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Emotional Stress as A-Major Risk Factor for Type 1 Myocardial Infarction

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ABSTRACT

Background: Acute mental stress has been known as an important precipitating factor of acute coronary syndrome (ACS) especially myocardial infarction events, through platelet activation resulting in hypercoagulability status. Type 1 myocardial infarction is due to coronary atherosclerotic plaque rupture. A previous autopsy study showed that not all ruptured atherosclerotic plaques result in thrombus formation. Data collected from previous study identified five differentially expressed platelet genes: (FKBP5, S100P, SAMSN1, CLEC4E and S100A12) at the time of acute myocardial infarction and the gene that showed the highest evidence of differential expression was FKBP5. Previous studies show that extreme emotions were associated with FKBP5 gene expression.

Objective: To evaluate emotional stress as a risk factor for type 1 myocardial infarction.

Patients and Methods: This prospective study was performed on 90 cases divided into two main groups: healthy participant group (30) and ACS group (60) that was further subdivided into ST-elevation MI (STEMI) group (30) and unstable angina (UA) group (30) who underwent percutaneous coronary intervention and polymerase chain reaction.

Results: Our results demonstrated that there was statistically significant increase in the percentage of patients with emotional stress in STEMI group than control group and UA groups with p-value <<0.001. FKBP5 gene expression was statistically significant higher in STEMI group followed by UA group and lastly the lower value was found in control group with p-value <0.001. FKBP5 gene expression level was significantly higher in cases with emotional stress in STEMI group with p-value = 0.007.

Conclusion: Emotional stress is a major risk factor for type 1 MI. Emotional stress can cause activation of FKBP5 platelet gene that in turn can cause platelet activation resulting in thrombus formation.

Keywords: Unstable Angina, FKBP5, STEMI, PCI, Polymerase chain reaction.

INTRODUCTION

It is commonly recognized that acute mental stress is a significant risk factor for myocardial infarction events, and that strong emotions like rage and severe depression raise the chance of developing ACS within two hours by at least two times. Acute mental stress promotes platelet activation resulting in hypercoagulability status but the exact mechanism is unknown [1,2].

Type 1 myocardial infarction is due to coronary atherosclerotic plaque rupture that promotes platelet activation and aggregation then activation of the coagulation cascade resulting in thrombus formation [2].

Only a small percentage of ruptured plaques lead to thrombus development, despite the fact that atherosclerotic plaque rupture or fissuring is the final consequence of the atherosclerotic process. According to a prior autopsy research, a significant number of individuals who pass away unexpectedly from non-cardiac causes had fissured atherosclerotic plaques in their coronaries, indicating that not all ruptured atherosclerotic plaques cause thrombus development and a myocardial infarction [2,3].

It has been proposed that the clinical event of acute myocardial infarction is significantly influenced by platelets' response to plaque rupture or fissuring [4].

Even though platelets are a-nuclear cells, they include RNAs such as messenger RNA (mRNA), long non-coding RNA, and micro-RNA, which together make up around 9,000 transcripts in healthy human subjects [2,5,6].

At the time of acute myocardial infarction, data from a prior investigation revealed that five genes were differently expressed: FKBP5, S100P, SAMSN1, CLEC4E, and S100A12; FKBP5 was the gene with the strongest indication of differential expression [2].

FKBP5 contributes to thrombus development by activating platelets [6].

Our objective was to evaluate emotional stress as a risk factor for type 1 myocardial infarction.

PATIENTS AND METHODS

Study Design:

This prospective study was performed between (June 2022 to Mars 2023) on 90 participants who were divided into two main groups: healthy participant group (30) and ACS group (60) that was further subdivided into STEMI group (30) and UA group (30) who underwent percutaneous coronary intervention (PCI) and polymerase chain reaction (PCR) at Menoufia University Hospital and Nasr City Insurance Hospital.

We included 90 participants aged (from 46 to 78), including (74) male and (16) females. Type 1 MI patients were defined according to the fourth MI universal definition as typical chest pain with the ST elevation in electrocardiogram (ECG). Unstable angina group was defined according to the latest guidelines definition of ACS with ECG ischemic changes, negative cardiac enzymes. Healthy participants hadn't any acute cardiovascular events.

