ORIGINAL ARTICLE

PROGNOSTICATION OF COMPLICATED COURSE OF ACUTE MYOCARDIAL INFARCTION WITH CONCOMITANT TYPE 2 DIABETES MELLITUS BASED ON USE OF ENDOTHELIAL MONOCYTE ACTIVATING POLYPEPTIDE-II

DOI: 10.36740/WLek202201112

Diana A. Feldman, Nataliya G. Ryndina, Pavlo G. Kravchun, Dobrovolska I. Mykolayivna
KHARKIV NATIONAL MEDICAL UNIVERSITY, KHARKIV, UKRAINE

ABSTRACT

The aim: To determine the prognostic value of endothelial monocytic peptide II in the course of AMI (acute myocardial infarction) in combination with type 2 diabetes mellitus (DM)

Materials and methods: The study involved 120 patients divided in 2 groups: Group 1 – patients with acute myocardial infarction (AMI) with concomitant type 2 DM (n=69); Group 2 – patients with AMI without concomitant type 2 DM (n=51). Control group was composed with 20 almost healthy persons.

Results: It was determined that in patients with AMI in combination with type 2 diabetes, the level of endothelial monocyte-activating polypeptide II (EMAP-II) was 1.65 times higher than in patients without concomitant type 2 DM ($p < 0.05$). The patients with AMI and type 2 DM who were included in the group of the 3rd tertile according to level of EMAR-II had the complicated course compared to patients in the groups of the 1st and 2nd tertiles. Q-positive AMI was found in 100% of patients who belonged to the group of the 3rd tertile; recurrence of AMI occurred only in patients whose EMAR-II index was included in the 3rd tertile.

Conclusions: According to the results of endothelial function analysis with usy ща the marker of EMAP-II endothelial dysfunction in patients with AMI and concomitant type 2 DM, the increased level of this parameter was characteristic of pronounced violation of dilatation properties of the vascular wall and of the other indicators of complicated comorbid conditions.

KEY WORDS: endothelial dysfunction, comorbid conditions, acute myocardial infarction, type 2 diabetes mellitus

Wiad Lek. 2022;75(1 p.1):65-69

INTRODUCTION

The acute myocardial infarction (AMI) occupies a special place in the structure of incidence of the coronary heart disease (CHD) [1], while also being one of the major causes for death and disability of the working population [2,3].

It is known that the course and prognosis of the coronary heart disease depend on the presence of comorbid pathology. The type 2 diabetes mellitus (DM) is a significant factor for the unfavorable course of coronary heart disease.

The risk of mortality is increased in patients with AMI and concomitant type 2 diabetes. The complications (heart failure, arrhythmia, cardiogenic shock, etc.) in patients with AMI and concomitant type 2 diabetes represent a top issue in modern cardiology [4, 5].

According to the OAZIS (Organization to assess strategies for ischemic syndromes) study, the in-hospital mortality of patients with type 2 diabetes from cardiovascular complications was 2.9% compared to 2.0% in patients without type 2 diabetes ($p<0.033$).

According to the information of the SHOCKTrial register (Should we emergently revascularize occluded coronaries for cardiogenic shock), the in-hospital mortality of patients with AMI and type 2 diabetes was higher totaling in 67% compared to 58% for patients with AMI without type 2 diabetes ($p<0,007$) [6].

According to the REACH register (register of clinical signs of atherosclerosis), the mortality of patients with AMI without type 2 diabetes is 8.6% compared to 16.1% for patients with AMI and type 2 diabetes ($p<0.01$) [7].

The risk of death from AMI in patients with diabetes is higher than in people without impaired carbohydrate metabolism. According to the GRACE register (The Global Registry of Acute Coronary Events), in case with patients previously diagnosed of diabetes, the in-hospital mortality from AMI with ST segment elevation, from AMI without ST segment elevation, and unstable cardiac angina, totaled in 11.7%, 6.3% and 3.9%, respectively. These indicators are significantly higher than the corresponding data in patients without diabetes - 6.4%, 5.1% and 2.9% [8].

