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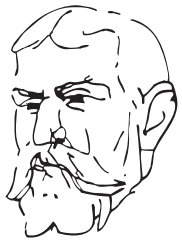

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CONTENTS

ORIGINAL ARTICLES

ORIGINAL ARTICLE

ESTIMATION OF PREDICTORS AND DEVELOPMENT OF PROGNOSTIC MODEL FOR COMORBID COURSE OF DIABETES MELLITUS AND ISCHEMIC HEART DISEASE

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Marharyta V. Koshkina, Volodymyr D. Babadzhan, Olga I. Kadykova
KHARKIV NATIONAL MEDICAL UNIVERSITY, KHARKIV, UKRAINE

ABSTRACT

The aim: To determine predictors and develop the model of prognosis of comorbidity of ischemic heart disease and type 2 diabetes mellitus.

Materials and methods: 126 patients were involved in the study and divided into three groups. Main group involved 70 patients with comorbid T2DM and IHD; comparison group included 36 IHD-only patients; 20 patients were included into control group.

Results: Predictors of comorbid T2DM and IHD included titin (OR = 0.001 [95.0 % CI 0.001–0.105], p = 0.021); I and II grade hypertension (respectively OR = 28.993 [95.0 % CI 1.595–526.940], p = 0.023 and OR = 19.050 [95.0 % CI 1.078–336.620], p = 0.044); left ventricle hypertrophy (OR = 3.169 [95.0 % CI 1.103–3.108], p = 0.032); very low density cholesterol level (OR = 49.032 [95.0 % CI 4.155–578.644], p = 0.022); and stenocardia symptoms in significant physical load (OR = 6.199 [95.0 % CI 1.129–34.039], p = 0.036).

Conclusions: developed model can be used in prediction of comorbid course of T2DM in patients with IHD for early diagnosis of cardiovascular complications in such patients.

KEY WORDS: prediction, comorbidity, type 2 diabetes mellitus, ischemic heart disease

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INTRODUCTION

According to International Diabetes Federation, worldwide prevalence of diabetes is 415 million cases, of which 91.0 % is Type 2 diabetes mellitus (T2DM) [1]. By 2040 it is expected that prevalence of T2DM will rise to 642 million cases [1,2].

Among all cases of T2DM more than 50 million cases are in Europe [3]. In recent decades incidence of the disease increased almost three times and will additionally double in next decades [4].

Frequently T2DM triggers development of various cardiovascular diseases [5]. The most frequent of them is chronic insufficiency of coronary blood stream (leads to hypoxia and violations of contractility and relaxation of myocardial) [6]. Moreover T2DM the development of the diastolic dysfunction (up to 75% of cases), which relates to excessive weight, violation of glucose metabolism and development of ischemic heart disease (IHD) [7], which burdens the course of T2DM [8].

According to data, T2DM decreases live duration on more than 10 years [9], mostly due to cardiovascular diseases which are the common causes of morbidity and mortality in T2DM [10]. To date, comorbidity, accompanied with aging, and deterioration of overall health, is significant medical burden [10-21]. According to meta-analysis [1] weighted mortality rates in T2DM 9.9% [95% CI 8.6–11.3%], and comparison causes of death for IHD, stroke or cerebrovascular diseases (respectively 29.7 % [95.0% CI 25.1–34.4 %] and 11.0 % [95.0 % CI: 8.8–13.3 %]).

Data show that T2DM is the comparison risk factor of IHD [11]. According to the study in China 52.9% of hospitalized patients with IHD had diabetes mellitus, and 25.1% of patients with diabetes had IHD [10].

To date significant researchers are trying to study various clinical, instrumental, and epidemiological characteristics of patients with comorbid course of T2DM and IHD in order to provide early diagnosis and treatment for prophylaxis of possible complications. Among biochemical markers, one of the most promising is assessment of titin levels in blood serum, which was shown to have good prognostic possibility.

