Al-Azhar Med. J.(Medicine). *Vol. 50(3), July, 2021, 2185-2200*
DOI: 10.21608/amj.2021.178680
https://amj.journals.ekb.eg/article_178680.html

MICROPARTICLES AS A PREDICTIVE BIOMARKER IN ACUTE MYOCARDIAL INFARCTION

By

Ahmed Awad Ibrahim Ahmed, Majid Abdul-Fattah Ismael Shalaby*, Mohamed Abd El-Hameed kheder* and Mohamed Seleem Mohamed**

Department of Clinical Pathology, Al-Azhar Faculty of Medicine* & National Heart Institute**

E-mail: ahmed_awad_@hotmail.com

ABSTRACT

Background: Microparticles are small vesicles, between 0.1 and 1 μm in diameter. There are found in low concentrations in the plasma under physiological conditions and increased in pathological conditions.

Objective: To find the correlation between circulating microparticles levels and thrombotic burden in acute myocardial infarction.

Patients and methods: The study was conducted on 86 patients presented with acute myocardial infarction with ST-elevation, to the emergency Department at Ahmed Maher Teaching Hospital from September 1st 2019 till February 28th 2020. They were compared with 14 healthy individuals with identical demographic characteristics not suffering from any disease. Serum microparticles (CD41a) & (CD62E) and serum CKMB, troponin I, AST, and creatinine levels were measured in both groups.

Results: There were significant elevation of all parameters cardiac marker, CD41, and CD62E levels were observed in all patients of STEMI patients compared to the control group (p=<0.001).

Conclusion: In STEMI patients, the serum CD41a and CD62E levels rise due to their property as proinflammatory and thrombtic CD41 & CD62E can be used as a predictor of STEMI.

Keywords: Microparticles, Coronary artery disease, Acute Myocardial Infarction, STEMI, CD41a, CD62E.

INTRODUCTION

Acute coronary syndrome (ACS) are including unstable angina, non-ST elevated myocardial infarction, or ST elevated myocardial infarction "STEMI *"Smith et al., 2015).* Acute myocardial infarction (AMI) is a common and critical illness with an in-hospital mortality rate of up to 11.9% *(Sahin et al., 2017).*

Vascular biomarkers can be used to modify patient management and contribute to a steady decline in CVD morbidity and mortality over the past decades *(Braunwald, 2012)* may help to understand the biology of atherothrombosis *(Libby et al., 2010).*

Microparticles are vascular biomarkers defined as small-sized (<1000 nm) cell membranous originated from various cells (platelets, red and white blood cells, endothelial cells) into human fluids *(Juan et al., 2018* and *Chen et al., 2019).* Microparticles contain proteins, lipids, and genetic information and carry and transfer bioactive molecules, surface receptors, and genetic information. They

could modify the phenotype and function of target cells in healthy and diseased tissues *(Bei et al., 2017)*.

Platelet microparticles (PMP) are the most abundant MPs in healthy subjects, accounting for 60%-90% *(Zaldivia et al., 2017)*. PMPs express specific platelet markers such as CD41 and CD42b *(Boilard et al., 2015)*. 60–90% of PMPs are positive CD41 staining *(Brisson et al., 2017)*. PMPs are highly prothrombotic, support thrombin generation and thrombus formation *(Nomura et al., 2015)*. Only CD62E and CD144 are specific for endothelial MP and could be considered as truly endothelial *(Dignat-George et al., 2011)*.

PATIENTS AND METHODS

The subjects were 86 patients with acute myocardial infarction (AMI) presented to the emergency Department at Ahmed Maher Teaching Hospital from September 1st 2019 till February 28th 2020. Besides 14 apparently healthy subjects were enrolled as a control group. The clinical spectrum of ACS comprised AMI ST-elevation AMI (STEMI) only. All adult patients were diagnosed with CK-MB, troponin test, and ECG as ST-elevation myocardial infarction (STEMI) was approached.