This negative trend is related to a number of metabolic disorders associated with type 2 diabetes, such as hyperglycemia, insulin resistance, dyslipidemia, and oxidative stress, which lead to endothelial damage and the development of intravascular inflammation. The endothelial damage is now being actively studied as a predictor of adverse course of the coronary heart disease [9, 10].

The endothelial monocyte activating polypeptide – II (EMAP-II) is a multifunctional peptide with proinflammatory and angiogenesis activity, which activates a number

Table I. Characteristics of EMAP-II based on presence or absence of concomitant type 2 diabetes mellitus in patients.

Parameter	Group 1 (patients with AIM with concomitant type 2 DM) (n_2=69)	Group 2 (patients with AIM without concomitant type 2 DM) (n_1=51)	Control group (n_0=20)	Mann-Whitney criterion, p
EMAP-II	4,54±0,331	2,74±0,21	1,1±0,037	p_{01}=0,495 p_{02}= 0,0008 p_{12}=0,0005

Table II. Examined quantitative parameters based on EMAP-II tertiles.

Parameter	Tertile 1	Tertile 2	Tertile 3
GRACE	118,78	135,71	165,67
EDV, cm	110,11	122,73	130,33
EDD, cm	5,14	5,28	5,23
ESV, cm	70,91	73,67	68,22
ESD, cm	3,99	4,11	4,02
Size of left atrium, cm	4,14	4,45	4,15
Ejection fraction	46,44%	44,56%	42,91%
Tropinin I, ng/ml	1,45	2,35	3,21

of proinflammatory cytokines, namely interleukin-1β, interleukin-8, tumor necrosis factor in α, thus inducing inflammatory changes in vessels, [11].

The EMAP-II plays an important role in the process of myocardial tissue revascularization in patients with AMI. The EMAP-II blockade by monoclonal antibodies promotes angiogenesis and improves cardiac function after myocardial infarction. It has been demonstrated that vasodilation during EMAP-II-induced inflammation is associated with the nitric oxide (NO) system. This has been proven in a model of isolated pulmonary arteries. In case of NO-LAME blockade by a NO-synthase inhibitor, the EMAP-II-induced vasodilation was reduced [12].

THE AIM

To determine the prognostic value of the endothelial monocyte-activating polypeptide II in the course of acute myocardial infarction in combination with type 2 diabetes mellitus.

MATERIALS AND METHODS

The study involved 120 patients, who were divided in 2 groups: group 1 consisted of patients with AMI and concomitant type 2 DM (n = 70), group 2 consisted of patients with AMI without concomitant type 2 DM (n = 50). The patients in both groups were comparable in terms of age and sex (60 men (50%) and 60 women (50%); average age - 66.35 ± 0.91 years, p <0.05). The control group consisted of 20 almost healthy individuals, including 12 women (60%) and 8 men (40%). The average age was 45.17 ± 2.88 years. The level of the examined indicator of EMAP-II was divided into 3 tertiles (1st tertile - up to 3.59 ng/ml, 2nd tertile -3.59 - 5.67 ng/ml, 3rd tertile - above 5.67 ng/ml).

The diagnosing was made according to the current criteria. The AMI diagnosing was made in accordance with the Order of the Ministry of Health of Ukraine No. 455 dd. 02.07.2014 "On approval and implementation of medical and technological documents for standardization of medical care in acute coronary syndrome with ST segment elevation", Order of the Ministry of Health of Ukraine No. 436 dd. 03.07.2006 "Protocol for provision of medical care to patients with acute coronary syndrome without ST elevation".

The diagnosing of type 2 DM was made in accordance with the joint recommendations of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) - 2015.

All the patients enrolled in the study signed a voluntary informed consent as prerequisite for participation.

All the patients underwent general clinical and instrumental examinations.

During the first day of study, the participants with AMI underwent assessment of the level of EMAP-II using commercial test systems "Human Endothelial monocyte-activating polypeptide II ELISA KIT".