Titin is large sarcomere protein and is responsible for strength of cardiomyocytes. According to database (Universal Protein Resource, 2017), titin relates to various cardiovascular processes: contraction of heart muscle, development of heart muscle, hemostasis, heart hypertrophy, production of heart myofibrils etc. [12]. Several researchers found that violations of regulation titin are closely connected with different cardiovascular diseases (heart failure (HF), IHD, hypertension etc.) [13]. It was also found in other researchers [12], that titin has high prognostic value, as activity of myocardial exone N2B (cardiac titin) patients with cardiovascular diseases could serve as myocardium damage marker [14].

Thus, assessment of titin levels in blood serum of patients with T2DM and ischaemic heart disease and finding of associations with additional clinical and anamnestic parameters is actual task of modern medicine.

Table I. Frequency analysis of comparison and co-existent pathology (no., %)

Index		Control (n = 20)	IHD (n = 36)	IHD+T2DM (n = 70)	p_1	p_2
HF stage	I	0 (0.0)	14 (38.9)	20 (28.6)	< 0.001	0.503
	II A	0 (0.0)	20 (55.6)	47 (67.1)		
HTN stage	No	20 (100.0)	6 (16.7)	1 (1.4)	< 0.001	0.011
	2	0 (0.0)	21 (58.3)	47 (67.1)		
	3	0 (0.0)	9 (25.0)	22 (31.4)		
Functional classes						
Significant load (I functional grade)		0 (0.0)	29 (80.6)	67 (95.7)	< 0.001	0.011
Walking with regular speed > 500 m (II functional grade)		0 (0.0)	19 (52.8)	40 (57.1)	< 0.001	0.668
Walking with regular speed < 500 m (III functional grade)		0 (0.0)	11 (30.6)	14 (20.0)	0.023	0.225
Any physical load or rest (IV functional grade)		0 (0.0)	4 (11.1)	3 (4.3)	0.173	0.180

Note: p_1 – significance of differences between all groups; p_2 – significance of differences between main and comparison groups

Table II. Lipid metabolism and titin levels in studied patients, M ± SD

Index	Control (n = 20)	IHD (n = 36)	IHD+T2DM (n = 70)	p_{1-2}	p_{1-3}	p_{2-3}
TC, mmol/L	4.50 ± 0.32	4.93 ± 1.10	5.21 ± 1.51	0.087	0.083	0.443
HDL, mmol/L	1.42 ± 0.16	1.27 ± 0.30	1.34 ± 0.25	< 0.001	0.039	0.045
TG, mmol/L	0.80 ± 0.11	1.41 ± 0.47	1.88 ± 0.81	< 0.001	< 0.001	0.005
LDL, mmol/L	2.89 ±0.27	2.80 ± 1.26	2.90 ± 1.40	0.784	0.763	0.889
VLDL, mmol/L	0.40 ± 0.01	0.65 ± 0.19	0.91 ± 0.38	< 0.001	< 0.001	< 0.001
AC	2.53 ± 0.17	2.97 ± 1.06	2.96 ± 1.35	0.266	0.337	0.684
Titin, ng/ml	0.37 ± 0.05	0.24 ± 0.05	0.22 ± 0.04	< 0.001	< 0.001	0.05

Note: p_{1-2} – significance of differences between control group and isolated IHD; p_{1-3} – significance of differences between control group and common orbit IHD+T2DM; p_{2-3} – significance of differences of differences between isolated IHD and comorbid IHD+T2DM.

THE AIM

The aim was to investigate predictors and develop the modal of prognosis of comorbidity in IHD and T2DM.

MATERIALS AND METHODS

The study included 126 patients. Main group included 70 patients with comorbid IHD and T2DM (28 (40.0%) of men and 42 (60.0%) of women); comparison group included 36 patients with isolated IHD (21 (58.3%) of men and 15 (41.7%) of women). Control group included 20 individuals (11 (55.0%) of men and 9 (45.0%) of women.

The ethical approval was obtained from Bioethics Committee of the Kharkiv National Medical University. All the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008, as well as the national law.

RESULTS

Distribution of patients by heart failure stage showed non-significant (p=0.503) prevail of heart failure of I functional class in comparison compared to main group (respectively 38.9% and 28.6%). In comorbid IHD+T2DM group there were more patients with heart failure of IIA functional class then in comparison group (respectively 67.1% and 55.6%) — table I.