The inclusion criteria were: (1) Patients presented with typical angina pain (chest pain in the left side radiating to the arms, shoulder, or neck, (2) patients aged from 30 to 75 years, (3) patients voluntarily participated in this study by signing an informed consent form and (4) patients undergoing primary percutaneous coronary intervention or thrombolysis in this episode of ACS.

The exclusion criteria were: (1) Patients with a known history of chronic kidney disease (CKD), chronic heart failure (CHF), hepatic cirrhosis and valvular heart disease (VHD), (2) patients with concomitant acute stroke, acute infection, sepsis, chronic inflammatory diseases and other thromboembolic diseases, and (3) patient with a known history of malignancy.

Cardiac enzymes CK MB, Troponin I tests and ECG were tested for the patients for AMI diagnosis. Complete Blood Count, AST, Creatinine and Cholesterol were tested for all participants of the study (both patients and controls).

The tubes were subjected to differential centrifugation to produce platelet-poor-plasma (PPP). Citrated blood samples were centrifuged at low speed 2500 X g for 15 minutes to collect platelet-poor-plasma (PPP). Subsequently, PPP was then centrifuged again at 2500g for 15 minutes to produce platelet-poor-plasma (PPP). Two 250µl aliquots of platelet poor-plasma were frozen immediately and stored at -80°C. 250µl aliquots of platelet-poor-plasma were thawed at room temperature, centrifuged at 14000 X g for 5 minutes, 200µl of supernatant was removed and 450µl of PBS-Citrate 0.32% was added (1/10 of the original volume).

fifty µl of PPP was incubated with antibody CD41a-FITC (Miltenyl Biotec, Germany) for 30 min to detect platelet microparticles. 50 µl of PPP was incubated with antibody (CD62E-PE) (Miltenyl Biotec, Germany) for 30 min to detect endothelial microparticles. Then, 450 µl of saline buffer was added for each sample. The sample was then run and analyzed with flow cytometry (BD

FACSCanto 10 colors) with FACS Diva software. The microparticles gate was checked with 1 μM beads. The positivity gates were checked by fluorescence-minus-one staining.

Thrombus burden assessment was defined based on the evaluation by coronary angiography by thrombolysis in myocardial infarction risk Scores (TIMI Risk Scores or TS).

Statistical analysis:

The statistical analysis of the data were performed by using excel (Microsoft office 2013) program and SPSS (Statistical Package for the Social Science) program (SPSS, Inc, Chicago, IL) version 20.

Kolmogorov-Smirnov test was performed to assess the normality of the data. Qualitative data were presented as frequency and percentage. **Chi-square test** was used to compare groups. Quantitative data were presented as median and range. For comparison between two groups; the **Mann-Whitney test (for non-parametric data)** was used.

Correlation analysis: Spearman correlation was used to assess the strength of association between two quantitative variables. **The ROC Curve (receiver operating characteristic)** provided a useful way to evaluate the sensitivity and specificity for quantitative diagnostic measures that categorize cases into one of two groups. **Regression analysis:** regression analyses were used for the prediction of risk factors. Significance was considered when $P \leq 0.05$.

RESULTS

Individuals in the study were 84 males and 16 females aged from (25 to 77). Demographic data among studied groups. STEMI patients were significantly older than controls. Also, BMI was significantly elevated in STEMI compared to control. Male gender was more frequently in STEMI compared to the control **(Table 1)**.

Table (1): Participants' characteristics

Parameters \ Groups		Controls (N=14)		STEMI (N=86)		P
Age (years)	Median	31.0		54.0		<0.001
	Min-Max	25-42		30-77		
Sex	Males	8	57.1%	76	88.4%	0.003
	Females	6	42.9%	10	11.6%	
BMI	Median	25.5		28		0.034
	Min-Max	21-29		22-30		

Chi-Square test, Mann-Whitney*

There was significant elevation of WBCS in STEMI patients compared to control. Otherwise no other significance could be detected. There was significant elevation of AST, cholesterol, in STEMI patients compared to control. Otherwise creatinine no significance could be detected. There was significant elevation of cardiac marker, CD41 and CD62E among in STEMI patients compared to control **(Table 2)**.

