Interactions between Some Inflammatory and Clotting Components in Patients Affected with Myocardial Infarction

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Abstract
Myocardial infarction (MI), it means irreversible injury that cardiac muscle and can lead to sudden death. The present study was employed to explore whether the MI affects some inflammatory and clotting components, also the gender, body mass index (BMI) and age. A complete number of subjects involved in this research were 80 subjects of both patients and healthy individuals (men and women) and they classified into four categories according to their ages (40-49, 50-59, 60-69, and 70-79 years old). The results of this work had been explained that the incidence of MI proportionate with increase body mass index (25-33 kg/m was 70% of patients) compared to patients with BMI 19-23 kg/m was 30% out of patients. Data of inflammatory and clotting components including interleukin-6 (IL-6), D-dimer, and tissue plasminogen activator-1 (tPA-1) recorded a significant increase in men and women affected with MI in matching with those healthy individuals. Concerning the levels of studied parameters according to ages and gender groups, their levels were significantly higher ($p<0.05$) of old ages compared with those healthy counters of both sexes. In regard to BMI, the levels of IL-6, tPA-1, and D-dimer were significantly heightening ($p<0.05$) in patients who have high BMI (25-33 kg/m2) compared to those have BMI within 19-23 kg/ m2. The ROC analyses (AUC) of studied parameters (D-dimer=0.740, tPA=0.60, and IL-60.767) associated with cutoff 298.5, 5.175, 8.950, respectively. In conclusion, the changes in studied parameter may be return to systemic inflammation, increase BMI, and activation of fibrinolytic system of patients affected with MI.
Keywords: Cardiovascular diseases, MI, BMI, tPA-1.

1. Introduction

Atherosclerosis is a complicated inflammatory disease that begins with endothelial dysfunction and concludes with plaque growth, instability, and rupture, this disease is characterized by the involvement of abnormal immune and tissue repair responses [1].
ST-elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI), and unstable angina are all conditions that fall under the umbrella of acute coronary syndrome (ACS), which is an abbreviation for the medical term, it is a subtype of coronary heart disease (CHD), the most common kind of heart disease in adults over the age of 35 and the cause of one-third of all fatalities in that age group, while some types of coronary heart disease may not present any symptoms, acute coronary syndrome (ACS) usually does [2-4]. Macrophages in the atherosclerotic plaque are capable of releasing a number of inflammatory cytokines, including proinflammatory cytokines (IL-1, IL-6, IL-12, IL-15, IL-18, TNF family members [such as TNF-], and MIF) and anti-inflammatory cytokines, including IL-10 and members of the TGF- family (TGF-1, BMPs, GDFs) [5]. As a marker of rapid fibrin turnover and high thrombotic activation in both the arterial and venous system, interest in D-dimer has grown over time, and its predictive role has been investigated in a variety of acute and chronic cardiovascular care settings, D-dimer is a protein that can be found in blood and urine. High levels of circulating D-dimer have been found to be associated with recurrent MI and a poor prognosis in individuals who had previously suffered from MI [6]. Tissue plasminogen activator, also known as tPA, is a type of protease known as a serine (enzymes that cleave peptide bonds in proteins), therefore, it is one of the crucial components that contributes to the breakdown of blood clots, Its principal role is to catalyze the transformation of plasminogen into plasmin, which is the primary enzyme involved in the process of breaking down blood clots [7]. IL6 is a cytokine with several functions that acts as a link between the innate and adaptive immune systems, IL6 is a pleiotropic cytokine that bridges the innate and adaptive immune systems, when there is a disruption or failure in the transition from the innate immune system to the adaptive immune system [8].

2. Materials and Methods

The research subjects

The present investigation was carried out at a variety of establishments, such as Marjan teaching hospital (the ischemic heart disease unit), Imam Al-sadiq hospital, private laboratories, and Babylon university/college of science for women. These establishments were all included. The current investigation started during the months of November 2021 and April 2022.
A total of eighty (80) people, including both men and women, were chosen to participate in the study. Twenty men out of those eighty reported symptoms of myocardial infarction, while another twenty men out of those eighty appeared to be in good health

doi.org/10.31838/hiv22.02.339 Received: 22.05.22, Revised: 23.05.22, Accepted: 11.08.22

and served as a control group. Twenty (20) of the remaining forty (40) women were diagnosed with myocardial infarction, and twenty (20) of the remaining forty (40) women were recruited to serve as a control group.