Regarding the presents and stage of hypertension (HTN) the results show to the next data. Significantly (p=0.011) comparison group compared to main group had more patients with no hypertension (16.7% and 1.4%). Hypertension of II and III grade was observed frequently in IHD+T2DM group than in IHD-only group (respectively 67.1% vs. 58.3% and 31.4% vs. 25.0%) — table I.

Analysis of limitations of physical activity showed that patients with comorbid T2DM developed symptoms under significant load more frequently than patients with IHD+T2DM: respectively 95.7 % and 80.6 % (p = 0.011). Symptoms development during walking in regular speed > 500 m was equal in both groups (p = 0.668) and during walking with regular speed < 500 m was also similar (p = 0.225). 11.1 % of patients of comparison group and 4.3 % of patients of main group (p = 0.180) developed cardiac symptoms during any physical load or at rest — table I.

Total cholesterol (TC) levels were lower in control group (4.5±0.32 mmol/L) than in comparison (4.93±1.10

Table III. Associations of clinical-anamnestic and clinical-instrumental parameters with presence of T2DM (univariate analysis)

Index	OR	95.0 % CI	p
Clinical and anamnesis parameters			
Gender (female)	1.556	0.586–4.133	0.375
Age, years	1.018	0.961–1.079	0.543
No HF	Reference		0.708
I grade HF	0.817	0.105–6.322	0.846
II grade HF	1.279	0.156–10.456	0.819
No hypertension	Reference		0.199
I stage hypertension	8.088	0.755–86.640	0.084
II stage hypertension	8.889	0.770–102.671	0.080
Obesity	1.665	0.301–9.093	0.562
Current smoker	0.603	0.141–2.577	0.495
Duration of IHD	1.355	0.635–2.888	0.432
Heart morphology			
Left ventricle hypertrophy	2.661	1.113–6.359	0.028
No cardiosclerosis	Reference		0.609
Anterior wall cardiosclerosis	1.375	0.225-8.411	0.730
Posterior wall cardiosclerosis	0.378	0.146–2.074	0.378
Lipid metabolisms parameters			
TC, mmol/L	0.407	0.162–1.023	0.056
HDL, mmol/L	12.109	1.450–101.120	0.021
TG, mmol/L	1.156	0.390–3.426	0.793
LDL, mmol/L	1.976	0.846–4.613	0.115
VLDL, mmol/L	112.065	4.509–2785.087	0.004
Stenocardia functional class			
Significant load (I functional grade)	6.300	1.358–29.235	0.019
Walking with regular speed > 500 m (II functional grade)	1.204	0.411–3.525	0.735
Walking with regular speed < 500 m (III functional grade)	0.484	0.141–1.663	0.249
Any physical load or rest (IV functional grade)	0.477	0.081–2.807	0.413
Titin levels			
Titin, ng/ml	0.001	0.001–0.138	0.018

mmol/l) and main group (5.21±1.51 mmol/L). However, high density lipoproteins (HDL) in control group were significantly lower than in comparison ($p<0.001$) and main ($p = 0.039$) group and patients with comorbid IHD+T2DM had significantly higher levels of HDL ($p = 0.045$) than in isolated IHD. The lowest level of triglycerides (TG) was found in control group (0.80±0.11 mmol/L), which was significantly ($p<0.001$) higher than in comparison and main groups. Noteworthy that low density lipoproteins level did not differ significantly between all study groups. On the other hand, very low-density lipoproteins (VLDL) were significantly lower in control group ($p<0.001$) than in comparison and main group. Despite being higher atherogenicity coefficient (AC) in control group, parameter did not differ significantly between groups — table II.

Titin levels were the highest in control and significantly ($p<0.001$) prevailed over comparison (0.24±0.05 ng/ml) and main group (0.22±0.004 ng/ml) — table II.