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We excluded patients with disseminated intravascular coagulopathy, advanced liver disease, thrombocytopenia, malignancies like "leukemia" and patients on antiplatelet therapy except aspocid tablets. Healthy participants were excluded if they had any symptom like chest pain, dyspnea and palpation and any prior CV events.

Study Procedure:

Full medical history: Name, age, gender, smoking, hypertension, diabetes, dyslipidemia as current or previous treatment with antidyslipidemic medication, liver disease, any drug history and history of any previous CV events.

Physical examination: Clinical examination was very important in patient with ACS, in risk stratification, and in the diagnosis of impending heart failure.

12 leads-surface ECG: For detection of QRS morphology, ST-segment elevation denoting presence of acute MI.

Laboratory investigations: Serum creatinine and cardiac biomarkers including creatine kinase (CK), troponin, creatine kinase myocardial band (CK-MB).

Echocardiography: Pre-PCI bedside echocardiographic study was performed to exclude any mechanical complications of STEMI and presence of LV thrombus.

Emotional stress score: The participants were asked about any of the symptoms of the" stress symptoms scale" that have been experienced during last month and took 1 point for each one and the total number was calculated and whose score above 15 was considered to have emotional stress (**Figure 1).**

Stress Symptom Checklist

Check each item that describes a symptom you have experienced to any significant degree during the last month; then total the number of items checked.

Physical Symptoms

- ☐ Headaches (migraine or tension)
- ☐ Backaches
- ☐ Tight muscles
- ☐ Neck and shoulder pain
- ☐ Jaw tension
- ☐ Muscle cramps, spasms
- ☐ Nervous stomach
- ☐ Other pain
- ☐ Nausea
- ☐ Insomnia (sleeping poorly)
- ☐ Fatigue, lack of energy
- ☐ Cold hands/feet
- ☐ Tightness or pressure in head
- ☐ High blood pressure
- ☐ Diarrhea
- ☐ Skin condition
- ☐ Allergies
- ☐ Teeth grinding
- ☐ Digestive upsets (cramping, bloating)
- ☐ Stomach pain, ulcer
- ☐ Constipation
- ☐ Hypoglycemia
- ☐ Appetite change
- ☐ Colds
- ☐ Profuse perspiration
- ☐ Heart beats rapidly or pounds, even at rest
- ☐ Use of alcohol, cigarettes, or recreational drugs when nervous

Psychological Symptoms

- ☐ Anxiety
- ☐ Depression
- ☐ Confusion or spaciness
- ☐ Irrational fears
- ☐ Compulsive behaviors
- ☐ Forgetfulness
- ☐ Feeling overloaded or overwhelmed
- ☐ Hyperactivity – feeling like you can't slow down
- ☐ Mood swings
- ☐ Loneliness
- ☐ Problems with relationships
- ☐ Dissatisfied/unhappy with work
- ☐ Difficulty concentrating
- ☐ Frequent irritability
- ☐ Restlessness
- ☐ Frequent boredom
- ☐ Frequent worrying or obsessing
- ☐ Frequent guilt
- ☐ Temper flare-ups
- ☐ Crying spells
- ☐ Nightmares
- ☐ Apathy
- ☐ Sexual problems
- ☐ Weight change
- ☐ Overeating

Number of Items Checked	Stress Level
0 – 7	Low
8 – 14	Moderate
15-21	High
22+	Very High

Figure (1): Stress symptoms scale checklist.

Ethical considerations:

Approval of the institutional review board was taken. Informed written consent was also taken from every participant. The study adhered to the Helsinki Declaration throughout its execution.

Blood collection and Purification of Platelet:

Methods:

The procedure of platelet purification involved two principal steps: platelet inhibition cocktail preparation and blood collection to generate platelet rich plasma (PRP).

I-Platelet inhibition cocktail preparation:

The volumes stated below applied to 100 mL whole blood collected into twelve 15 mL tubes. We mixed 12 µl of 1 mM PGE1, 18 mL ACD, 480 ML of 0.5MEDTA and120 µl of 30 mM Acetylsalicylic acid. Every tube of the twelve 15 mL tubes was filled with 1.5 mL of the cocktail.

