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Original Research

Interaction of asymmetric dimethylarginine, troponin I level, and diabetes mellitus 2 type severity in patients with acute myocardial infarction

Diana Arkadiivna Feldman*, Nataliya Gennadyevna Ryndina

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ABSTRACT

Introduction: The most important cause of mortality in the world is cardiovascular disease (CVD). Dysfunction of the endothelium is the initiating and exacerbating cause of atherosclerosis. Acute myocardial infarction (AMI) in patients with a history of diabetes mellitus (DM) leads to a higher mortality and severe disease course. **Methods:** The research design included 120 patients: Group 1 – AMI patients and concomitant DM type (n = 70) and Group 2 – AMI patients (n = 50) without concomitant DM type 2. 20 practically healthy persons were part of the reference groups. All patients were treated using instrumental and laboratory examinations in compliance with the current orders of the Ministry of Health of Ukraine. **Results:** The average level of ADMA on the first day of the AMI in patients of Group 1 was 1.57 ± 0.11 μmol/l; Group 2 – 0.61 ± 0.06 μmol/l; reference group – 0.17 ± 0.023 μmol/l ($p_{1,2} < 0.00001$, $p_{1,3} < 0.001$, $p_{2,3} < 0.01$). The average level of troponin I on the first day of the AMI in Group 1 was 4.89 ± 2.46 ng/ml; Group 2 – 2.67 ± 2.06 ng/ml; reference group – 0.06 ± 0.04 ng/ml ($p_{1-2} < 0.00001$, $p_{1-3} < 0.00001$, $p_{2-3} < 0.00001$). The direct marked correlation between ADMA and troponin I levels was revealed in the course of the correlation analysis ($r = 0.687$; $p < 0.05$). **Conclusion:** Asymmetric dimethylarginine is concluded to act as a marker of endothelial dysfunction. This has a high diagnostic value in cases of the acute myocardial infarction, especially where the patients have diabetes mellitus type 2. The research revealed the hyperactivity of troponin I in patients with the examined comorbid pathology. In the course of the correlation analysis, a direct marked correlation was revealed between the levels of asymmetric dimethylarginine and troponin I ($p < 0.05$). Correlation analysis between the marker of endothelial dysfunction and the marker of myocardial damage in the patients in Group 1 as per the form of diabetes mellitus type 2 demonstrated a direct marked correlation in the case of a mild form of carbohydrate metabolism disorder and a strong correlation in the case of moderate and severe forms of carbohydrate metabolism disorder.

Key words: acute myocardial infarction, diabetes mellitus type 2, endothelial dysfunction, asymmetric dimethylarginine, troponin I.

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INTRODUCTION

Cardiovascular disease (CVD) is the highest cause of mortality worldwide. For the development of an effective and timely strategy to overcome the CVD epidemic, it is necessary to clearly understand the modern epidemiological features of the main types of this disease and the consequences regarding the prevention and treatment of the pathology. Some of the features are related to changes in demographic, environment, lifestyle, and healthcare, including an increase in the percentage of atherosclerotic CVD (coronary heart disease (CHD)), reduced mortality due to hemorrhage, various regional epidemiological trends for the subtypes of these diseases, an increase in the number of patients with stable types of CHD, and age changes in this group of patients. Other features highlight the issues that require special attention, in particular, a high rate of outpatient mortality for the patients with CHD in the case of insufficient prehospital treatment. There are large gaps between the recommended guidelines and goals according to levels of indicator for lifestyle, as well as a large number of patients with untreated, uncontrolled, and undiagnosed hypertension hypercholesterolemia and diabetes mellitus (DM) [1].

Atherosclerosis is the pathological basis of many types of cardiovascular disease: coronary heart disease, acute myocardial infarction (AMI), and stroke among them. The dysfunction of the endothelium is an initiating and aggravating factor of atherosclerosis. Recent studies link oxidative stress and mitochondrial damage to endothelial dysfunction [2–6].

AMI in patients with DM leads to a higher mortality and more severe course. AMI is a global public

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health problem that causes irreversible damage to the heart tissue and sudden death, requiring new prevention and treatment strategies[7].

