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Study of Diagnostic Value of Cyclooxygenase-2 and Matrix Metalloproteinases in Atherosclerosis

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Authors' contributions

This work was carried out in collaboration among all authors. Author EH designed the study, wrote the protocol, managed the literature searches, edited the manuscript and supervised the work. Author AE collected data, did Lab. investigations and wrote the first draft of the manuscript. Author NAA selected the subjects and diagnosed the cases. Authors EH and MA revised the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Background and Aim: Atherosclerosis is a chronic systematic disease where lesion (plaque) develops results in activation of inflammatory reaction that leads to arterial obstruction. Atherosclerosis is the underlying cause for many cardiovascular diseases (CVD) which were estimated with 42 percent of total death in Saudi Arabia while Coronary artery diseases (CAD) accounted for 35 percent of total chronic diseases death in Saudi Arabia by 2008. Risk factors that attribute in progression of atherosclerotic lesion and subsequent complications are smoking, high Low Density Lipoprotein –Cholesterol (LDL-C), high blood pressure, obesity and alcohol.
Materials and Methods: This study was carried on 20 healthy individuals as a control group, 15 patients with stable angina, 15 patients with recent myocardial infraction (MI) and 15 patient 24-hours post MI. All subjects were males with age 45±65 years and underwent exclusion/inclusion

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criteria. COX-2, MMPs levels were quantitatively measured by enzyme-linked immunosorbent assay (ELISA).

Results: There is insignificant differences in both COX-2 and MMP-2 levels among studied groups (P = 0.450 and 0.246 respectively) .On other hand, MMP-9 demonstrate a significant elevation in its level in studied groups (P = 0.014): its level significantly increase in stable angina (31.474 ± 12.188 ng/ml) compared to both control (9.920 ± 0.075 ng/ml) and Post MI groups (16.012 ± 13.852 ng/ml) (P = 0.001 and 0.004 respectively) and significantly increase in MI group (26.020 ± 14.792 ng/ml) when compared to both control (P = 0.006) and post MI (P = 0.038) groups.

Conclusion: We can conclude that both COX-2 and MMP-2 cannot be used as markers for diagnosis of stable angina or MI. While MMP-9 as it showed significant elevation in its level in MI and then decrease in post MI, it can be considered as a good marker for confirming the diagnosis of MI and post MI stage.

Keywords: Cardiovascular disease; atherosclerosis; myocardial infarction; cyclooxygenase-2; matrix metalloproteinase-2; matrix metalloproteinase-9; troponin-t; creatinine kinase.

1. INTRODUCTION

Atherosclerosis, the underlying cause of myocardial infarction (MI), is an inflammatory lesion that is characterized by mononuclear infiltration and smooth muscle cell proliferation [1,2]. The inflammatory aspects of atherosclerosis include the cyclooxygenase (COX) dependent prostaglandin cascade. Activation of this pathway in arterial macrophages precedes, and could affect, their transformation into foam cells [3]. The most abundant isoform of COX in inflammation episodes, especially in atherosclerosis is COX-2 [4–6]. COX-2 is expressed in several cell types such as macrophages, endothelial cells, fibroblasts, and smooth muscle cells, and is highly inducible by cytokines, growth factors, hormones, and oncogenes [7]. The induction of COX-2, with resultant production of prostanoids, can contribute to inflammation, pain, parturition, and certain types of cancer [8]. COX-2 contributes significantly to systemic Prostaglandin I2 (PGI2) and Prostaglandin E2 (PGE2) synthesis [9,10] PGE2 has an important role in activation of proteolytic enzymes called matrix metalloproteinases (MMPs), among them there are MMP-2 and MMP-9 which cause plaques instability and rupture due to their action in thinning the plaques' extracellular matrix fibrous [11,12]. The present study will estimate the levels of COX-2 and metalloproteinases, MMP- 2 and MMP-9 in serum of patients with atherosclerosis and MI and whether they have a diagnostic value among these cases.

2. MATERIALS AND METHODS

Study was conducted on 65 subjects divided into four groups: Group I (20 healthy individuals), Group II (15 patients with stable angina), Group III (15 patients with myocardial infarction), Group IV (15 patients with 24 hours post myocardial infarction). All healthy subjects and patients were males with age ranging from 45-65 years and selected according to inclusion/exclusion criteria in (Table 1). Patients were examined by a cardiologist and they were undergoing stress test, angiogram and ECG to confirm a correct diagnosis. Moreover, routine blood tests were collected as renal function test, hepatic function, lipid profile, Troponin T, creatinine kinase (CK) ,Creatine kinase-Myocardial Band (CK-MB), C-reactive protein (CRP), fasting blood glucose, Complete blood count (CBC) (was done on a whole blood sample).

COX-2, MMP-2 and MMP-9 were tested using enzyme linked immunosorbent assay (ELIZA) kits with an excellent specificity with no significant cross- reactivity and with high sensitivity lower limit of detection (LLD) is less than [0.284 ng/ml]. A correlation test was used to assess a possible linear association between MMP-9, Troponin-T, creatinine kinase (CK) and CK-MB.

2.1 Statistical Analysis

Data presented as Mean ± Standard deviation in (ng/ml) and were obtained using GraphPad prism version 7.2 and SPSS. Statistical test One Way ANOVA was used to compare COX-2, MMP-2 AND MMP-9 levels among stable angina, MI, Post MI and Control groups and Tukey's multiple comparisons test were used to determine the significant differences between two groups. The level of significance is when the P< 0.005. Person's correlation coefficient test was used to assess a possible linear association between MMP-9, Troponin-T, CK and CK-MB.

3. RESULTS

The results of the routine biochemical tests among the studied groups in comparison to the control subjects are presented in Table 2.