II- Blood collection and generation of PRP:

Before insertion of a cannula and ensuring that the patient does not have clopidogrel, the appropriate ethical approval must be acquired to withdraw human blood. We first weight the empty 15 mL tube and it was noted down. While the patient is sitting, comfortable, the flexible tubing was connected to the 1.2 mm diameter intravenous cannula, which was used to collect 8.5 mL of blood by self-propagating flow into each tube that held 1.5 mL of the platelet inhibition cocktail. When there was 10 mL of blood combined with the platelet inhibition cocktail, the cap was reinstalled and the tube was gently inverted. For each patient 50 mL of fresh blood was collected using 6 tubes for each patient.

We transferred 85% of the top layer to new 15 mm tube carefully to form PRP "Plasma rich platelets". Then we span the tubes at room temperature (10 min, 200 x g) using (Sigma centrifuge, Sigma laborazentrifugen Gmbh, Osterode am Harz, Germany) to further remove red blood cells and leukocytes. Carefully, 85%of the top PRP layer was transferred to a 50 mL tube.

The drained 50 mL tube was injected manually into a filter at a flow rate of 15 mL/minute and collected in a 50 mL tube. Then, centrifugation was done at room temperature for 10 minutes at 800 x g. The supernatants were discarded. The 15 mL tubes containing the platelet pellets were weighted and the weight of every platelet pellet was calculated by subtracting the weight of the empty tube from the above step.

Coronary angiography:

All ACS patients including STEMI and UA were performed through femoral access in all patients after local anesthesia, short guide wire was introduced through a needle, and then we put the femoral sheath, then though a guide wire the diagnostic catheters were introduced. We used the standard views to fully visualize coronaries.

Intravascular ultrasound (IVUS):

Thirty patients in the UA group underwent IVUS examinations following standard catheterization procedures. A gradual manual or mechanical (1 mm/s) pullback was used to remove the ultrasonic transducer (45 MHz, 3.2F, Phillips Volcano rotation, Phillips North America corporation, Jacops str. Cambridge, USA) after it had been advanced as far away as feasible along a guidewire (0.014 in.). Pullback was momentarily stopped if a substantial atherosclerotic plaque was seen, and the plaque was closely inspected. There didn't seem to be any thrombus covering the atherosclerotic plaque in any of the individuals who were evaluated.

Estimation of gene expressions:

I- RNA Isolation from blood (Direct –zol RNA Miniprep)

For total cellular RNA purification from blood, direct –zol RNA Mini protocol was used.

Procedure:

100 µl whole blood was mixed in an appropriate volume of TRIzol reagent (300 µl) (Canvax reagent, Valladolid, Spain), after the material was centrifuged to eliminate any particle matter, the supernatant was moved into a fresh tube.

After thoroughly mixing the supernatant with an equivalent volume of ethanol (95–100%), it was placed in a collecting tube, placed on a Zymo-Spin IIC column, and centrifuged.

After adding 400 µl of RNA wash buffer to the column, it was centrifuged.

After mixing 5 µl of DNaseI with 75 µl of DNA digestion buffer in an RNase-free tube, the mixture was applied straight to the column matrix.

At room temperature, the mixture was incubated for fifteen minutes. After centrifuging 400 µl of Direct-zol RNA pre-wash into the column and discarding the flow-through, we repeated this process.

To fully remove the wash buffer, we next added 700 µl of RNA wash buffer to the column and centrifuged it for two minutes. After that, we cautiously moved the column into a tube devoid of RNase. To elute RNA, we introduced 50 µl of DNase-RNase free water straight to the column matrix and centrifuged.

II- First Step - PCR: cDNA Synthesis (RT- Step).

(QuantiTect Reverse Transcription Kit, Applied Biosystems and Foster City, California, USA), (RNeasy kits (QUIAGEN GmbH, Hilden, Germany) were used.