Hyperglycemia and hypoglycemia are known to be risk factors for CVD development. An examination of 392 DM patients with acute heart failure (AHF) treated in intensive care revealed major cardiovascular events (MACE) in 227 patients (57.9%) including AMI, ischemic stroke, and heart death. In total, 92 patients died from cardiac causes (23.5%) and 107 were hospitalized for heart failure (27.3%), 19 had the first onset of AMI (4.8%), and 9 had an ischemic stroke (2.3%). Logistic multivariate regression analysis showed that glucose level disturbances were associated with the patients older than 75 years old, a reduced indicator of the ejection fraction of the left ventricle (< 30%), and the female gender as the significant predictors of MACE. These were hazard ratio (HR) 3.16 (confidence interval (CI)) 2.25 – 4.43; $p < 0.001$), HR 1.54 (CI 1.14 – 2.08; $p = 0.005$), HR 1.47 (CI 1.06 – 2.07; $p = 0.02$), and HR 1.43 (CI 1.05 – 1.94; $p = 0.03$), respectively. In this research, it was found that among the other well-known risk factors for the occurrence of heart failure, the importance of glucose level disturbances, especially hyperglycemia, was the strongest independent predictor for medium-term MACE in patients with DM and AHF[8].

Impaired glycemic level is especially important in acute coronary syndrome (ACS). Gerbaud E. *et al.* examined patients with DM and ACS (n=327). MACE was observed in 89 patients (27.2%) during the 16.9 months of follow-up. During the follow-up period, 24 patients (7.3%) died of cardiac causes, 35 (10.7%) underwent AMI for the first time, and 30 (9.2%) were hospitalized for ACS. The multifactor logistic regression analysis showed that hyperglycemia and the decreased ejection fraction of the left ventricle (< 40%) were independent predictors of MACE with an odd ratios (ORs) of 2.21 (95% CI 1.64 – 2.98; $p < 0.001$) and 1.71 (CI 1.14 – 2.54; $p = 0.009$), respectively. Thus, hyperglycemia was determined to be the most important independent prognostic factor of medium-term MACE in patients with MD and ACS[9–14].

Today, bone marrow progenitor endothelial cells are considered to be triggers that promote cardiac neovascularization while exacerbating ischemic injury[15–27].

The role of the biomarkers of fibrosis and the remodeling of the myocardium (galectin-3, a soluble isoform for the suppression of tumorigenicity 2, matrix metalloproteinases, osteopontin, interleukin-6, syndecan-4, myostatin, procollagen type I C-terminal propeptide, procollagen type III N-terminal propeptide, vascular endothelial growth factor, nitric oxidase synthetase and asymmetric dimethylarginine (ADMA)), myocyte damage (heart-type fatty acid-binding protein, glutathione S-transferase P1, and heat shock protein 60), as the cardiovascular biomarkers of clinical significance and prospectives, are now being studied[28].

ADMA is an endogenous inhibitor of nitric oxide synthase[29–32], a marker related to endothelial dysfunction and atherosclerosis, as well as the illness severity of patients with chronic flammable illnesses[33].

ADMA is a metabolite of arginine, the determination of which is useful to evaluate cardiovascular disease, kidney disease, and nonalcoholic fatty liver disease[34]. The increased concentration of ADMA in the blood plasma is connected to the increased risk of mortality and unacceptable cerebrovascular diseases, as is especially evident in the case of AMI[35–40].

In AMI, the necrotic death of cardiomyocytes occurs, characterized by the rupturing of the sarcolemma in response to a critical level of energy depletion after more than 15 minutes of ischemia. The gold standard, a biomarker for the rapid identification of acute coronary syndrome (ACS), is troponin. Troponin I and troponin T are highly specific and reference the death of cardiomyocytes. It has been proven that in normal ventricular remodeling and pathophysiological conditions, the level of troponin is directly proportional to the degree of myocyte apoptosis[41].

METHODS

In the course of this study, 120 patients were examined who were divided into two groups, specifically one group consisting of AMI patients with concomitant DM type 2 (n = 70) and the second group consisting of AMI patients (n = 50) without concomitant DM type 2. The gender composition of the examined patients consisted of 60 men (50%) and 60 women (50%). The average age of the examined patients was 66.35 ± 0.91 years ($p < 0.05$). Additionally, 20 practically healthy people were included in the reference group.