Table (2): Comparison of some laboratory parameters among studied groups:

Parameters \ Groups			Controls (N=14)		STEMI (N=86)		P
Hb (g/dl)	**Median**		12.6		12.7		0.367
	Min	**Max**	12	14	12	14	
WBCS (cells /mm3)	**Median**		5.9		7.7		0.001
	Min	**Max**	4.8	8.5	4.8	12.5	
PLT (plts/mcl)	**Median**		315.0		302		0.474
	Min	**Max**	225	355	238	389	
AST (U/L)	**Median**		35.0		149.0		<0.001
	Min	**Max**	16	46	80	164	
Creatinine (mg/dl)	**Median**		0.7		0.8		0.055
	Min	**Max**	0.5	1.1	0.5	1.2	
Cholesterol (mg/dl)	**Median**		177		211		0.002
	Min	**Max**	155	205	147	277	
CKMB (IU/L)	**Median**		2.4		75.0		<0.001
	Min	**Max**	2.0	<0.001	12.0	777.0	
Troponin I (ng/L)	**Median**		0.04		2.03		<0.001
	Min	**Max**	0.02	<0.001	0.11	360.0	
CD41 (%)	**Median**		18.0		77.0		<0.001
	Min	**Max**	11.0	27.0	13.0	94.0	
CD62E (%)	**Median**		12.0		77.0		<0.001
	Min	**Max**	5.0	19.0	8.0	94.0	