Non-significant associations were found with age and gender (respectively OR = 1.556 [95.0 % CI 0.586–0.375], $p = 0.375$ and OR = 1.018 [95.0 % CI 0.961–1.079], $p = 0.543$); of I grade HF and II grade HF (respectively OR = 0.817 [95.0 % CI 0.105–6.322], $p = 0.846$ and OR = 1.279 [95.0 % CI 0.156–10.456], $p = 0.819$) with presence of T2DM. Moreover, presence of obesity, current smoking and IHD duration were also associated with T2DM non-significantly in univariate analysis (respectively OR = 1.665 [95.0 % CI 0.301–9.093], $p = 0.562$, OR = 0.603 [95.0 % CI 0.141–2.577], $p = 0.495$ and OR = 1.355 [95.0 % CI 0.635–2.888], $p = 0.432$) — table III.

Trend to significant association was found with I and II grade hypertension: OR = 8.088 [95.0 % CI 0.755–86.650],

Table IV. Association of clinical-laboratory and clinical-instrumental parameters with comorbidity of IHD and T2DM (multivariate backward Wald analysis)

Predictor	B-coefficient	OR	95.0 % CI	p
Titin, ng/ml	-14.843	0.001	0.001–0.105	0.021
No hypertension		Reference		0.074
I grade hypertension	3.367	28.993	1.595–526.940	0.023
II grade hypertension	2.947	19.050	1.078–336.620	0.044
Left ventricle hypertrophy	1.153	3.169	1.103–3.108	0.032
VLDL	3.892	49.032	4.155–578.644	0.002
Stenocardia under significant load (I functional grade)	1.824	6.199	1.129–34.039	0.036
Constant	-2.007	0.134		

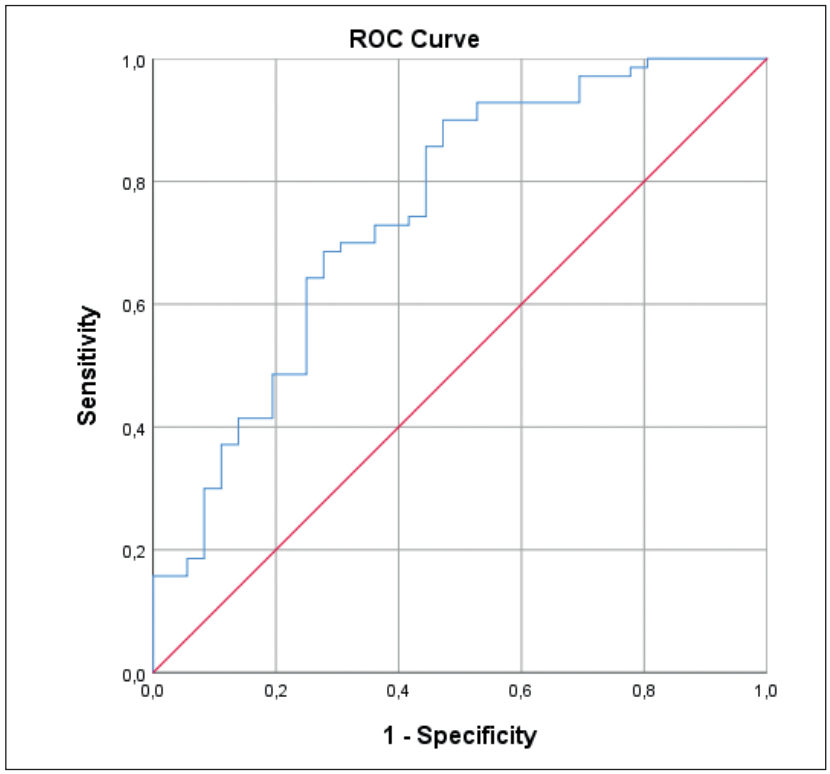

Fig. 1. ROC-analysis of developed prognostic model (AUC = 0.751 [95.0 % CI 0.649–0.852], p < 0.001).

p = 0.084 and OR = 8.889 [95.0 % CI 0.770–102.671] (p = 0.080) — table III.