Procedure:

The following procedures were followed in order to create, mix, and store the reverse-transcription master mix on ice: Four microliters of Quantiscript RT

buffer, one microliter of RT Primer Mix, and one microliter of Quantiscript reverse transcriptase were combined. With the exception of template RNA, all the ingredients required for the synthesis of first-strand cDNA were present in the reverse-transcription master mix.

To every tube containing reverse transcription master mix, we added 20 ng of extracted RNA, then mixed with optimum volume of RNase-free water to achieve reverse-transcription reaction of 20 µl overall volume and stored on ice. Then we incubated it at 42°C for 1 hour. For Quantiscript Reverse Transcriptase inactivation, it was incubated at 95°C for 5 min, then at 4°C for 5 min. Then refrigerated at -20°C for real-time PCR, the reverse-transcription reactions.

III- Second Step- PCR.

Amplification of cDNA with SYBR Green II with low ROX to detect HoxA9 and HoxA5 genes expression (QuantiTect SYBR Green PCR Kit, Applied Biosystems, Foster City, California, USA).

A designated quantity of the buffer was added to each primer to reconstitute it. Following centrifugation, the contents of the vial were combined by vortexing.

Forward primer1GCGAAGGAGAAGACCACGACAT22
Template888.....909
Reverse primer1TAGGCTTCCCTGCCTCTCCAAA22
Template1010.....989
NM_001357943.2 Homo sapiens glyceraldehyde-3-phosphate dehydrogenase (GAPDH), transcript variant 7, mRNA product length = 131
Forward primer1GTCTCCTCTGACTTCAACAGCG22
Template866.....88
Reverse primer1ACCACCCTGTTGCTGTAGCCAA22
Template996.....975.
(Primer kits, Biomol GmbH, Hamburg, Germany).

Procedure:

After thawing, the separate solutions of cDNA, primers, RNase-free water, and two QuantiTect SYBR Green PCR Master Mix were combined. After that, the reaction mixture was made in a different well, according to table (1) for each primer.

The volume of every component was multiplied per the number of reactions to prepare reaction master mix. Then appropriate amounts of the master mix were dispensed into PCR tubes after thorough mixing. Then cDNA of each sample was added to appropriate PCR tube containing the reaction master mix (Real-time PCR, Applied Biosystems Deutschland GmbH, Darmstadt, Germany).

The real-time cycler programming is shown in table (1). Melting curve analysis was performed of the PCR products to verify their identity and specificity. The software of real-time cyclers has a step for melting curve analysis. The melting curve cycling routine, which uses 7500 software version 2.0.1, is 95°C for 15 seconds, 55°C for 1 minute of fluorescence data collecting, 95°C for 30 seconds, and 55°C for 15 seconds.

Table (1): Master mix for each gene and the cycle of real time PCR.

Master Mix for each gene			
Component			**Volume/reaction**
2x QuantiTect SYBR Green PCR Master Mix			10 µl
Forward and reverse primers of gene			1ul for each
RNase-free water			4 µl
reaction mix volume			16 µl
Cycle of real time PCR			
Step	**Time**	**Temperature**	**Additional comments**
1- PCR initial activation step	15 min	95°C	HotStar Taq Plus DNA Polymerase is activated by this heating step
2-Three step cycling			
Denaturation	15 s	94°C	
Annealing	30 s	60°C	
Extension	34 s	72°C	Fluorescence data collection
Number of cycles	45 cycle		
Run duration	210 min		
PCR: polymerase chain reaction. DNA: deoxyribonucleic acid			

Figure (2) shows the amplification plot produced by Applied Biosystems 7500 software version 2.0.1, which was used to analyze the data.