Mann-Whitney,

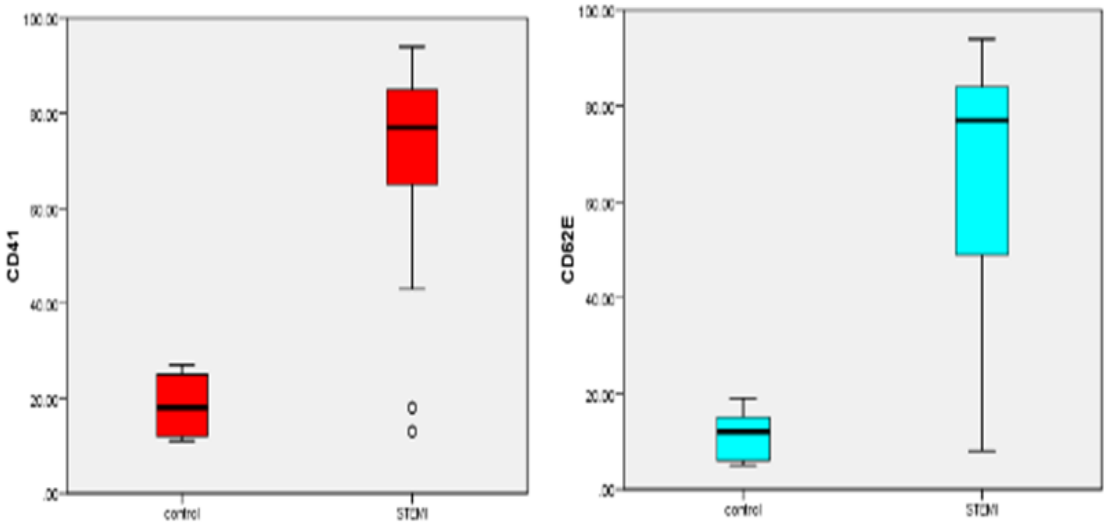

Figure (1): CD41& CD62E among studied groups

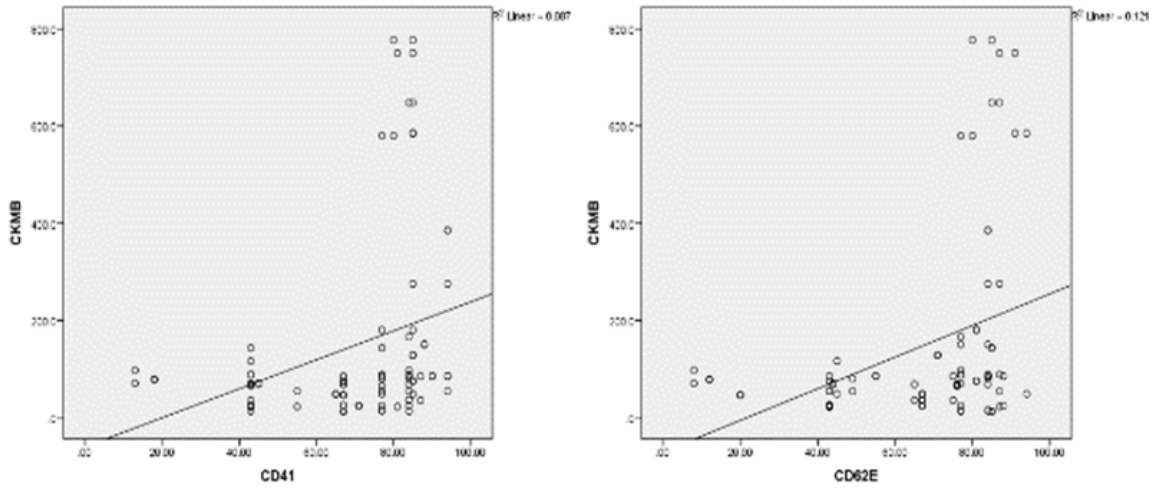

Figure (2): correlation between CKMB and CD62E &correlation between CKMB and CD41

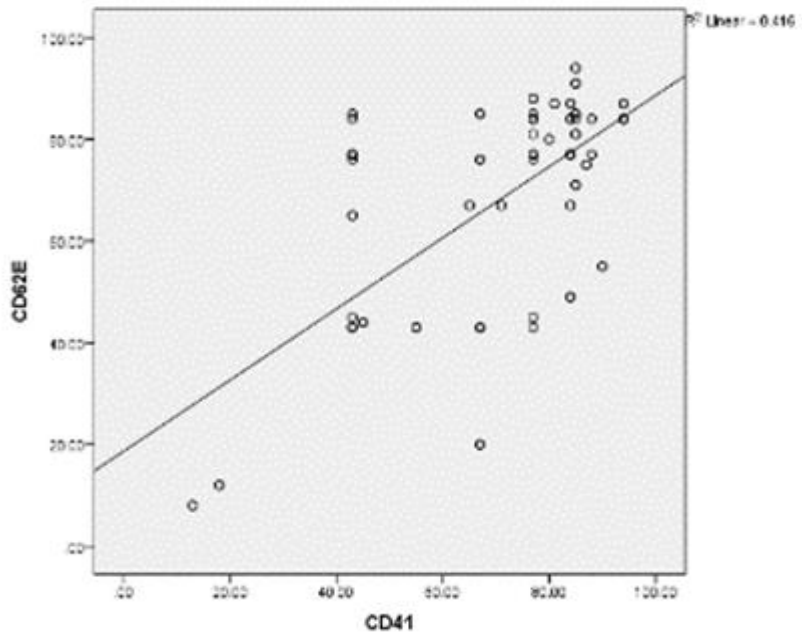

Figure (3): Correlation between CD41 and CD62E

Correlation between parameters with CD41 & CD62E in STEMI patients. Cholesterol and CKMB positively correlated with both CD41 & CD62E. CD41 showed significant positive correlation with CD62E **(Table 3** and **Figures 1, 2 &3)**.

Table (3): Correlation between parameters with CD41 & CD62E in STEMI patients.