Group 1 was divided into 3 subgroups according to the degree of DM type 2: subgroup 1 — a mild form of DM type 2 (5 patients), subgroup 2 — a moderate form of DM type 2 (30 patients), and subgroup 3 — a severe form of DM type 2 (35 patients).

The patients who participated in this research were examined on the basis of the skills of the Municipal Non-Profit Enterprise "City Clinical Hospital No. 27" of Kharkiv City Council (Cardiology Department for patients with acute myocardial infarction) and Kharkiv Railways Clinical Hospital No. 1 of

the branch "Health Center" owned by the Joint-Stock Company "Ukrainian Railways" (1st Cardiology Department).

According to the current orders of the Ministry of Health of Ukraine, the diagnoses of AMI and Type 2 diabetes were established.

According to the orders of the Ministry of Health of Ukraine No. 455 dated 02.07.2014 "Unified clinical protocol of emergency, primary, secondary (specialized) and tertiary (highly specialized) medical care and medical rehabilitation - acute coronary syndrome with an elevation of ST segment" and No. 1957 dated 15.09.2021 "Unified clinical protocol of emergency, primary, secondary (specialized) and tertiary (highly specialized) medical care and medical cardiorehabilitation — Acute coronary syndrome without ST an elevation," a diagnosis of AMI was established.

The diagnosis of DM type 2 was established in compliance with the order of the Ministry of Health No. 1118 dated 21.12.2012 "Unified clinical protocol of primary and secondary (specialized) medical care for patients with diabetes mellitus type 2."

In accordance with the current orders of the Ministry of Health of Ukraine, the sampled patients underwent laboratory and instrumental examinations. The laboratory examinations included the determination of the levels of troponin I, alanine aminotransferase, aspartate aminotransferase, potassium, sodium, bilirubin, creatinine, blood lipid profile (total cholesterol, low-density lipoprotein cholesterol, extra-low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, atherogenic factor, the determination of the marker of endothelial dysfunction — ADMA), blood glucose, general blood, and urine tests twice. The first was on the first day of hospitalization and then 6 months after the coronary event.

This study was conducted in strict compliance with the main ethical provisions of the "Rules of ethical principles of scientific medical research with human participation", approved by the Helsinki Declaration (1964 - 2013), ICH GCP (1996), EEC Directive No. 609 (dated 24.11.1986), orders of the Ministry of Health of Ukraine No. 690 dated 23.09.2009, No. 944 dated 14.12.2009, No. 616 dated 03.08.2012. a). Each patient who participated in this research signed the form of primary accounting documentation No. 003-6/o "Informed voluntary consent of the patient to diagnosis, treatment and surgery, conducting analgesia and presence or participation of the educational process members." Complete anonymity was ensured for each patient.

The statistical processing of the results obtained during the study was carried out using the StatSoft Inc USA software package, "Statistica 6.0." During the research, a standard program of correlation analysis through calculation was used, specifically involving $M \pm m$, probability, and the level of reliability (p) for the comparison of the samples. The analysis of the independent samples not subject to Gaussian distribution laws was performed using the Mann-Whitney U-test. The correlation rate (r) was used to estimate the degree of relationships between the samples.

RESULTS

The average level of ADMA in the patients of Group 1 on the first day of AMI was 1.57 ± 0.11 μmol/l, while for Group 2 it was 0.61 ± 0.06 μmol/l and for the reference group, 0.17 ± 0.023 μmol/l ($p_{1,2} < 0.00001$, $p_{1,3} < 0.001$, $p_{2,3} < 0.01$), as shown in **Figures 1 and 2** and**Table 1**.

For Group 1, the average level of ADMA was determined separately for each stage of DM type 2. In the patients with a mild form of DM type 2, the average level of ADMA was 0.43 ± 0.15 μmol/l; in patients with a moderate form of DM type, it was 2 – 1.27 ± 0.14 μmol/l, and those with a severe form of DM type 2 had a result of 1.97 ± 0.05 μmol/l ($p < 0.05$), as shown in **Figure 3** and **Table 2**.