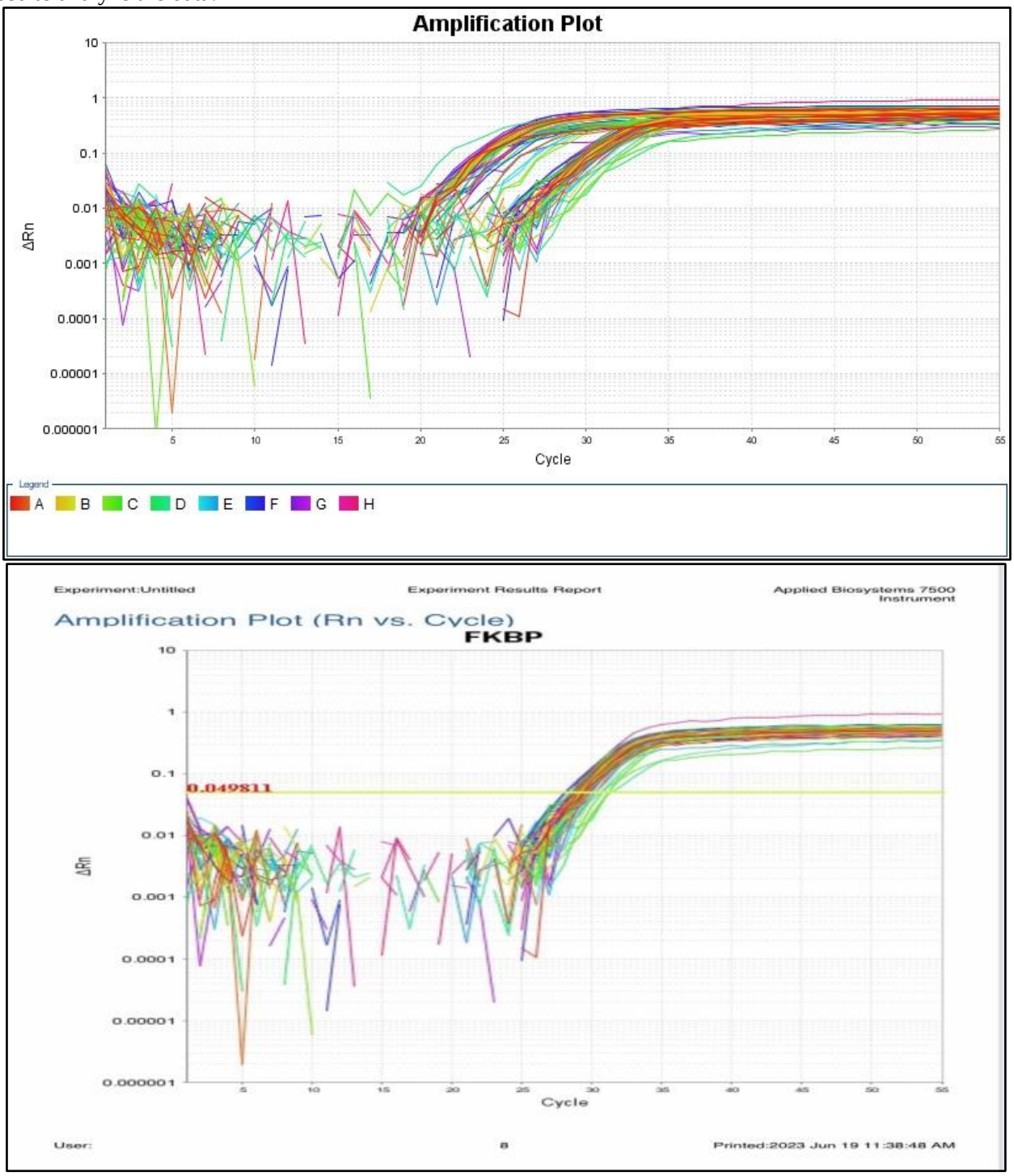

Figure (2): Amplification plot.

Statistical analysis

The data that were captured was analyzed using SPSS version 23.0. Both percentages and numbers were used to display categorical data. The mean ± SD was used to display parametric quantitative data, whereas the median with IQR was used to display non-parametric quantitative data. A 2-tailed P value was considered statistically significant if it was less than 0.05.

RESULTS

Our research was carried out on 90 participants, divided into two main groups; healthy participant group (30) and ACS group (60) that was further subdivided into STEMI group (30) and UA group (30) who underwent PCI and PCR.

There was no statistically significant difference between STEMI group and UA group regarding age while there was statistically significant increase found in the age of both sick groups than the control group, while no statistically significant difference was found between the three studied groups regarding gender distribution (Table 2).

Table (2): Comparison between control group, STEMI group and (UA) group regarding demographic data.