Among morphological parameters of heart, it was found that left ventricle hypertrophy was significantly (p = 0.028) associated with comorbid T2DM (OR = 2.661 [95.0 % CI 1.113–6.359]). Cardiosclerosis of different localization was associated with T2DM non-significantly: anterior wall — OR = 1.375 [95.0 % CI 0.225–8.411] (p = 0.730) and posterior wall –– OR = 0.378 [95.0 % CI 0.146–2.074] (p = 0.378) –– table III.

Noteworthy, that total cholesterol was inversely associated with comorbid T2DM (OR = 0.407 [95.0 % CI 0.162–1.023], p = 0.056) and direct association was found with HDL and VLDL: respectively OR = 12.109 [95.0 % CI 1.450–101.120] (p = 0.021) and OR = 112.065 [95.0 % CI 4.509–2785.078] (p = 0.004). Non-significant associations were found with TG and LDL (respectively OR = 1.156 [95.0 % CI 0.390–3.426], p = 0.793 and OR = 1.976 [95.0 % CI 0.846–4.613], p = 0.115) –– table III.

Only limitations under significant load were significantly associated with T2DM: OR = 6.300 [95.0 % CI 1.358–29.235], p = 0.019, other parameters showed non-significant associations. Titin showed reverse association with T2DM comorbidity: OR = 0.001 [95.0 % CI 0.001–0.138], p = 0.018 –– table III.

Multivariate analysis (table IV) revealed that significant predictors of comorbid course of IHD and T2DM are titin levels (OR = 0.001 [95.0 % CI 0.001–0.105], p = 0.021); I and II grade hypertension (respectively OR = 28.993 [95.0 % CI 1.595–526.940], p = 0.023 and OR = 19.050 [95.0 % CI 1.078–336.620], p = 0.044); left ventricle hypertrophy (OR = 3.169 [95.0 % CI 1.103–3.108], p = 0.032); VLDL (OR = 49.032 [95.0 % CI 4.155–578.644], p = 0.022) and presence of stenocardia under significant load (OR = 6.199 [95.0 % CI 1.129–34.039], p = 0.036).

Next step was to develop and test prognostic model for prediction of comorbid IHD+T2DM:

IHD+T2DM = -2.007 – (14.843 × titin, ng/ml) + (3.367, if I grade HNT) + (2.947, if II grade HTN) + (1.153, if has

LV hypertrophy) + (3.892 × VLDL, mmol/L) + (1.824, if has stenocardia under significant load)

Classification parameters of developed model were estimated using ROC-analysis (fig.). Cut-off point is = -2.0312, with sensitivity of 85.7 % and specificity of 55.6 %.

DISCUSSION

Significant associations of titin levels were determined (OR = 0.001 [95.0% CI 0.001–0.105] with the comorbidity of T2DM and IHD. It should be noted that Rahim M. et al. [12] established a high sensitivity of the heart-specific N2B fragment of titin to cardiomyocyte damage in myocardial infarction (MI) with comorbidity of T2DM compared to controls (patients with T2DM without MI): patients with MI STEMI and T2DM –– OR = 0.60 [95.0% CI 0.38–0.83)], p < 0.0001 and with MI NSTEMI and T2DM — OR = 0.46 [95.0% CI 0.22–0.70)], p < 0.0001.

Another study (2781 patients with atrial fibrillation and 4959 patients of the control group) [15] also determined the significant sensitivity of titin levels in the blood serum in CVD and found a statistically significant relationship between loss-of-function variants of the gene that encodes the sarcomere titin protein (TTN) and atrial fibrillation (OR = 1.76 [95.0% CI 1.04–2.97].

Also, high sensitivity of titin levels to cardiomyocyte damage was recorded by Kötter S. et al. [16], who established a significant decrease in the relative phosphorylation of N2B-taitin in the tissues of patients with heart failure with dilated and hypertrophic cardiomyopathy: respectively by 35±5% and by 38±6% –– under the condition of using Ser4010 polyclonal antibodies; respectively by 27±3% and 27±5% –– when using Ser4099 and by 23±7% and 26±8% –– when using Ser4185. These results indicated an excessive compensatory activation of the β-adrenergic system, which provokes an increase in the passive stiffness of the myocardium during the progression of HF.