The ages of all of the participants in the current study ranged anywhere from 40 to 79 years old. The participants in this study, which included both patients and healthy controls, had their ages recorded and were placed into one of four categories, according on how old they were (40-49, 50-59, 60-69, and 70-79 years old). Patients with diabetes mellitus, malignant diseases, lung diseases, thyrotoxicosis, and hypertension, as well as auto immune diseases, do not meet the criteria for inclusion in this study. The women who participated in this research project did not take any form of hormonal replacement treatment or oral contraceptives.

All of the victims were sent to hospitals and other medical facilities to have their individual myocardial infarctions checked out and were given treatment medications. Concerning the control individuals, those who signed up for the study came from public health centers, workers in hospitals, and people who had previously had good health.

3. Methods

Measurements of IL-6 and tissue plasminogen activator were carried out according to instructions of Biotech and BT lab companies. In addition to this, D.dimer was measured in accordance with the directives provided by the Biotech Company.

4. Statistical Analysis

The findings of this investigation were presented in the form of means together with standard deviations (SE). A statistical analysis was performed on the data with the SPSS 23 program, and an explanation of analysis of variance was provided. The least significant differences (LSD) between the groups that were analyzed were p values less than 0.05 [9, 10].

5. Results

Relation of body mass index and MI: -

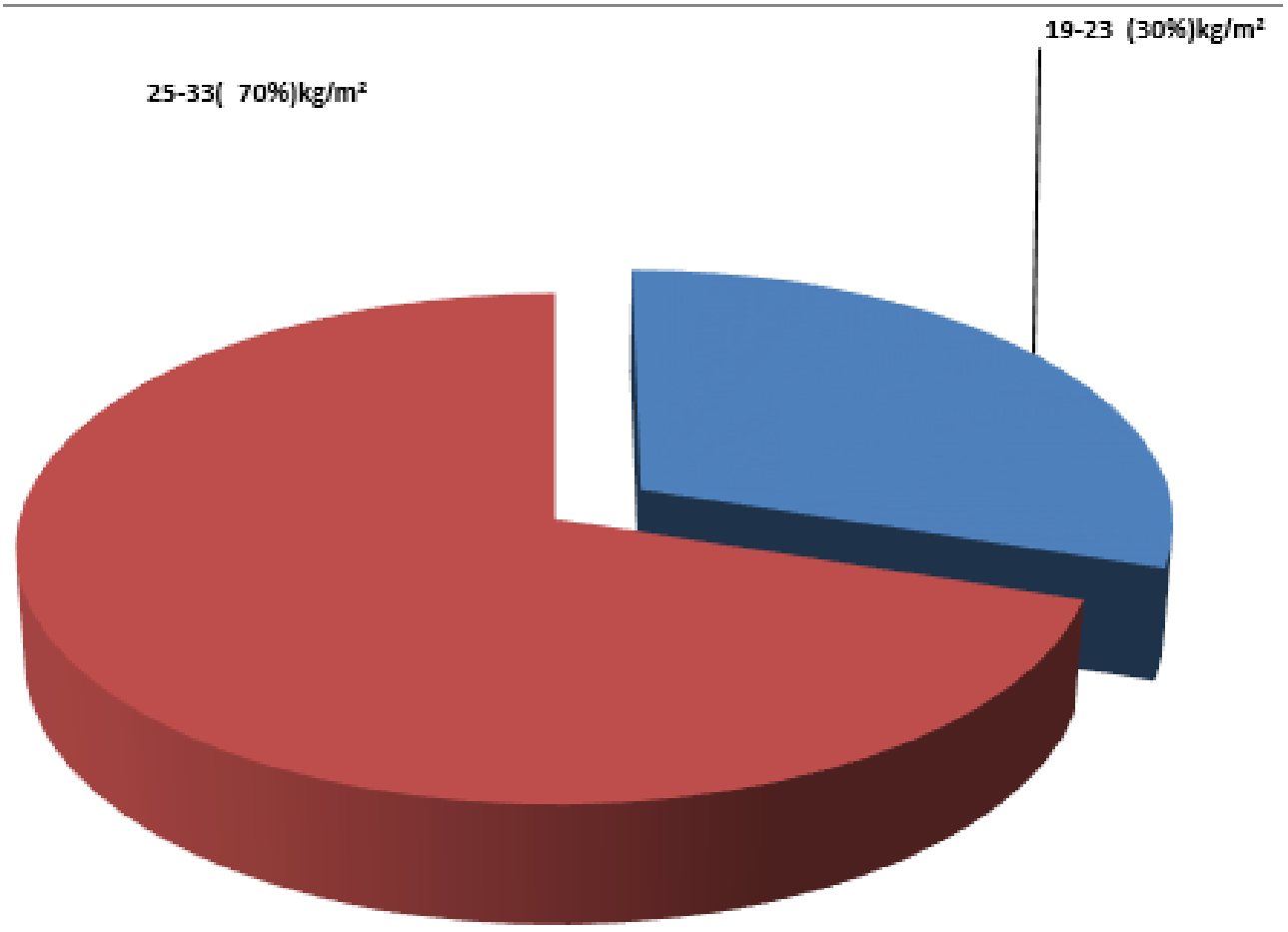

Figure (1): Shows the percentage ratio (%) of body mass index for patients affected with myocardial infarction.