The average level of troponin I on the first day of AMI in the patients of Group 1 was 4.89 ± 2.46 ng/ml, while for Group 2 it was 2.67 ± 2.06 ng/ml and for the reference group, 0.06 ± 0.04 ng/ml ($p_{1-2} < 0.00001$, $p_{1-3} < 0.00001$, $p_{2-3} < 0.00001$), as shown in **Table 3**.

The research undertaken determined the average level of troponin I for each stage of DM type 2 in the patients from Group 1. In the patients with a mild form of DM type 2, the average level of troponin I was 1.53 ± 1.03 ng/ml, while for those with a moderate form of DM type 2, it was 2.93 ± 1.91 ng/ml. The result for a severe form of DM type 2 was 7.04 ± 5.21 ng/ml ($p < 0.005$), as shown in **Table 4**.

The direct marked correlation between ADMA and troponin I levels was revealed in the course of the correlation analysis ($r = 0.687$; $p < 0.05$).

The correlation between ADMA and troponin I levels in the patients in Group 1 according to the stages of DM type 2 demonstrated the following results: between the indicators of patients with a mild form of DM type 2, there was found to be a direct marked correlation ($r = 0.500$; $p > 0.05$), between the indicators of patients with a moderate form of DM type 2 there was a direct strong correlation ($r = 0.797$; $p < 0.05$), and between the indicators of patients with a severe DM type 2, there was a direct strong correlation ($r = 0.757$; $p < 0.05$), as shown in **Table 5**.

Table 1: Average level of ADMA in the examined patients (M ± m)

Показник	Patients with AMI and DM type 2 (n = 70)	atients with AMI without concomitant DM type 2 (n =50)	Reference group (n = 20)	P
	1	2	3	
ADMA, μmol/l	1,57 ± 0,11	0,61 ± 0,06	0,17 ± 0,023	p1,2<0,00001 p1,3<0,001 p2,3<0,01

Note: $p_{1,2}$ – reliability of differences between the level of ADMA of Group 1 and Group 2; $p_{1,3}$ – reliability of differences between the level of ADMA of Group 1 and the reference group; $p_{2,3}$ – reliability of differences between the level of ADMA of Group 2 and the reference group.

Table 2: Average level of ADMA in patients of Group 1 depending on the stages of DM type 2

Parameter	Patients with AMI and mild form of DM type 2 (n = 5)	Patients with AMI and moderate form of DM type 2 типу (n = 30)	Patients with AMI and severe form of DM type 2 (n = 35)	p-value
	1	2	3	
ADMA, μmol/l	0,43 ± 0,15	1,27 ± 0,14	1,97 ± 0,05	$p_{1,2}$ > 0,05 $p_{1,3}$ <0,05 $p_{2,3}$ <0,001

Note: $p_{1,2}$ – reliability of differences between the level of ADMA in patients with mild and moderate forms of DM type 2; $p_{1,3}$ – reliability of differences between the level of ADMA in patients with mild and severe forms of DM type 2; $p_{2,3}$ – reliability of differences between the level of ADMA in patients with moderate and severe forms of DM type 2.

Table 3: Average level of troponin I in the examined patients (M ± m)

Parameter	Patients with AMI and DM type 2 (n = 70)	atients with AMI without concomitant DM type 2 (m = 50)	Reference group (n = 20)	P
	1	2	3	
Troponin I, ng/ml	4,89 ± 2,46	2,67 ± 2,06	0.06 ± 0.04	p1,2 < 0,00001 p1,3 < 0,00001 p2,3 < 0,00001

Note: $p_{1,2}$ – reliability of differences between the level of troponin I of Group 1 and Group 2; $p_{1,3}$ – reliability of differences between the level of troponin I of Group 1 and the reference group; $p_{2,3}$ – reliability of differences between the level of troponin I of Group 2 and the reference group.