		Control group	STEMI group	(UA) group	Test value	P-value	Sig.
		No. = 30	No. = 30	No. = 30			
Age	Mean ± SD	55.30 ± 6.58	58.97 ± 6.17	60.60 ± 7.87	4.628•	0.012	S
	Range	46 – 69	46 – 70	48 – 78			
Gender	Female	6 (20.0%)	5 (16.7%)	5 (16.7%)	0.152*	0.927	NS
	Male	24 (80.0%)	25 (83.3%)	25 (83.3%)			

Non significant (NS); Significant (S); *Chi-square test; •: Independent t-test. ACS: Acute coronary syndrome, STEMI: ST elevation myocardial infarction, UA: Unstable angina.

There was statistically significant increase in the percentage of patients with DM, smokers, dyslipidemic patients, patients with IHD and DD in STEMI group and ACS (UA) group than control group, while no statistically significant difference was found between the three studied groups regarding the percentage of patients with HTN (Table 3).

Table (3): Comparison between control group, STEMI group and (UA) group regarding medical history and risk factors.

		Control group		STEMI group		(UA) group		Test value*	P-value	Sig.
		No.	%	No.	%	No.	%			
DM	No	25	83.3%	13	43.3%	17	56.7%	10.473	0.005	HS
	Yes	5	16.7%	17	56.7%	13	43.3%			
HTN	No	16	53.3%	7	23.3%	11	36.7%	5.767	0.056	NS
	Yes	14	46.7%	23	76.7%	19	63.3%			
Smoker	No	24	80.0%	14	46.7%	14	46.7%	9.109	0.011	S
	Yes	6	20.0%	16	53.3%	16	53.3%			
Dyslipidemia	No	24	80.0%	11	36.7%	18	60.0%	11.657	0.003	HS
	Yes	6	20.0%	19	63.3%	12	40.0%			
IHD	No	28	93.3%	19	63.3%	24	80.0%	8.139	0.017	S
	Yes	2	6.7%	11	36.7%	6	20.0%			
DD	No	24	80.0%	0	0.0%	3	10.0%	81.875	<0.001	HS
	I	6	20.0%	15	50.0%	27	90.0%			
	II	0	0.0%	15	50.0%	0	0.0%			

Non significant (NS); Significant (S); highly significant (HS), *Chi-square test; •: Independent t-test. DM: Diabetes mellitus, HTN: Hypertension, IHD: Ischemic heart disease, DD: diastolic dysfunction.

FKBP5 gene expression was statistically significantly higher in STEMI group followed by UA group and lastly the lower value was found in control group (Table 4).

Table (4): Comparison between control group, STEMI group and (UA) group regarding FKBP5 gene expression.

FKBP5 Gene Expression	Control group	STEMI group	(UA) group	Test value	P-value	Sig.
	No. = 30	No. = 30	No. = 30			
Median (IQR)	2 (1.2 - 2.9)	4.85 (3.9 - 10.6)	3.15 (2.2 - 4.7)	27.052	<0.001	HS
Range	1.1 – 12	1.6 – 12.9	1.3 – 14.7			
Post Hoc analysis						
Control group Vs STIMI group		STIMI group Vs ACS (UA) group				
<0.001		0.005				

There was statistically significant increase in the percentage of patients with emotional stress in STEMI group than control and ACS (UA) groups (Table 5).

Table (5): Comparison between control group, STEMI group and ACS (UA) group regarding emotional stress score.

		Control group		STEMI group		ACS (UA) group		Test value*	P-value	Sig.
		No.	%	No.	%	No.	%			
Emotional stress	No	24	80.0%	8	26.7%	24	80%	24.202	<0.001	HS
	Yes	6	20.0%	22	73.3%	6	20.0%			

*:Chi-square test

FKBP5 gene expression level was significantly higher in cases with emotional stress in STEMI group (Table 6).

Table (6): Relation between FKBP5 gene expression and emotional stress score in STEMI group.

		STEMI group		Test value	P-value	Sig.
		FKBP5 Gene Expression				
		Median (IQR)	Range			
Emotional stress	No	3.75 (2.25 – 4.55)	1.6 – 4.9	-2.701‡	0.007	HS
	Yes	7.7 (3.9 – 10.8)	1.8 – 12.9			

‡: Mann Whitney test; ‡‡: Kruskal Wallis test.