Results that explained in the Figure (1) explained an increased incidence of MI was 70% in patients who had BMI equal 25-33 kg/m² compared to those with BMI equal 19-23 kg/m² were lower 30%.

2- Levels of biochemical markers (D-dimer ng/ml, tissue plasminogen activator-1 (TPA-1) ng/ml and interleukin-6 (IL-6) pg/ml) of patients affected with myocardial infarction according to gender.

Means which were illustrated in following table (1) explained the means ±SE of all mentioned above parameters of both patients and controls, showed a significant decrease d-dimer, TPA-1 and IL-6 (860.55±16.9 ng/ml, 10.28±1.1 ng/ml and 13.46±2.4 pg/ml) in males and females (993.30±35.4

ng/ml, 10.44±1.6 ng/ml and 14.20±1.1 pg/ml) at p<0.05 value was obtained for all parameters.

Table (1): Display the biochemical indicators (D-dimer, tissue plasminogen activator-1 (TPA-1) and interleukin-6 (IL-6)) of myocardial infarction patients based on their gender.

Groups Parameters	Males		Females		LSD (0.05) (gender*group)
	Patient	Control	Patient	Control	
	Mean ±S. E				
D-dimer (ng/ml)	* 860.55±16.9	259.90±25.4	*993.30±35.4	272.90±20.9	76.840
TPA-1 (ng/ml)	*10.28±1.1	4.88±0.9	*10.44±1.6	4.99±1.2	0.511
IL-6 (pg/ml)	* 13.46±2.4	5.33±1.3	*14.20±1.1	5.21±0.9	0.614

-All values were mean ±SE

-Means with asterisk were have significant differences (LSD) at level of p value <0.05.

-Means with no asterisk were have no significant differences (LSD) at level of p value >0.05.

3- The finding of biochemical markers (D-dimer ng/ml, tissue plasminogen activator-1 (TPA-1) ng/ml and interleukin-6 (IL-6) pg/ml) of patients affected with myocardial infarction and control group according to gender and age.

The levels which were illustrated in following table (2) explained the means ±SE of all mentioned above parameters of both patients and controls, they were statistical differences among all studied age groups (40-49, 50-59, 60-69, and 70-79 years old). Also, significant difference (LSD) value was obtained for all groups that were illustrated in the following figures in this study.

Table (2): Display the biochemical markers (D-dimer, tissue plasminogen activator-1 (TPA-1) and interleukin-6 (IL-6)) of myocardial infarction patients belonging to healthy age and gender groups.

Groups Parameters	Age (year)	Males		Females		LSD (0.05)
		Patient	Control	Patient	Control	
		Mean ±S. E				
D-dimer (ng/ml)	40-49	* 872.20±45.1	283.00±12.5	* 849.00±20.3	238.00±16.4	296.031
	50-59	* 864.60±36.2	249.20±10.4	* 1091.6±45.1	255.20±17.2	
	60-69	* 858.40±27.8	238.80±13.7	* 1078.80±50.6	335.00±13.9	
	70-79	* 847.00±19.8	268.60±17.8	* 953.80±37.4	263.40±12.7	
TPA-1 ((ng/ml)	40-49	* 10.32±1.6	4.74±0.9	* 10.83±1.7	5.12±0.9	0.332
	50-59	* 10.09±1.7	4.88±0.5	* 9.94±1.2	4.60±0.2	
	60-69	* 9.90±0.9	5.12±0.5	* 11.54±1.2	5.42±0.3	
	70-79	* 10.81±1.3	4.79±0.3	* 9.43±1.2	4.80±0.1	
IL-6 (pg/ml)	40-49	* 12.56±1.1	5.96±1.6	* 12.18±1.1	9.52±2.1	1.264
	50-59	* 12.70±1.3	5.30±0.9	* 14.84±1.2	4.64±1.7	
	60-69	* 15.14±2.1	5.30±0.7	* 14.82±1.3	6.08±0.9	
	70-79	* 13.44±1.9	4.76±0.6	* 14.96±2.3	5.58±1.1	

-All values were mean ±SE

-Means with asterisk were have significant differences (LSD) at level of p value <0.05.