The statistical processing of the obtained results was performed using the software package "Statistica 6.0» (StatSoft Inc, USA). In case with comparative analysis of samples, we used a standard program of correlation analysis with calculation of arithmetic mean values: M±m, probability and level of reliability (p). In case with analysis of the samples not subject to Gaussian distribution laws, we used the U-criterion of Mann-Whitney U-test for independent samples. The correlation coefficient (r) was used to estimate the degree of relationship between the samples.

RESULTS

According to the results of the study, it was found that in patients with AMI in combination with type 2 diabetes, the level of EMAP-II was by 1.65 times (p <0.05) higher than in

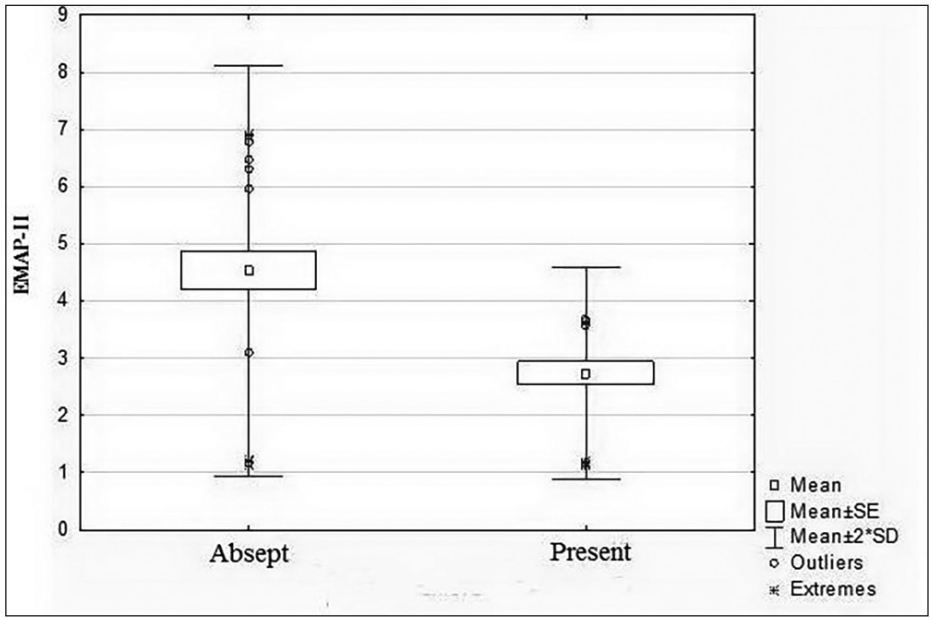

Fig. 1. Characteristics of EMAP-II average value based on presence or absence of concomitant type 2 diabetes mellitus in patients.

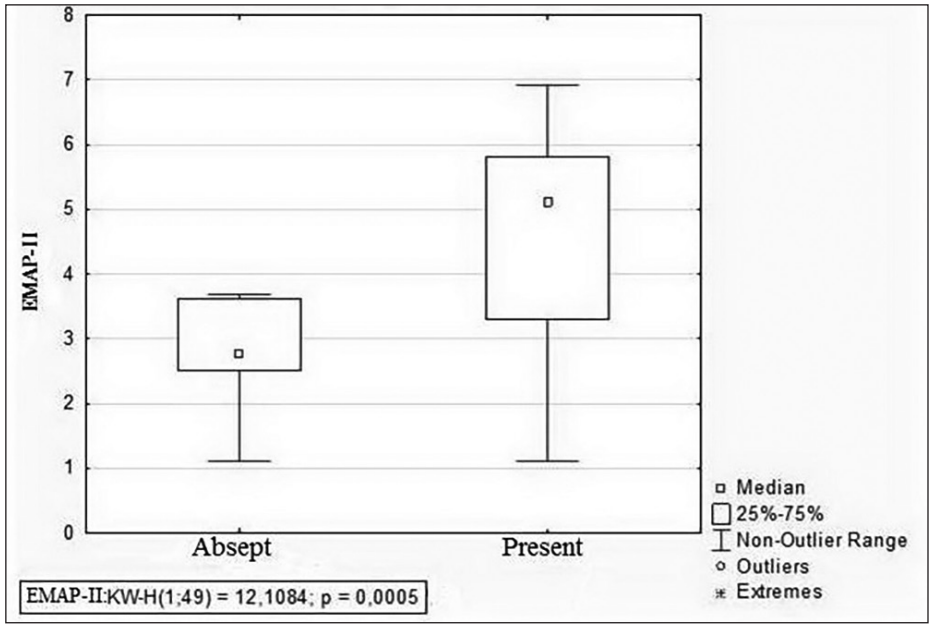

Fig. 2. Characteristics of EMAP-II based on presence or absence of concomitant type 2 diabetes mellitus in patients, median value.

