Local ethics committee according to principles outlined in the Helsinki declaration. The study included men (n=39) aged 45 to 75 years with HF according to Europeans Society of Cardiology (ESC) guidelines and estimated diagnosis of BPH according to European Association of Urologists (EAU) guidelines [15]. Patients with acute myocardial infarction (<6 months), past Q-myocardial infarction, stable angina with functional class 4, diabetes mellitus, kidney insufficiency, hepatic failure, and prostate cancer were excluded.

Standard laboratory blood tests for erythrocyte sedimentation rate, C-reactive protein (CRP), haematological parameters, lipid profile, glucose, renal and liver function tests were performed in all patients. In order to evaluate the state of androgen deficiency the testosterone level was determined by the method of immune-enzyme analysis with the reagent test kit "AccuBind ELISA".

The fluorescent AGEs in plasma were analysed by quantitative autofluorescence (fluorometer Hoefer DQ 2000, USA) with fixed spectrum of excitation at 460 nm with 20% quinine solution as a standard with results expressed with conversion to glycated albumin [2].

The MMP-9 activity was analyzed by separating serum proteins (100 µg/track) in 7.5% SDS-PAGE gel copolymerized with gelatin (3 mg/ml). After electrophoresis, the gel was washed twice for 30 min in gold 2.5% (v/v) Triton X-100 to remove SDS, and then 5 times for 5 min in cold deionized water. After washing, gel were incubated overnight at 37°C in developing 50 mM tris-HCl buffer (pH 7.6), containing 0.15 M NaCl, 5 mM CaCl₂, 1 mM ZnCl₂, and 0.02% Tween-80. The zymograms were visualized and analyzed densitometrically. The results of the analysis were interpreted semi-quantitatively in arbitrary units (a.u.) of optic density compared to the control sample (men with HF without BPH) [11]. The level of galectin-3, CRP was determined by the method of immune-enzyme analysis with the commercial kit "AccuBind ELISA".

All patients were divided into two main groups: 1st group with 20 men with HF and BPH with testosterone deficiency (testosterone level less than 2.5 ng/ml); 2nd group – 19 men with HF and BPH without testosterone deficiency.

Control group consisted of 33 healthy men without HF and normal testosterone level.

Clinical characteristics of patients were summarized in Table 1.

Statistical analysis of the obtained results was performed using the licensed program STATISTICS (license No. AGAR909E415822FA). Non-parametric statistics were used. The data was presented in the form of a median (Me) and the interquartile segment [25%; 75%]. Continuous data were described as median (interquartile range) and compared with Mann-Whitney U test. Categorical were described as n (valid %) with account for missing data and compared using Fisher's exact test. For comparison of indicators in two independent groups, Mann-Whitney U test was used. The Spearman rank-order correlation analysis was performed. We used the Receiver Operating Characteristic (ROC) curve to evaluate the potential of AGEs, galectin-3, CRP and MMP-9 as putative biomarkers for the development of the clinical forms of HF. Statistically significant differences in research results were determined at a level of p<0.001 [1].

Table 1

Baseline characteristics of the study patients

Characteristic	Study patients (n=39)	Control group (n=33)	p
Median of age, years	66 [57.5; 74.4]	64 [54.4; 72.8]	0.25
Median level of left ventricle ejection fraction, %	62 [51; 68]	64 [53; 69]	0.33
Glomerular filtration rate (GFR), ml/(min 1.73 m ²)	74 [61; 79]	76 [65.4; 81.5]	0.36
Systolic blood pressure, mm Hg	138.5 [125.8; 144.6]	134.2 [127.4; 142.8]	0.61
Diastolic blood pressure, mm Hg	75.6 [71.4; 78.3]	72.4 [70.3; 76.2]	0.47
Heart rate per minute	68.7 [62.4; 75.9]	68.7 [62.4; 75.9]	0.24
Functional class (FC) (NYHA), %:			
II	64	62	0.35
III	33	39	0.14
Patients, received cardiology treatment (%):			
ACE inhibitors/ACE receptors blockers	82	77	0.25
Diuretics	77	73	0.38
Aldosterone antagonists	82	76	0.44
β-blockers	74	76	0.42
Calcium antagonists	69	62	0.31
Statins	56	54	0.36
Antiplatelet agents	77	70	0.58

Note: p – between study and control groups (Mann-Whitney U test).