Table 4: Average level of troponin I in patients of Group 1 depending on the stage of DM type 2

Parameter	Patients with AMI and mild form of DM type 2 (n = 5)	Patients with AMI and moderate form of DM type 2 типу (n = 30)	Patients with AMI and severe form of DM type 2 (n = 35)	P
	1	2	3	
Troponin I, ng/ml	1,53 ± 1,03	2,93 ± 1,91	7,04 ± 5,21	p1,2 < 0,005 p1,3 < 0,005 p2,3 < 0,00001

Note: $p_{1,2}$ – reliability of differences between the level of troponin I in patients with mild and moderate forms of DM type 2; $p_{1,3}$ – reliability of differences between the level of troponin I in patients with mild and severe forms of DM type 2; $p_{2,3}$ – reliability of differences between troponin I levels in patients with moderate and severe forms of DM type 2.

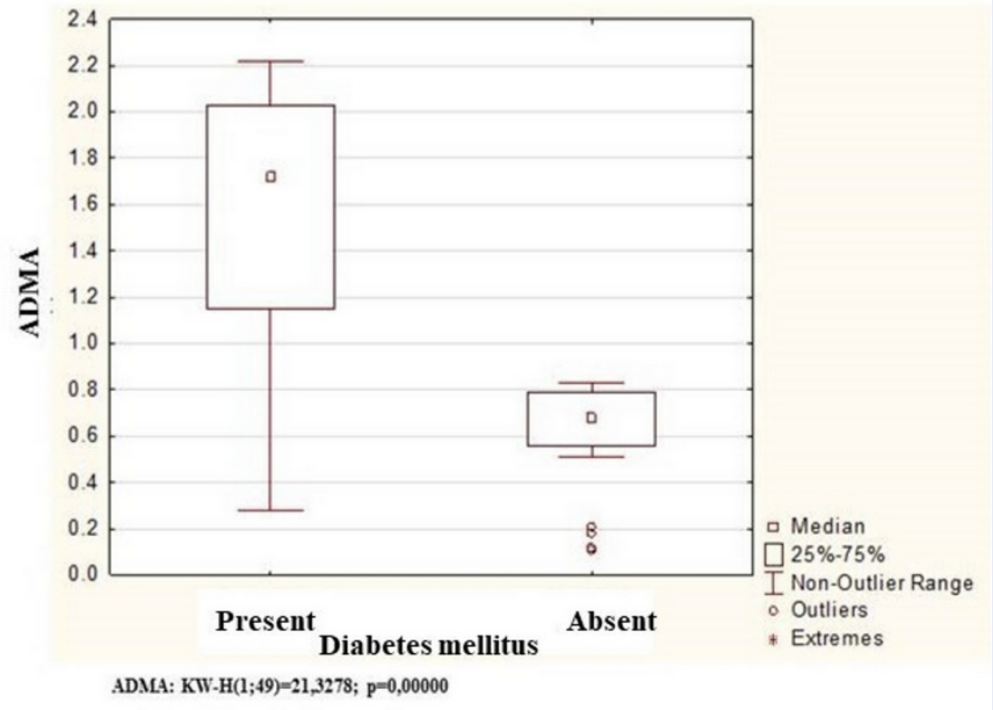

Figure 1: **Average level of ADMA in the surveyed groups (median).**

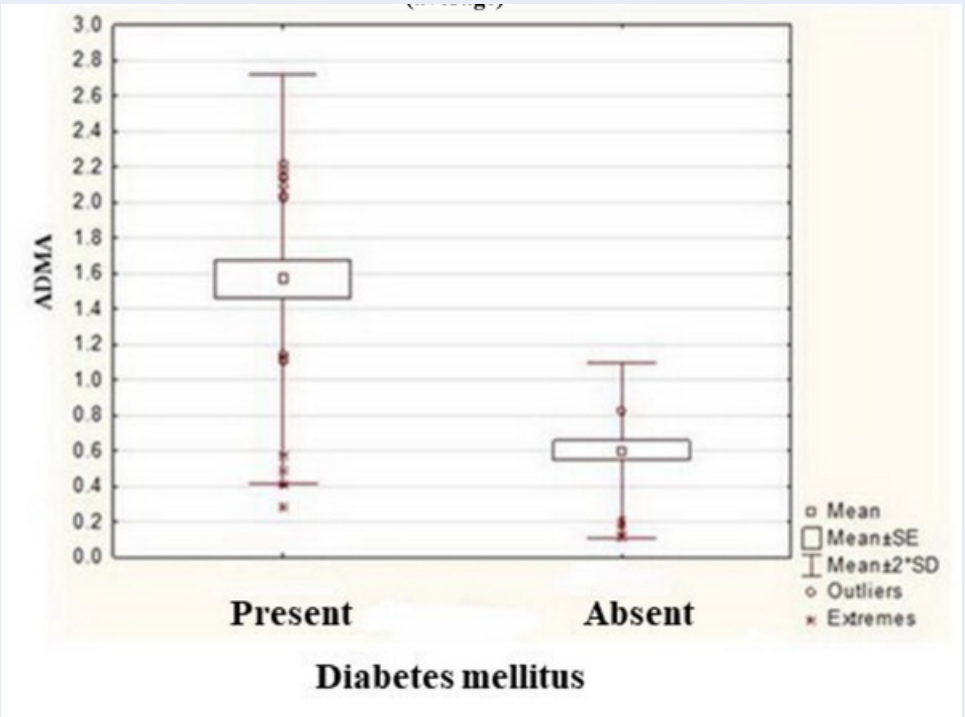

Figure 2: **Average level of ADMA in the surveyed groups (average).**

Table 5: Correlation between the levels of ADMA and troponin I in patients of Group 1 depending on the stage of DM type 2

Parameter	Patients with AMI and mild form of DM type 2 (n = 5)	Patients with AMI and moderate form of DM type 2 типу (n = 30)	Patients with AMI and severe form of DM type 2 (n = 35)
	1	2	3
АДМА (μmol/l) - Troponin I (ng/ml)	0,500	0,797*	0,757*

Note: * – reliability of obtained differences ($p < 0.05$).

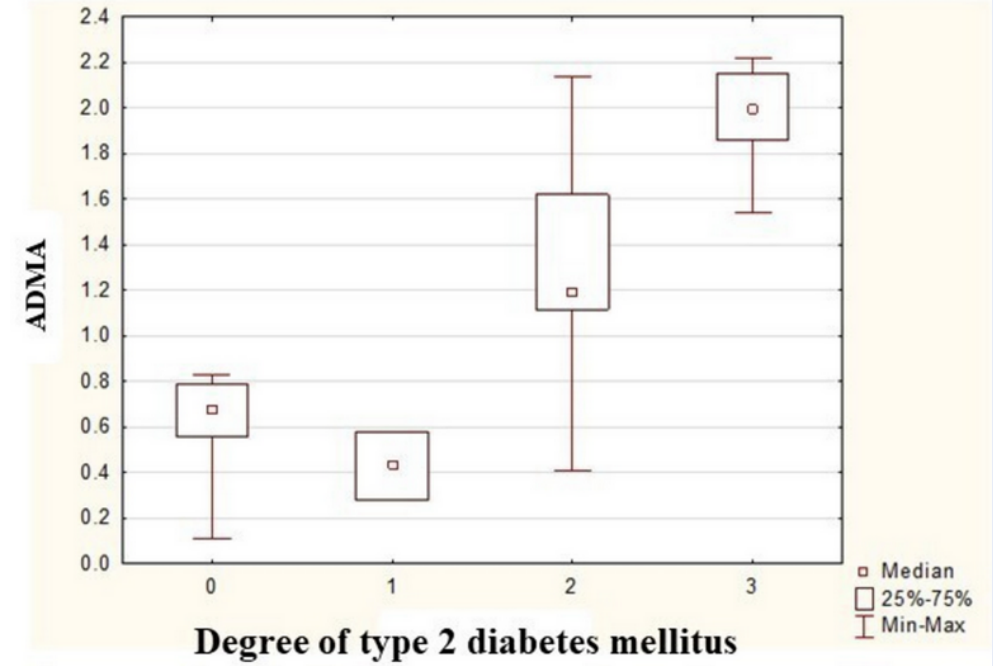

Figure 3: The average level of ADMA according to the forms diabetes mellitus type 2.