Parameters \ Microparticles		CD41	CD62E
Age (years)	R	-0.035	0.018
	P	0.747	0.870
Hb (g/dl)	R	-0.145	0.001
	P	0.182	0.989
WBCS (cells /mm3)	R	-0.049	-0.059
	P	0.651	0.592
PLT (plts/mcl)	R	-0.072	-0.161
	P	0.508	0.139
AST (U/L)	R	0.088	-0.150
	P	0.422	0.167
Creatinine (mg/dl)	R	-0.049	-0.151
	P	0.652	0.165
Cholesterol (mg/dl)	R	0.267	0.226
	P	0.013	0.036
CKMB (IU/L)	R	0.405	0.361
	P	0.000	0.001
Troponin I (ng/L)	R	-0.121	-0.008
	P	0.269	0.939
TIMI (0,1,2,3)	R	-0.063	0.020
	P	0.566	0.856
CD41 (%)	R	10.000	0.536
	P	0.000	0.000
CD62E (%)	R	0.536	10.000
	P	0.000	0.000

R: correlation- b: significance value

ROC analysis was used to detect the optimal CD41 & CD62E for the prediction of STEMI. CD41 best cut-off values were 26.0. (AUC) was 0.973(p=<0.001). CD62E best cut-off values were 17. AUC) was 0.972 (p=<0.001) **(Table 4** and **Figure 4)**.

Table (4): Performance characteristics of CD41 and CD62E for prediction of STEMI

Performance \ Microprticles	AUC	SE	*P*	95% CI	Cut off	Sensitivity (%)	Specificity (%)
CD41	0.973	0.015	<0.001	0.945-1.00	26.0	95.3	85.7
CD62E	0.972	0.015	<0.001	0.942-1.00	17.0	95.3	85.7

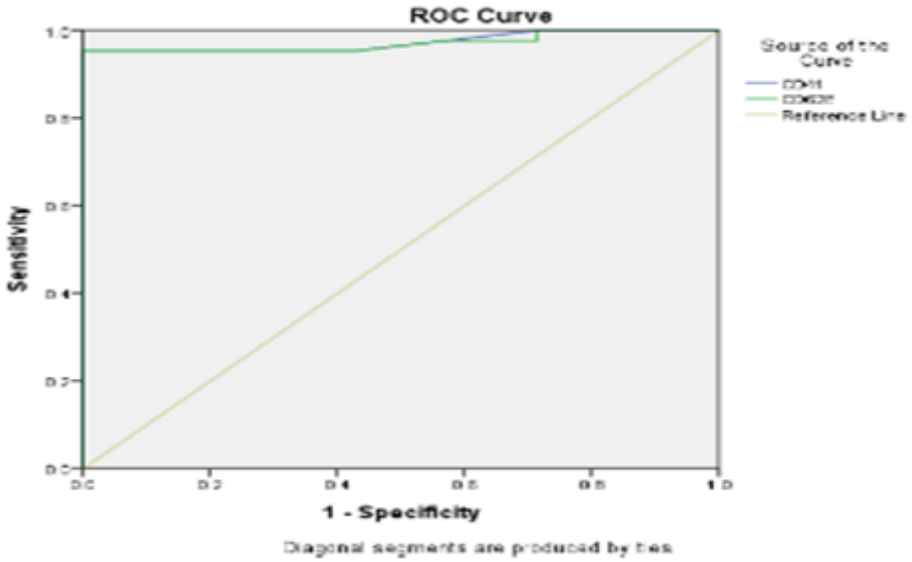

Figure (4): ROC analysis CD41 & CD62E

Logistic regression analysis was conducted for prediction of STEMI, using laboratory data, age, sex, and BMI as covariates. Age, WBCS and CD62E were significant risk factors for STEMI. Female gender was a significant protective factor **(Table 5)**.