RESULTS AND DISCUSSION

The level of AGEs in patients with with HF and BPH with testosterone deficiency ranged from 0.112 to 0.184 a.u./ml, the median was 0.157 [0.069; 0.197] a.u./ml, in the control group – 0.082 [0.048; 0.101] a.u./ml respectively (p=0.0003). Increased level of AGEs was established in 21 (53.8%) patients of main group and 13 (39.4%) of controls (p<0.001). It was found that men with HFpEF and BPH with testosterone deficiency had a

significantly higher level of AGEs in comparison with men with HF with reduced EF (HFpEF) and testosterone deficiency and with controls (p<0.001) (Table 2). Correlation relations between serum AGEs in patients of the main group with age, EF, testosterone level were determined – r=0.48 (p<0.001), r= -0.62 (p<0.001), r= -0.66 (p<0.001) respectively.

Table 2

Serum levels of AGEs, galectin-3 in men with HF and BPH with testosterone deficiency depending on EF

Indicator	1 st group HFpEF and testosterone deficiency n=20 Me [25%;75%]	2 nd group HFpEF and testosterone deficiency n= 19 Me [25%;75%]	Control 1 HFpEF without testosterone deficiency n=18 Me [25%;75%]	Control 2 HFpEF without testosterone deficiency n=15 [25%;75%]
Advanced glycation end products (AGE), a.u./ml	0.106 [0.082; 0.128]	0.156 [0.134; 0.199] *	0.099 [0.070; 0.111] @	0.095 [0.084; 0.116]@
Galectin-3, ng/ml	5.2 [3.9; 7.8]	7.3 [6.8; 9.1] *	4.6 [3.1; 6.5]	5.1 [4.0; 6.4]@

Notes: * – p<0.001 between 1 and 2 groups; @ – p<0.001 between 1 and 2 groups and control 1, 2 respectively.



Increased level of galectin-3 was established in 27 (69%) patients of main group and 13 (32%) of controls ($p<0.001$). The median galectin-3 level in patients with HF and BPH with testosterone deficiency was 6.4 [6.1; 9.5] ng/ml, in the control group – 5.2 [4.1; 6.3] ng/ml ($p<0.001$). The significant difference was established between 1st, 2nd and control groups ($p<0.001$) (Table 2). The galectin-3 level correlated with age ($r=0.74$, $p<0.001$),

serum AGEs level ($r=0.57$, $p<0.001$), GFR ($r= -0.48$, $p<0.001$).

The level of MMP-9 activity in patients with HF and BPH accompanied by testosterone deficiency ranged from 11.2 to 18.4 a.u., the median was 215.7 [165.9; 225.7] a.u., in the control group 178.2 [154.8; 186.1] a.u. respectively ($p=0.003$). It was established significant differences between study groups in activity of MMP-9 level (Table 3).

Table 3

Levels of MMP-9, CRP in men with HF and BPH with testosterone deficiency depending on EF

Indicator	1 st group HF rEF and testosterone deficiency n=20 Me [25%;75%]	2 nd group HF pEF and testosterone deficiency n=19 Me [25%;75%]	Control 1 HF rEF without testosterone deficiency n=18 Me [25%;75%]	Control 2 HF pEF without testosterone deficiency n=15 [25%;75%]
MMP-9, a. u.	221.8 [195.4; 236.9] *	180.4 [172.4; 192.5]	178.2 [158.9; 184.7] @	168.8 [150.9; 177.2]@
CRP, mmol/l	6.3 [4.8; 8.1]	5.2 [3.9; 7.8]	5.1 [4.0; 6.4]@	4.6 [3.4; 6.9]

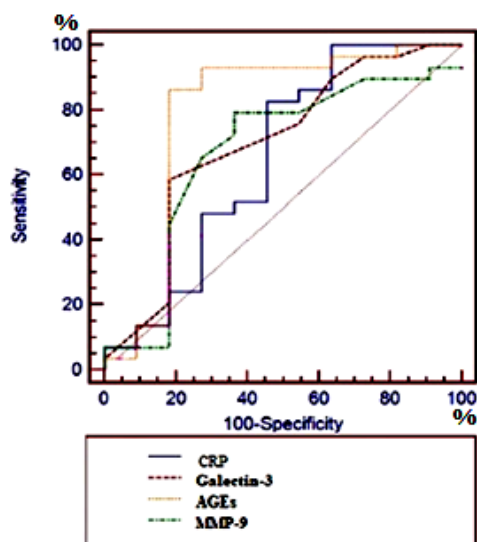
Notes: * – $p<0.001$ between 1 and 2 groups; @ – $p<0.001$ between 1 and 2 groups and control 1, 2 respectively.