-Means with no asterisk were have no significant differences (LSD) at level of p value >0.05.

4-levels of biochemical markers (D-dimer ng/ml, tissue plasminogen activator-1 (TPA-1) ng/ml and interleukin-6 (IL-6) pg/ml) of patients affected with myocardial infarction according to body mass index (BMI Kg/m2).

Means which were depicted in the table (3) indicated a notable increasing in the level of d-dimer, TPA-1 and IL6 (918.60±46.2 ng/ml, 11.01±0.5 ng/ml and 14.56±0.7 pg/ml respectivly) in patient at level p<0.01 compared to control (255.00±22.2 ng/ml, 4.91±0.3 ng/ml and 5.46±0.5 pg/ml respectivly).

Table (3): Display the biochemical markers (D-dimer, tissue plasminogen activator-1(TPA-1) and Interleukin-6(IL-6)) of myocardial infarction patients in accordance with their body mass index (BMI Kg/m2).

BMI groups Parameters	BMI (Kg/m2)		p≤0.05
	Patient (25-33)	Control (19-23)	
	Mean±S.E		
D-dimer (ng/ml)	918.60±46.2	255.00±22.2	≤0.0001**
TPA-1 (ng/ml)	11.01±0.5	4.91±0.3	≤0.0001**
IL-6 (pg/ml)	14.56±0.7	5.46±0.5	≤0.0001**

-All values were mean ±SE

-Results with two asterisks were significantly different at p≤0.0001.

Table (4): The optimal cutoff, sensitivity, and specificity for disease activity prediction by parameters.						
Parameter	Sensitivity	Specificity	AUC	Cut off	95% confidence	p-value
D-dimer (ng/ml)	80	0.58	.740	298.5	0.629-0.851	≤0.0001
TPA-1 (ng/ml)	0.78	0.60	0.724	5.175	0.608-0.840	0.001
IL-6 (pg/ml)	0.800	0.750	.767	8.950	0.661-0.874	≤0.0001

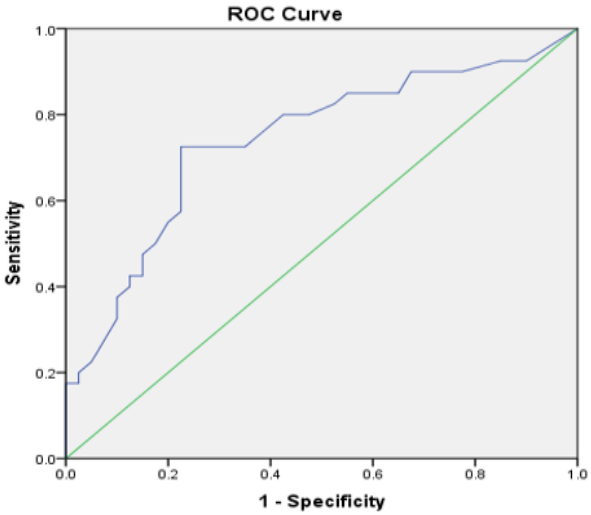

Figure (2): ROC curve for disease activity prediction by D-dimer

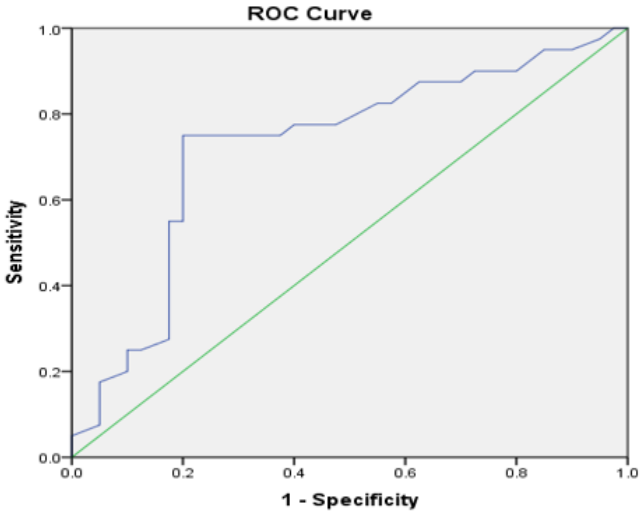

Figure (3): ROC curve for disease activity prediction by TPA.