Table (5): Regression analysis for prediction of STEMI

Analysis / Parameters	Univariate analysis				Multivariate analysis			
	p	**OR**	**95% CI**		***P***	**OR**	**95% CI**	
Age (years)	<0.001	1.252	1.121	1.399	0.003	1.450	1.131	1.859
BMI	0.017	1.380	1.058	1.798	0.288	0.643	0.284	1.454
WBCS (cells /mm3)	0.007	2.099	1.226	3.592	0.009	2.620	1.316	5.216
AST (U/L)	0.991	2.563	0.986	3.264				
Cholesterol (mg/dl)	0.006	1.035	1.010	1.060	0.150	1.032	0.989	1.076
CKMB (IU/L)	0.957	18.15	0.912	19.57				
Troponin I (ng/L)	0.619	6.549	0.887	7.564				
CD62E (%)	<0.001	1.164	1.069	1.267	0.049	1.171	0.1.124	1.346
CD41 (%)	0.006	1.177	1.048	1.322	0.371	1.047	0.947	1.158

OR, odds ratio; CI, confidence interval; logistic regression was used.

DISCUSSION

In our study, there were statistical significant higher MPs in patients with STEMI patients than in healthy controls. In fact, both PMPs and EMPs levels were significantly high in the blood samples in STEMI patients undergoing PCI, supporting their role as markers of acute thrombosis and the association of an elevated plasma PMP level and ACS is significant.

Similar to our study, other authors stated that AMI patients have high levels of PMPs and EMPs *(Han et al., 2015* and *Ye et al., 2017)*. PMPs are higher in acute coronary syndrome than healthy controls *(Cui et al., 2013, Fang et al., 2013* and *Giannopoulos et al., 2014)*. High concentrations of both PMPs and EMPs

were associated with the severity of AMI *(Jung et al., 2012* and *Chiva-Blanch, et al., 2017)*. MPs expressed P-selection (CD63), CD31, and CD41a, are elevated strongly correlated with the infarct size *(Vagida et al., 2016* and *Loguinova et al., 2018)*. There are conflicting results regarding the effect on MP levels after PCI. A study found decreased levels of PMPs, but augmented levels of EMPs, reflecting the acute endothelial injury after PCI *(Ye et al., 2017)*.

PMPs and EMPs are higher in acute coronary syndrome (ACS) patients than stable angina patients *(Lee et al., 2012)*. PMPs are higher in acute coronary syndrome than stable angina *(Biasucci et al., 2012)*. However, controversial reports indicating that PMPs are higher in stable angina than ACS *(Empana et al., 2015)*.

Microparticles (MPs) are involved in the pathogenesis of CV diseases through several biological mechanisms that support microvascular inflammation, arterial stiffness, vascular calcification, atherosclerotic plaque shaping and rupture, endothelial dysfunction, hypercoagulation, and thrombosis & cardiac remodeling *(Nawaz et al., 2018)*.

Plasma levels of MPs increased in diseases that involve a degree of vascular injury. Plasma levels of endothelial & platelet MPs are elevated in several diseases such as diabetes mellitus, chronic kidney disease, hypertension, atherosclerosis and pulmonary hypertension *(Han et al., 2015, Nomura, 2016* and *Boulanger et al., 2017)*.

Endothelial dysfunction can lead to loss of endothelial monolayer's anticoagulant, antiplatelet, and fibrinolytic properties. During endothelial dysfunction, considerable cell damage occurs due to apoptosis *(George et al., 2015)*. Endothelial dysfunction is an early hallmark of atherosclerosis and cardiovascular disease EMPs correlate with the level of endothelial activation in cardiovascular disease and may reflect dysfunction or damage *(Paudel et al., 2016)*.

EMP contributes to endothelial dysfunction in acute myocardial infarction pathophysiology which suggests EMP were found to be potential biomarkers for acute MI *(Wang et al., 2017)*. Platelet-derived microparticles are a biomarker of endothelial dysfunction and pro-coagulative activity, which can be considered as a predictor of poor outcomes in ACS/AMI *(Berezin et al., 2019)*.