patients without concomitant type 2 diabetes. Accordingly, the patients with AMI in combination with concomitant type 2 DM demonstrated the hyperactivity of the marker of endothelial dysfunction - EMAP-II, as detailed in Table I, Figure 1 and Figure 2.

The results of examination based on EMAP-II tertiles with regard to quantity parameters are detailed in Table II.

The patients with AMI with concomitant type 2 DM included in the group of the 3rd tertile based on EMAP-II level had higher scores on the GRACE scale compared to the patients included into the groups of the 1st and 2nd tertiles. The assessed level of troponin I in the patients with AMI with concomitant type 2 diabetes mellitus, who were part of the 3rd tertile group based on EMAP-II level, was significantly higher compared with the same parameter in the patients of the 1st and 2nd tertile groups. The study of parameters of the structural and functional state of myocardium of the left ventricle revealed an increase in EDV in the groups of patients who were part of the 3rd tertile group based on EMAP-II level compared to the patients who were part of the 1st and 2nd tertile groups. As regards the other parameters, no significant differences in the level were detected.

The distribution of Killip classes based on tertiles is shown in Table III.

The table III contains the information on the development of acute heart failure (AHF) based on Killip classes in patients with AMI and type 2 DM, depending on the EMAP-II tertiles.

As can be seen from Table III, the patients who were part of the 1st tertile group based on EMAP-II mostly had a lower AHF class according to Killip class. In patients with

Table III. Distribution of Killip classes based on EMAP-II tertiles.

Killip-based class	Tertile 1	Tertile 2	Tertile 3
I	54,54%	66,67%	33,33%
II	9,09%	22,22%	11,11%
III	36,36%	11,11%	11,11%
IV	-	10%	44,44%

Table IV. Qualitative parameters of patients with AIM and concomitant type 2 DM based on tertiles of EMAP-II.

Parameter	EMAP-II		
	Tertile 1	Tertile 2	Tertile 3
AIM with Q wave	36%	55,56%	100%
AIM recurrence	-	-	11,11%
AHF	36,36%	43,33%	66,65%

AMI and concomitant type 2 DM, the level of EMAP-II was related to the 2nd tertile. Mainly, there were cases of class IV acute heart failure according to Killip.

The results of examination based on EMAP-II tertiles with regard to qualitative indicators were as follows: Q-positive AMI was found in 36% of patients belonging to the Tertile 1 group, in 55.56% of patients belonging to the Tertile 2 group, and in 100% of patients belonging to the Tertile 3 group. Recurrence of AMI was not registered in patients whose EMAP-II was referred to the 1st and 2nd tertiles, while registered in 11.11% of patients with the EMAP-II included in the 3rd tertile group.

The EMAP-II showed prognostic properties with regard to 6-month mortality after AMI in patients with type 2 DM. Thus, if the level of EMAP-II is > 3.44 ng/ml, this marker can be used to detect a cohort of patients with high risk of mortality.

Today, the incidence of cardiovascular disease in Ukraine is 1,639.9 people per 100,000 population. According to statistics from around the world, clinical forms of coronary heart disease are diagnosed in 15-20% of the adult population [13].

DISCUSSION

According to statistics in Ukraine in the first half of 2020, cardiovascular disease is the leading cause of death among the population. Thus, 196,567 people died of cardiovascular diseases in the first 6 months of 2020, including 135,867 people with CHD [14].