DISCUSSION

In the course of this study, it was determined that the patients with AMI had an increased level of ADMA compared to individuals who were part of the control group. In patients with concomitant DM type 2, the level of ADMA was 2.57 times a higher than in the patients with isolated AMI ($p < 0.05$). This indicates an even greater hyperactivity of the marker of endothelial dysfunction, ADMA, because it is this dysfunction that combines the pathogenesis of comorbid pathology. It should be noted that the level of ADMA is directly proportional to the stage of DM type 2.

The results of recent research associate ADMA with AMI prognosis. Researchers examined 66 patients with AMI, measuring their level of ADMA, symmetric dimethylarginine (SDMA), marker of myocardial damage (troponin T), and inflammation marker (C-reactive protein (CRP)) at the point of hospitalization (< 24 h) and on the third day of inpatient treatment. The results of the research demonstrated the following: the concentration of ADMA in the blood on the first day was positively correlated with registered daily sleep hours ($r = 0.497$; $p < 0.001$) and the frequency of meals ($r = 0.285$; $p < 0.05$), while it was negatively correlated with the registered physical condition ($r = -0.304$; $p = 0.013$). Hypertension in the patient's medical history indicated a higher concentration of ADMA on the first day of AMI in contrast to the patients without hypertension at 1.818 and 1.568, respectively ($p < 0.05$). The age of the patients who participated in this study was also positively correlated with SDMA on the first day of measurement ($r = 0.320$; $p < 0.01$). All con-

centrations of the biomarkers were reduced following repeated measurement on the third day of inpatient treatment ($p < 0.001$). A positive correlation was found between a normal body mass index (BMI) and both an absolute ($r = 0.366$; $p < 0.01$) and percentage ($r = 0.262$; $p < 0.05$) reduction in ADMA. Thus, modifiable factors (BMI, physical condition and sleep, and eating habits) affect the level of ADMA and SDMA within AMI patients. Other values of these factors can influence the prognosis of AMI by influencing the level of ADMA [42–44].

When measuring the level of troponin I, in the examined persons it was found that in case of AMI, the level of this marker of myocardial damage was significantly higher than normal (up to 0.5 ng/ml) in contrast to the participants of the research who were in the reference group. The level of this indicator was directly proportional to the size of the necrosis. In the case where the patients had a carbohydrate disorder with insulin resistance and hyperglycemia in the form of DM type 2, the level of this indicator was almost two times higher than it was in patients with isolated AMI ($p < 0.00001$). When determining the level of the marker of myocardial necrosis (troponin I) in the patients in Group 1, it was found to be directly proportional to the stages of DM type 2.

Scientists examined 164 patients with decompensated chronic heart failure to assess the 30-day risk of mortality by determining the level of glucose, troponin, N-terminal pro-cerebral sodium naturetic peptide, creatinine clearance, and undertaking electrocardiogram analysis (ECG). The research found that the persons with a lethal outcome within 30 days had significantly elevated levels of N-terminal pro-cerebral sodium naturetic peptide, troponin, fasting glucose, creatinine clearance, and an abnormal ECG repolarization. That is, changes in the above parameters acted as the markers of a short-term risk of mortality among this group of patients [45–47].

Mohebi R. *et al.* found there to be an association between the troponin I concentration and obstructive CHD. They examined 978 patients, and 607 patients (62%) from among that number had obstructive CHD. The highest concentration of troponin I was found in relation to CHD, chronic kidney disease, heart failure, high low-density lipoprotein, anemia, male gender, smoking, and advanced age. CHD in the patient's medical history, being male, type 2 DM, hs-cTnI, anemia, advanced age, and high-density lipoprotein cholesterol were identified as the most influential factors for CHD. The gradient amplification model in this case had an area under the curve of 0.82, an accuracy level of 75%, sensitivity of 88%, specificity of 52%, positive predictive value of 76%, and negative predictive value of 72% as a predictor of CHD. The gradient amplification model in this study had an area under the curve of 0.82, accuracy of 75%, sensitivity of 88%, specificity of 52%, positive predictive value of 76%, and negative predictive value of 72% for predicting CHD. A 1 logarithmic unit increase in troponin I was significantly associated with an increased risk of AMI development (HR 1.34, 95% CI 1.22 to 1.47; $p < 0.001$), adverse cardiovascular events (HR 1.24, 95% CI 1.11 to 1.39; $p < 0.001$), as well as an increase in mortality from AMI and other unfavorable cardiovascular diseases (HR 1.29, 95% CI 1.20 to 1.40; $p < 0.001$). Researchers have shown that high concentrations of troponin I have been associated with CHD and a high risk of future cardiovascular events [48–50].