Platelet and endothelial microparticles increased in acute myocardial infarction (AMI) and contribute to coronary thrombosis and subsequent myocardial injury. MPs may also provide information regarding the thrombotic state in individuals as MPs increased in hypercoagulable status *(Park et al., 2012)*. Conversely, individuals with Scott syndrome, who have a defect in procoagulant activity, exhibit decreased plasma MP levels *(Badimon et al., 2016)*.

Platelet MPs play an effective role in the development of damaged vessel wall contributing to atherothrombotic events which support the formation of platelet-derived vesicles is important for increased coagulation activation in AMI patients *(Chiva-Blanch et al., 2017)*.

In a recent study, circulating apoptotic (phosphatidylserine +) MPs increase two-fold in a STEMI subgroup of ACS

patients and impaired endothelial function could predispose to plaque rupture and thrombotic complications in ACS patients *(Zacharia et al., 2020)*.

Increased platelet microparticles are detected in patients with AMI reflecting platelet activation. Increased platelet microparticles lead to intracoronary occlusion due to their procoagulant properties. In various cases circulating platelets are likely to adhere to leukocytes or endothelial cells at the activation site *(Nasiri Kenari et al., 2019* and *Vagner et al., 2019)*.

In AMI, the thrombus formation at the site of injury is dependent on complex interactions between activated platelets, circulating PMPs, activated endothelial cells, and the coagulation system *(Badimon et al., 2016)*.

MPs are considered as inflammation contributors and consequence, circulating endothelial and platelet MPs increased in inflammatory diseases e.g. psoriasis *(Pelletier et al., 2011)*. Fundamental studies describe their involvement in oxidative stress and inflammation *(Bodega et al., 2018)*. These processes are important in the pathogenesis of myocardial infarction (MI) and post-stroke survival *(Kurian et al., 2016)*.

Inflammation is the main causal event in the development of plaques, plaque rupture and thrombus formation *(Bentzon et al., 2014)*. The possible link between MPs and inflammation, vascular dysfunction, and pro-thrombosis were demonstrated in an in vitro study, PMP enriched blood was able to increase deposition of platelets and fibrin in human atherosclerotic vessels directly contributing to thrombosis formation *(Suades et al., 2012)*.

Atherosclerosis is the most leading cause of most cardiovascular disease and acute myocardial infarction is mostly caused by acute thrombosis in atherosclerotic plaque with an eroded surface *(Bona et al., 2011)*. PMP has been verified to possess a powerful proinflammatory effect *(Wong et al., 2012)*. PMPs and EMPs are useful biomarkers of atherosclerosis and cardiovascular disease *(Boulanger et al., 2017)*.

However, there are also some studies demonstrating the opposite view that the plasma PMP concentration did not increase in patients with ACS. The likely reason is the high rate of administration of GPIIb/IIIa inhibitors before sampling in patients with ACS. Another potential mechanism is that the circulating procoagulant MPs in patients with arterial thrombosis were recruited from circulating blood to the surface of activating cells (such as monocytes and endothelial cells). It is noted that the contradictory study focused on the procoagulant MPs bearing tissue factor, not purely PMP. Thus, the contradictory conclusion might be at least due to design reasons *(Empana et al., 2015)*.

CONCLUSION

MPs appear interesting biomarkers to predict cardiovascular disease risk. Nevertheless, numerous issues remain to be addressed before MP measurement can be applied as routine biological tests to improve cardiovascular risk prediction of patients.

Several limitations of our study must be addressed, i.e. the small sample size of groups, which reduces the power to detect significant differences among groups and the field of MP research faces several challenges with regard to the standardization of methodology.

ACKNOWLEDGEMENT

We would like to thank the Clinical Pathology Department of Al-Azhar Faculty of Medicine and Emergency Department of Ahmed Maher Teaching Hospital for their help in the laboratory analyses and examining cases. We are also indebted to all the patients and our colleagues for their co-operation in this research.