According to the WHO, at the age of 50-54 deaths from coronary heart disease is 404-467 people per 100 thousand population in the world. AMI is one of the most common manifestations of CHD and one of the most common causes of death in developed countries. It is important to note that about half of deaths occur in the first hour after the onset of the disease. [15].

AMI and type 2 DM are common and often combined diseases [16].

Currently, 347 million people suffer from diabetes, 90% of them having the type 2 diabetes. The number of patients with diabetes in Ukraine is 1,264,500 persons [17]. Therefore, the type 2 diabetes is a global problem covering not only in Ukraine, but also the rest of the world.

There is a direct relationship between increased levels of markers of endothelial dysfunction and the progression of atherosclerotic process in patients with coronary heart disease in combination with type 2 diabetes. Endothelial dysfunction was accompanied by a violation of the balance of production of vasoactive substances that regulate vascular lumen and cell growth [18].

In patients with hypertension with type 2 DM, the EMAP-II value was 4.86 ± 2.3 ng / ml; in patients with arterial hypertension and obesity - 2.92 +/- 1.42 ng / ml; in patients with arterial hypertension - 2.02 +/- 0.33 ng / ml; in the control group - 1.08 ± 0.53 ng / ml ($p < 0,01$). A direct correlation was found between body mass index, blood lipid, glycosylated hemoglobin, glucose and EMAP-II. It was determined that in the presence of coronary heart disease in the blood increases the content of pro-inflammatory markers, one of which is EMAP-II [12].

A study of patients with type 1 DM with microangiopathies and hypertension showed the following results: in the presence of type 1 DM with microangiopathies and arterial hypertension, the level of EMAP-II was - 5.23 +/- 1.66 ng / ml; in the presence of type 1 DM with microangiopathy - 3.63 +/- 0.53 ng / ml [11].

CONCLUSIONS

The results of the analysis of endothelial function using the marker of endothelial dysfunction EMAP-II in patients with AMI with concomitant type 2 DM indicate that the increased level of this parameter is characteristic of a pronounced violation of dilatation properties of the vascular wall, manifested in echocardiographic changes, increase of parameter based on GRACE scale, presence of Q-positive AMI, recurrence of AMI, increase of troponin I, variability of Killip class, and other indicators that characterize the complicated course of comorbid conditions. Furthermore, it was found that the degree of violations was at maximum in patients with EMAP-II belonging to the 3rd tertile group.

The results of analysis of the indicators of endothelial dysfunction in terms of mortality are as follows: value of EMAP-II above 3.44 ng/ml predict the likelihood of cardiovascular death within 6 months.

It is advisable to further study the parameter of endothelial function - EMAP-II - as a predictor of adverse course of AMI in combination with concomitant type 2 DM.