Moreover, we obtained significant associations of stage I and II hypertension (respectively OR = 28.993 [95.0% CI 1.595–526.940], p = 0.023 and OR = 19.050 [95.0% CI 1.078–336.620], p = 0.044) with comorbidity of T2DM and IHD, corresponding to the results obtained by Sun C. D. et al. [17], who found a high association of genetically determined T2DM with the risk of developing hypertension (OR = 1.07 [95.0% CI 1.04–1.10], p = 0.34) in patients with coronary artery disease.

Moreover, significant associations were found within lipid metabolism parameters. Thus, increased VLDL was directly associated with T2DM (OR = 49.032 [95.0 % CI 4.155–578.644], p = 0.022). Patsouras A. et al. [18], who ascertained the marker properties of LDL cholesterol in predicting the development of coronary artery disease in patients with T2DM. It was reliably determined that patients with T2DM are characterized by a more severe course of IHD and have a significantly higher risk of developing cardiovascular complications (relative risk = 3.197 [95.0% CI 1.171–8.730], p = 0.023); and the risks of IHD in patients with T2DM significantly increased with increasing LDL levels (OR = 4.97 [95.0% CI 1.96–12.57], p = 0.001).

Other studies [19] also proved the interdependence of LDL levels and increased risks of IHD and T2DM. It was determined that a genetically determined increase in LDL levels by 38 mg/ml increased the risk of IHD (OR = 1.68 [95.0% CI 1.51–1.87) and T2DM (OR = 0.79 [95.0% CI 0.71–0.88].

CONCLUSIONS

According to the obtained results, the comorbid course of IHD and T2DM is associated with a significant decrease in titin levels, which pathogenetically can be an early predictor of abnormalities in the morphology, contractile and dilatation function of the heart, and of the development of HF. The presence of concomitant T2DM in patients with coronary heart disease is also associated with hypertension of both stage I and II, which confirms the involvement of T2DM in the pathogenesis of increased systemic blood pressure and deterioration of the course this disease. In such patients, LV hypertrophy, as one of the morphological manifestations of both hypertension and HF, and increased concentrations of VLDL cholesterol are more often determined. and the occurrence of angina symptoms during significant physical exertion (OR = 6.2, p = 0.036). The proposed prognostic model has high classification qualities and can be used in predicting the comorbid addition of T2DM in patients with CAD with the aim of early diagnosis of cardiovascular complications of this comorbidity.

REFERENCES

1. Einarson T. R. et al. Prevalence of cardiovascular disease in type 2 diabetes: a systematic literature review of scientific evidence from across the world in 2007–2017. Cardiovasc Diabetol. 2018;17:83. doi: 10.1186/s12933-018-0728-6.
2. International Diabetes Federation. idf diabetes atlas. 7th ed. Brussels: International Diabetes Federation; 2015. http://www.diabetesatlas.org. [date access 12.05.2022]
3. Severino P. et al. Diabetes Mellitus and Ischemic Heart Disease: The Role of Ion Channels. International J. of Molecular Sciences. 2018;19(3). doi: 10.3390/IJMS19030802
4. Jiménez-Lucena R.et al.Circulating miRNAs as Predictive Biomarkers of Type 2 Diabetes Mellitus Development in Coronary Heart Disease Patients from the CORDIOPREV Study. Molecular Therapy - Nucleic Acids. 2018;12:146–157. doi: 10.1016/j.omtn.2018.05.002.
5. Peters T. M. et al. Sex Differences in the Risk of Coronary Heart Disease Associated With Type 2 Diabetes: A Mendelian Randomization Analysis. Diabetes Care. 2021;44 (2):556–562. doi: doi.org/10.2337/dc20-1137.
6. D'Amato Severino P. et al.Ischemic heart disease and heart failure: Role of coronary ion channels. International J. of Molecular Sciences. 2020;21(9). doi: 10.3390/ijms21093167.
7. Kumarathurai P. et al. Effects of liraglutide on diastolic function parameters in patients with type 2 diabetes and coronary artery disease: a randomized crossover study. Cardiovasc Diabetol. 2021;20:12. doi: 10.1186/s12933-020-01205-2.
8. Severino P.et al. Myocardial ischemia and diabetes mellitus: Role of oxidative stress in the connection between cardiac metabolism and coronary blood flow. J. of Diabetes Research. 2019. doi: 10.1155/2019/9489826.