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الجسيمات الدقيقة كعلامة حيوية تنبؤية في احتشاء عضلة القلب الحاد

أحمد عوض إبراهيم محمد، ماجد عبدالفتاح اسماعيل شلبى*، محمد عبد الحميد خضر*، محمد سليم محمد**

قسم الباثولوجيا الإكلينيكية بكلية طب الأزهر*، معهد القلب القومي**

E-mail: ahmed_awad_@hotmail.com

خليفة البحث: الجسيمات الدقيقة عبارة عن دلالات حيوية وعائية تُعرَّف بأنها غشاء خلوي صغير الحجم (<1000 نانومتر) نشأ من خلايا مختلفة (الصفائح الدموية وخلايا الدم الحمراء والبيضاء والخلايا البطانية) في سوائل الإنسان. تحتوي الجسيمات الدقيقة على البروتينات والدهون والمعلومات الوراثية وتحمل وتنقل الجزيئات النشطة بيولوجيًا والمستقبلات السطحية والمعلومات الوراثية. يمكنهم تعديل النمط الظاهري ووظيفة الخلايا المستهدفة في الأنسجة السليمة والمريضة. توجد الجسيمات الدقيقة في بلازما الأفراد الأصحاء وتتغير تركيزاتهم في مختلف الظروف السريرية. تزداد تركيزات الجسيمات الدقيقة في المرضى الذين يعانون من عوامل الخطر القلبية الوعائية.

يرتبط مستوي الجسيمات الدقيقة في المرضى الذين يعانون من فرط كوليسترول الدم، وارتفاع ضغط الدم، وداء السكري، بمستوى الخلل في البطانة وضعف توسع الأوعية. قد أظهرت العديد من الدراسات على أن الجسيمات الدقيقة تمكن من التنبؤ بأحداث القلب والأوعية الدموية في المستقبل ويمكن أن تضيف قيمة كبيرة لعوامل الخطر ويكونوا مؤشرات حيوية تشخيصية قوية في مرضى أمراض القلب التاجية في المستقبل.

الهدف من البحث: إيجاد العلاقة بين مستويات الجسيمات الدقيقة المنتشرة والعبء الخثاري في احتشاء عضلة القلب الحاد.

المرضى وطرق البحث: أجريت الدراسة على 86 مريضاً مصابين باحتشاء عضلة القلب الحاد مع ارتفاع ST، في قسم الطوارئ بمستشفى أحمد ماهر

التعليمي، وتم مقارنتهم بـ 14 شخصاً يتمتعون بصحة جيدة بخصائص ديموغرافية متطابقة ولا يعانون من أي مرض.

هذا و قد أجريت الإختبارات التالية على جميع الأشخاص الخاضعين للدراسة (المرضى و المجموعة الضابطة).

أولا: التشخيص الإكلينيكي للمرضى عن طريق أطباء القلب بمستشفى أحمد ماهر التعليمي.

ثانيا: قياس مستوي إنزيم كرياتين كيناز إم بي، ومستويات تروبونين اي والتحاليل الروتينية (صورة دم كاملة, كوليسترول, وظائف كبد (AST) والكرياتينين).

ثالثا: قياس مستوى الجسيمات الدقيقة في الدم في كلا المجموعتين.

الاستنتاج: لوحظ ارتفاع معنوي في جميع المؤشرات القلبية، في جميع مرضى احتشاء عضلة القلب الناجم عن ارتفاع مقطع ST مقارنة بمجموعة التحكم (P = <0.001).

و في مرضى إحتشاء عضلة القلب الناجم عن ارتفاع مقطع ST، ارتفعت مستويات CD41a و CD62E في الدم بسبب خصائصها كمسببة للالتهاب ومسببه للجلطات ومسببه للاعتلال في الاغشية ويمكن استخدام CD41 و CD62E كمتنبئ بمرض احتشاء عضلة القلب المرتفع ST.

الكلمات الدالة: الجسيمات الدقيقة, إحتشاء , عضلة القلب الحاد, س د 41 و س د 62.