DISCUSSION

Type 1 MI is caused by coronary atherosclerotic plaque rupture followed by platelet activation that end into thrombus formation [2]. Emotional stress has been known as a trigger for MI, through its effect on platelet activation, **Zannas *et al.* [7]** have reported that extreme emotions increase FKBP5 gene expression.

Platelet gene expression in patients with STEMI was first reported by **Eicher *et al.* [6]** and the most expressed gene was FKBP5, this matches with **Gobbi *et al.* [2]** but against it was **Carubbi *et al.* [8]** who reported that S100A9 was the most expressed gene in STEMI patients with (P = 0.001).

Our aim was to evaluate emotional stress as a risk factor for type 1 myocardial infarction.

The mean age in CG group was 55.30 ± 6.58 ranged from (46 – 69 years), the mean age in STEMI group was 58.97 ± 6.17 ranged from (46 – 70 years), the mean age in UA group was 60.60 ± 7.87 ranged from (48 – 78 years). There were 6 females (20%) and 24 male (80%) in the HD, 5 females (16.7%) and 25 males (83.3%) in STEMI group and 5 females (16.7%) and 25 males (83.3%) in the UA group.

There was no statistically significant difference between STEMI group and UA group regarding age, while there was statistically significant increase found in the age of both sick groups than the control group with (P=0.012) (table 3). This matches with **Ricci *et al.* [9]** who revealed that age more than 53 y is a strong risk factor for ACS including STEMI and UA.

Regarding risk factors, there was statistically significant increase in the percentage of patients with DM, smokers, dyslipidemic patients, patients with IHD and patients with diastolic dysfunction in STEMI group and ACS (UA) group than control group with p-value=0.005, 0.011, 0.003, 0.017 and <0.001; respectively. This matches with **Sethi *et al.*[10], Konstantinou *et al.* [11], Yagi *et al.*[12], Dhungana *et al.* [13] and Steen *et al.* [14]** respectively indicating that DM, smoking, dyslipidemia, previous history of IHD and diastolic dysfunction are major independent risk factors for ACS. **Demirel *et al.* [15]** was against our results regarding DD may be due to inadequate number of patients in some groups.

Nevertheless, nothing is understood about how platelet genes contribute to the creation of thrombi, in our study, there was high significant difference in FKBP5 gene expression in STEMI patients' group in comparison to UA group and CG with (P-value<0.001). This matches with **Gobbi *et al.* [2]**, with (P-value<0.0026), **Eicher *et al.* [6]** with (P-value<0.000694) and **Carubbi *et al.* [8]** with (P-value < 0.004465), this demonstrates that FKBP5 gene have a causative role in thrombus formation after plaque rupture as **Eicher *et al.* [6]** demonstrated, through increasing platelet aggregation to ADP.

There was high statically significant increase regarding emotional stress with (STEMI group) in comparison to (UA group) and (HD group), with (P=<0.001), this matches with **Zupancic [16] and Santos *et al.*[17],** with (P=0.005) (p< 0.001) respectively. This indicates that emotional stress may be a major precipitating factor for type 1 MI.

There was also high significant increase in regarding emotional stress and FKBP5 gene expression in STEMI patients with (P=0.0007), this matches with **Zannas *et al.* [7] and Criado-Marrero *et al.* [18]**. This indicates that emotional stress increased FKBP5 gene expression. **Eicher *et al.* [6]** demonstrated that FKBP5 gene have a causative role in thrombus formation through increasing platelet aggregation to collagen and ADP, this may explain how emotional stress can cause type 1 myocardial infarction.

LIMITATIONS

Small sample size, our study conducted is one centre study, NSTEMI wasn't involved as a-part of ACS group and also our study didn't include the relation between FKBP5 gene and platelet activity.

CONCLUSION

Our study concluded that emotional stress is a major risk factor for type 1 MI. Emotional stress can cause activation of FKBP5 platelet gene that in turn can cause platelet activation resulting in thrombus formation.

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