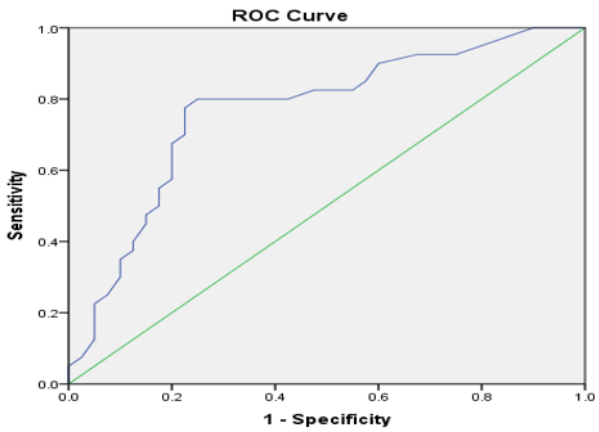

Figure (4): ROC curve for disease activity prediction by IL-6.

6. Discussion

It is well know that fibrin degradation (clotlysis) by plasmin produces D-dimer ,the clot formation and fibrinolysis (D-dimer production) represent the activity of coagulation and fibrinolysis mechanisms. Moreover, it was determined that people with D-dimer levels exceeding one-third are 70 percent more likely to have coronary heart disease [11].

D-dimer remains the essential marker for determining the activity of fibrinolytic system that carried out by plasmin also it used in identification of disseminated intravascular coagulation (DIC). Furthermore, It was discovered that the levels of D-dimer, creating kinase-MB, and troponin I were much higher in those who had coronary disease than in healthy people [12].

The severity of D-dimer has been shown to have a positive correlation with levels of D-dimer, and these levels of this marker have been shown to be significantly elevated during hypercoagulability states, in particular in a cute coronary artery [13].

Results that were obtained from the current study indicated a significant increase ($p< 0.01$) in the levels of tPA-1 in all patient groups according to sex, age, and asspciated with increase body mass index in all patients affected with MI, despite the fact that this biomarker is not correlated with studied parameters. ROC analysis of the disease activity by TPA-1, AUC result was (0.724).

Previous study was conducted by Lowe et al. [14], this study had been established that there was a strong relationship between tPA and other factors including cardiac heart diseases, body mass index, age, blood pressure, inflammatory markers (CRP) and white blood cells.

Another study carried out by Mulder et al. [15] indicated that tPA and tPI are associated with increased incidence of stroke and atrial fibrillation, also these observations do not dependent on sex.

[16] confirmed that patients suffering from myocardial infarction and those with angina pectoris having significant elevation in the levels of plasminogen activator ,fibrinogen and C-reactive proteins compared to those healthy subjects ,tissue plasminogen activator is antagonized by the tissue plasminogen in hibitor-1 ,there for the levels of tPAI-1 is associated with cardiovascular events ,so as the fibrinolytic activity become encountered by pro-coagulant factor and these effects may be equal on interactions between coagulation and fibrinolytic system [17, 18].

The present investigation revealed a statistically significant ($p<0.01$) increase in the levels of IL-6 in all MI-affected patients compared to those in the control group.

There are many cytokines that are involved with the incidence of acute coronary syndrome, including

TNF-, interleukins, adipokines, chemokines, and interferons. However, recent studies have been conducted to explore the association that occurs between cardiovascular diseases and IL-6, particularly acute coronary syndrome. In particular, IL-6 was found to have prominent prognostic levels in patients with acute coronary syndrome [19, 20].

It is well noticeable that IL-6 values are at maximum levels and significantly increased in patients who have coronary heart disease and also constitutes three times higher than those normal healthy people ,at the same times ,these values of IL-6 are strong associated with inflammatory markers particularly c-reactive protein [21].

Recent study confirmed that increased release of inflammatory mediators control whatever the vascular plague remain or dissolved and progressive of cardio and cerebrovascular events ,of those inflammatory markers ,IL-6 which is largerly cytokines and implicated in development of inflammatory process and oxidative stress that in turn can lead to incidence and progress atherosclerosis and myocardial infarction [22].

Additionally, it was investigated by Arakawa et al. [22]. This study confirmed that treatment with estrogen replacement therapy attenuate inflammatory effects through a decrease in the response to stressful conditions. The study also explained the role those sexual hormones, particularly 17 beta-estradiol and progesterone, play in the central nervous system to regulate the level of inflammatory cytokines such as IL-1 and IL-6.

7. Conclusion

From these observations, these changes may be attributed to systemic inflammation and evoke of fibrinolytic system in patients with MI.

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