Hjort M. *et al.* examined patients suffering from AMI with non-obstructive coronary arteries (MINOCA). This is a newly recognized condition for which the biomarkers and prognosis are less well studied than in AMI with obstructive coronary artery disease (MI-CAD). The research cohort consisted of 1,639 patients with MINOCA and 17,304 patients with MI-CAD. In the adjusted analyses, the troponin levels in MINOCA patients predicted all-cause mortality (HR 1.32, 95% CI 1.11 to 1.56), mortality due to cardiovascular events (HR 2.11, 95% CI 1.51 to 2.96), and serious cardiovascular events, also known as MACE (HR 1.44, 95% CI 1.20 to 1.72). A high level of troponin I also predicted re-hospitalization for cardiac failure (HR 1.51, 95% CI 1.51 to 2.96) but not for non-fatal AMI or stroke. The analysis showed that the troponin I level is the same prognostic marker for assessing the risk of mortality in patients with MINOCA compared to those with MI-CAD [51].

During the correlation analysis, a direct marked correlation was revealed between the levels of ADMA and troponin I in general and a direct strong correlation between the above indicators in patients with moderate and severe forms of DM type 2. This indicates the relationship between the predictor dysfunction of the endothelium and the marker of myocardial damage.

CONCLUSIONS

Thus, asymmetric dimethylarginine acts as a marker of endothelial dysfunction. This has a high diagnostic value in the case of patients with acute myocardial infarction, especially when in combination with diabetes mellitus type 2. When the above diseases combined in patients, the level of asymmetric dimethylarginine was 2.57 times higher than in patients with resolved acute myocardial infarction ($p < 0.05$). This

research has revealed the hyperactivity of the marker of myocardial damage, troponin I, in patients with acute myocardial infarction and diabetes mellitus type 2. In the combination the above conditions, the level of this indicator was almost twice as high as in the case of isolated myocardial infarction ($p < 0.00001$).

In the course of the correlation analysis, a direct marked correlation was found between the levels of asymmetric dimethylarginine and troponin I ($p < 0.05$). When determining the above indicators in the patients of Group 1 as per the form of diabetes mellitus type 2, a direct proportional relationship was found between the studied parameters (in the case of the patients with a severe form of diabetes mellitus type 2, the levels of asymmetric dimethylarginine and troponin I were significantly higher than in the cases with mild and moderate forms of diabetes mellitus type 2 ($p < 0.05$)). Correlation analysis between the marker of endothelial dysfunction and the marker of myocardial damage in the patients of Group 1 as per the form of diabetes mellitus type 2 demonstrated a direct marked correlation in the case of a mild form of carbohydrate metabolism disorder and a direct strong correlation in the case of moderate and severe carbohydrate metabolism disorders.

ABBREVIATIONS

None.

ACKNOWLEDGMENTS

None.

AUTHOR'S CONTRIBUTIONS

All authors equally contributed to this work. All authors read and approved the final manuscript.

FUNDING

None.

AVAILABILITY OF DATA AND MATERIALS

Data and materials used and/or analyzed in the current study and available from the corresponding author upon reasonable request.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was conducted in compliance with the basic bioethical provisions of the Council of Europe Convention on Human Rights and Biomedicine (March 4, 1997), the Helsinki Declaration of the World Medical Association on the ethical principles of scientific medical research involving humans (1964-2008), and the order of the Ministry of Health of Ukraine No./690 dated September 23, 2009.

The conclusion of the commission on ethics and bioethics of the Kharkiv National Medical University confirmed that the research, carried out with respect for human rights, in accordance with the current legislation of Ukraine, meets international ethical requirements and does not violate the ethical standards of biomedical research (protocol of the meeting of KhNMU No. 2 dated 04.02.2010). The purpose of each examination was received from all participants.

CONSENT FOR PUBLICATION

Not applicable.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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