9. International Diabetes Federation. Diabetes and cardiovascular disease. Brussels: International Diabetes Federation. 2016, 144p.
10. Wang L. et al. Efficacy and safety of liraglutide in type 2 diabetes mellitus patients complicated with coronary artery disease: A systematic review and meta-analysis of randomized controlled trials. Pharmacological Research. 2021;171:105765. doi: 10.1016/j.phrs.2021.105765.
11. Raygan F. et al. Melatonin administration lowers biomarkers of oxidative stress and cardio-metabolic risk in type 2 diabetic patients with coronary heart disease: A randomized, double-blind, placebo-controlled trial. Clinical Nutrition. 2019;38(1):91–196. doi: 10.1016/j.clnu.2017.12.004.
12. Rahim M.et al. Inverse changes in plasma tetranectin and titin levels in patients with type 2 diabetes mellitus: a potential predictor of acute myocardial infarction?. Acta Pharmacol Sin. 2018;39:1197–1207. doi: 10.1038/aps.2017.141.
13. Eldemire R. et al. The Sarcomeric Spring Protein Titin: Biophysical Properties, Molecular Mechanisms, and Genetic Mutations Associated with Heart Failure and Cardiomyopathy. Curr Cardiol Rep. 2021;23(121). doi: 10.1007/s11886-021-01550-y.
14. Bogomolovas J. et al. Cardiac specific titin N2B exon is a novel sensitive serological marker for cardiac injury. Int J Cardiol. 2016;212:232–234. doi: 10.1016/j.ijcard.2016.03.045.
15. Choi S. H. et al. Association Between Titin Loss-of-Function Variants and Early-Onset Atrial Fibrillation. JAMA. 2018;320(22):2354–2364. doi: 10.1001/jama.2018.18179.
16. Kötter S. et al. Differential changes in titin docomparison phosphorylation increase myofilament stiffness in failing human hearts. Cardiovascular Research. 2013;99(4):648–656. doi: 10.1093/cvr/cvt144.
17. Sun C. D. et al. Type 2 Diabetes and Hypertension A Study on Bidirectional. Circulation Research. 2019;124: 930–937. doi: 10.1161/CIRCRESAHA.118.314487.
18. Patsouras A. et al. Screening and Risk Assessment of Coronary Artery Disease in Patients With Type 2 Diabetes: An Updated Review. In Vivo. 2019;33(4):1039–1049. doi: 10.21873/INVIVO.11572.
19. White J. et al. Association of Lipid Fractions With Risks for Coronary Artery Disease and Diabetes. JAMA Cardiol. 2016;1(6):692–699. doi: 10.1001/jamacardio.2016.1884.
20. Moroz G. Z., Hidzynska I. M., Kravchenko A. M. et al. Comorbidity in patients with chronic coronary syndromes: prevalence and assessment. Wiad Lek. 2020;73(3):462-465. doi: 10.36740/WLek20200311.
21. Diachuk D., Hidzynska I., Moroz G., Tkachuk I. Current approaches to medical care optimization for patients with multimorbidity. Medical perspectives. 2020;25(4):4–11. doi: 10.26641/2307-0404.2020.4.221220.

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ORCID and contributionship:
Marharyta V. Koshkina: 0000-0003-3392-9599 [A-D]
Volodymyr D. Babadzhan: 0000-0002-3939-4209 [E, F]
Olga I. Kadykova: 0000-0002-0108-0597 [A, E, F]

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The Authors declare no conflict of interest.

CORRESPONDING AUTHOR
Marharyta V. Koshkina
Kharkiv National Medical University
4 Nauki ave, 61000 Kharkiv, Ukraine
tel: +380501854123
e-mail: maiorovarita2393@gmail.com

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A - Work concept and design, **B** – Data collection and analysis, **C** – Responsibility for statistical analysis, **D** – Writing the article, **E** – Critical review, **F** – Final approval of the article