REFERENCES

1. Gandziuk V.A. Analysis of cases of coronary heart disease in Ukraine [Analiz zahvorjuvanosti na ishemichnu hvorobu sercja v Ukrai'ni]. Ukrainian cardiologic journal. 2014;3:45-52. (In Ukranian).
2. Kovalenko V.M. Issues of health and medical care, and improvement model for present-day conditions (handbook) [Problemy zdorov'ja i medychnoi' dopomogy ta model' pokrashhennja v suchasnyh umovah (posibnyk)]. SO "National Scientific Center "M.D. Strajesko's Institute of Cardiology". Kyiv; 2016, 261 p. (In Ukranian).
3. Kravchuk N.G. Parameters of public health and use of health care resources in Ukraine in 2013-2014. [Pokaznyky zdorov'ja naselennja ta vykorystannja resursiv ohorony zdorov'ja v Ukrai'ni za 2013-2014 roky]. Analytical-statistical reference book. 2015, 325 p. (In Ukranian).
4. Diabetes mellitus. Information bulletin. 2013: No. 312. http://www.who.int/ru/. [date access 24.06.2020]
5. Ryden L. Guideline on diabetes, pre-diabetes, and cardiovascular diseases,executive summary. J Europ Heart. 2017; 28: 88-136.
6. Shindler D. M., Palmeri S.T., Antonelli T.A. et al. Diabetes mellitus in cardiogenic shock complicating acute myocardial infarction: a report from the SHOCK trial registry. Journal of the American college of cardiology. 2018; 36 (3): 1097–1103.
7. Zeymer U. Diabetes as coronary artery disease equivalent revisited. Results of the prospective REACH-registry. Journal European Heart. 2011; 32:65.
8. Ryden L. Guideline on diabetes, pre-diabetes, and cardiovascular diseases,executive summary. Journal Europ Heart. 2007; 28: 88-136.
9. Berezin A.Ye., Kruzliak P. Circulating endothelial apoptotic micriparticles as new marked of cardiovascular risk. [Cyrkuljujuchi endotelial'ni apoptychni mikrochastynky jak novyj marker kardiovaskuljarnogo ryzyku]. Ukrainian Medical Journal. 2014; 5(103):83-88. (In Ukranian).
10. Rajendran P., Rengarajan T., Thangavel J. et al. The vascular endothelium and human disease. Int. J. Biol. Sci. 2013;9(10): 1057-1069.
11. Mogilnytska L.A., Mankovskyi B.N. Content of endothelial monocyte-activating polypeptide II in patients with type 1 diabetes mellitus with microangiopathy and arterial hypertension. International Journal "Diabetes Mellitus". 2016:19(4):309-314.
12. Mogilnytska L.A., Mankovskyi B.N. Increase of endothelial monocyte-activating polypeptide II in blood serum of patients with arterial hypertension with concomitant type 2 diabetes mellitus and obesity. International Journal "Obesity and metabolism". 2016;13(3):49-53.
13. Kovalenko V.N. Epidemiological aspects of cardiovascular diseases. Compendium. 2020, 410p.
14. Gosstat. Diseases cardiovascular system and cancer - the most common causes of death among Ukrainians in 2020. [Bolezny serdechno-sosudystoj systemy y rak – naybolee chastыe prychynы smerty sredy ukrayncev v 2020 godu]. 2020. https://112.ua/zdorovie/bolezn. (In Ukranian) [date access 13.06.2020].
15. Menshikova I.G. Clinic, diagnosis, principles of treatment with the basics of physical rehabilitation of patients with acute myocardial infarction. [Klynyka, dyagnostyka, pryncypy lechenyja s osnovamy fyzycheskoj reabylytacyy bol'nyh ostrym ynfarktom myokarda]. Blagoveshchensk. 2015; 8p. (In Russian).
16. Oganov R.G., Maslennikova G.Ya., Koltunov I.E. et al. Necessary conditions for the prevention of cardiovascular and other non-infectious diseases. Cardiovascular therapy and prevention. 2010;9 (6): 4-9.
17. Health care establishments and incidence of diseases in Ukraine in 2013. [Zaklady ohorony zdorov'ja ta chastota zahvorjuvan' v Ukrai'ni v 2013 roci]. State Statistical Service of Ukraine. Statistical bulletin. Kyiv 2014. www.ukrstat.gov.ua. [date access 13.06.2020].
18. Teregulov Yu.E., Khusainova D.K., Mukhametshina F.N. et al. The role of arterial stiffness and hemodynamic parameters in the assessment of endothelial function. [Rol' arteryal'noj zhestkosty y gemodynamycheskyh parametrov v ocenke funkcyy endotelyja]. J Vestnik sovremennoy klinicheskoy meditsiny. 2014; 7(1): 17-21. (In Russian).

ORCID and contributionship:

Diana A. Feldman: 0000-0001-8050-824X [A-F]
Nataliya G. Ryndina: 0000-0003-2731-4491 [A,F]
Pavlo G. Kravchun: 0000-0002-8285-6763 [A,F]
Dobrovolska I. Mykolayivna: 0000-0003-0458-6734 [A]

Conflict of interest:

The Authors declare no conflict of interest.

CORRESPONDING AUTHOR

Diana A. Feldman
Kharkiv National Medical University
4 Nauki pr., 61000 Kharkiv, Kharkiv, Ukraine
tel: +380675892987
e-mail: f.d.a.diana@gmail.com

Received: 27.11.2020
Accepted: 28.08.2021

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