Patients with testosterone deficiency had significantly higher MMP-9 activity level by 16% than HFpEF men with BPH and testosterone deficiency, by 25% than HFpEF men without testosterone deficiency ($p<0.001$). The correlations were observed between MMP-9 activity and ejection fraction, serum AGEs level, testosterone level – $r=0.52$ ($p<0.001$), $r=0.58$ ($p<0.001$), $r=0.66$ ($p<0.001$) respectively in the patients of the HF and BPH.

The median CRP level in men with HF and BPH with testosterone deficiency was 6.6 [4.9; 7.1] mmol/l,

in the control group – 5.6 [3.5; 6.2] mmol/l ($p<0.001$). The significant differences were established between 1st group and control 1 group ($p<0.001$) (Table 3). HF rEF patients with testosterone deficiency had significantly higher CRP level by 23% than HF rEF men without testosterone deficiency ($p<0.001$). The CRP level correlated with MMP-9 activity level ($r=0.73$, $p<0.001$), serum AGEs level ($r=0.67$, $p<0.001$), GFR ($r= -0.58$, $p<0.001$).

ROC-analysis results for serum AGEs have shown a high degree of sensitivity and specificity (Fig.).



Indicator	AUC	SE	p level
CRP	0.648	0.102	0.0451
Galectin-3	0.694	0.099	0.0003
AGEs	0.790	0.073	0.0002
MMP-9	0.671	0.101	0.0009

ROC curve analysis for evaluation of prognostic role of biomarkers for development of HfpEF in men with HF and BPH with testosterone deficiency

Most patients with HFpEF are generally of the age group older age group and have multiple comorbidities including androgen deficiency. The study by Chung et al. explores possible cardiac mechanism of testosterone a modulatory role in cardiac fibrosis [5]. The authors reported no change in baseline cardiac fibroblast proliferative and migration potential, but described an androgen receptor-mediated antiproliferative, anti-collagen and anti-fibrotic effect of physiological testosterone levels in the myocardium unaffected by a pathological process. Although they recognized that the cardiac fibroblasts were from normal hearts, the authors' conclusion was that testosterone decreased the production of collagen after transforming growth factor- β 1 and angiotensin II stimulation which can attenuate the genesis of cardiac fibrosis under pathological conditions. However, in pathological conditions testosterone effects could be quite the opposite. There is a possibility that normal testosterone levels within a physiological range have beneficial biological effects only in relatively healthy individuals from the cardiovascular point of view. Although supplementation of testosterone in HF should be considered as potentially increasing the risk of cancer.

In the present study, we demonstrated that besides metabolic risk factors serum levels of AGEs were correlated with low testosterone levels in non-diabetic men with HFpEF and BPH. Besides, serum level of AGEs has demonstrated good prognostic characteristic concerning developing HFpEF while galectin-3, CRP, MMP-9 activity level had not

enough predictive strength. There is accumulating evidence that AGEs play a role in the development and progression of cardiovascular diseases in both animal models and humans [4]. In addition, Koska et al. has reported that serum levels of AGEs could predict total, cardiovascular disease and coronary heart disease mortality in non-diabetic subjects, especially women [3]. These observations suggest that high circulating levels of AGEs may partly explain the increased risk of future cardiovascular events in men with low testosterone.

In addition the present research demonstrates in men with BPH testosterone deficiency associates with increasing both of fibrosis and inflammation markers that correlates with intensive glycation process. Certainly further studies in respect with this area are required.

CONCLUSION

1. Middle-aged men with heart failure with preserved ejection fraction and benign prostatic hyperplasia are characterised by significantly increased serum advanced glycation end products, galectin-3, matrix metalloproteinase-9 activity, C-reactive protein levels.

2. Serum advanced glycation end products are potential biomarkers of development heart failure with phenotype of preserved ejection fraction in men with benign prostatic hyperplasia and testosterone deficiency.

Conflict of interests. The authors declare no conflict of interest.

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