COX-2 level in studied groups: COX-2 level was (2.730±0.021 ng/ml) in control group. Its level in stable angina group was (4.580 ±2.539 ng/ml). In MI, its level was (4.137 ±1.863 ng/ml), while in post MI group it was (5.155 ±1.971 ng/ml). The levels of COX2 were insignificantly higher in all patients' groups as compared to the control one (Fig. 1).

MMP-2 levels in studied groups (Table 3): MMP-2 level was (1.449 ±0.057 ng/ml) in control group. Its level in stable angina was (1.680±0536 ng/ml), In MI, it was (1.452 ±0.713 ng/ml) and in post MI was (2.025 ±1.319 ng/ml). The levels of MMP-2 in all patients' groups were insignificantly higher than its level in the control group (Fig. 2).

MMP-9 levels in studied groups (Table 3): MMP-9 level was (9.920 ±0.075 ng/ml) in control group. Its level in stable angina was (31.474 ±12.188 ng/ml), while its level in MI was (26.020± 14.792 ng/ml) Fig. 2: MMP-2 Level in The Different Studied Group: Matrix Metalloproteinas-2 levels were (1.449 ± 0.001) in control group, (1.68 ± 0.0536) in stable angina group, (1.452±0.713) in MI, and (2.025± 1.319) in post MI group and in post MI was (16.012 ±13.852 ng/ml). The level of MMP-9 was significantly higher in both stable angina and MI groups as compared to its level in the control group, while it was insignificantly higher in post MI comparing with that of the control group (Fig. 3).

COX-2, MMP-2 and MMP-9 levels in stable angina vs. MI group (Table 3): There was no statistical significant differences between the levels of COX-2 in stable angina and MI (P =0.657). Also the level of MMP-2 in MI group was insignificantly lower than its level in stable angina group (P = 0.793). Insignificant elevation was noticed in MMP-9 level in stable angina when compared with its level in MI group (P = 0.372).

COX-2, MMP-2 and MMP-9 levels in stable angina vs. post MI group (Table 3): There were no significant differences between stable angina and post MI groups in COX-2 levels (P = 0.364). The level of MMP-2 was insignificantly higher in post MI group than its level in stable angina group (P = 0.664). MMP-9 level was significantly higher in stable angina group as compared with its level in post MI group (P =0.004). COX-2, MMP-2 and MMP-9 levels in in MI vs. post MI group: There were no significant differences between MI and post MI groups in the levels of COX-2 (P =0.188) and MMP-2 (P = 0. 496) while it shows significant differences in MMP-9 level (P =0.038).

COX-2, MMP-2 MMP-9 levels comparison in different studied groups (Table 3): As per the results above, we can conclude that no significant differences in both COX-2 and MMP-2 between studied groups (P = 0.45 and P =0.246 respectively) while there are significant differences in MMP-9 levels between studied groups P = 0.014; control and MI and between control and post MI. Moreover, significant differences were found between stable angina and post MI group (Fig. 4).

Correlation between MMP-9 and cardiac markers in MI group (Table 3):

A. Correlation between MMP-9 and Troponin-T levels in MI group:
   No positive correlation was found between MMP-9 and Troponin-T (r^2 = 0.0821, P = 0.771. The value of r^2, the coefficient of determination, is 0.0067 (Fig. 5A).
B. Correlation between MMP-9 and CK-MB levels in MI group:
   Weak positive correlation was found between MMP-9 and CK-MB(r =0.0321 ,P = 0.909,r^2 =0.001) (Fig. 5B).
C. Correlation between MMP-9 and CK levels in MI group:
   Weak negative correlation was found between MMP-9 and CK(r = –0.2457, P =0.378, r^2 =0.0604 (Fig. 5C).

Correlation between MMP-9 and cardiac markers in Post MI group:

A. Correlation between MMP-9 and Troponin-T levels in post MI group:
   Weak positive correlation was found between MMP-9 and Troponin-T in post MI group(r = 0.1894, P = 0.498, r^2 = 0.0359) (Fig. 5D).
B. Correlation between MMP-9 and CK-MB levels in post MI group:
   Weak positive correlation was found between MMP- 9 and CK-MB in post MI group(r = 0.107, P = 0.704, r^2 =0.0114 (Fig. 5E).
C. Correlation between MMP-9 and CK levels in post MI group:

Weak negative correlation was found between MMP- 9 and CK in post MI group(r = -0.3154 , P = 0.252, r^2 =0.0995) (Fig. 5F).

Table 1. Inclusion and exclusion criteria for study subjects

Risk Factors	Group 1	Group 2	Group 3	Group 4
Smoking	X	√	√	√
Diabetes				
High blood pressure	X	√	√	√
Common cold				
History of inflammation (cystitis, Sinusitis, Arthritis)	X	X	X	X
Chest pain	X	√	√	√
High LDL	X	√	√	√
History of Cardiac disease	X	√	√	√
Current Cardiac attack	X	X	√	X

Table 2. Comparison between COX-2, MMP-2 and MMP-9 level in the studied groups

Studied Group	COX-2		MMP-2		MMP-9	
Control	2.73	±0.001	1.449	±0.001	9.92	±0.001
Stable Angina	4.58	±2.539	1.68	±0.0536	31.474	±12.950
MI	4.137	±1.863	1.452	±0.713	26.02	±14.792
Post MI	5.155	±1.971	2.025	±1.319	16.012	±13.852
P value						
For each enzyme	0.45		0.246		0.014	
Control vs. Stable Angina	0.520		0.267		0.001	
Control vs. MI	0.869		0.173		0.006	
Control vs. Post MI	0.118		0.537		0.608	
Stable angina vs. MI	0.657		0.793		0.372	
Stable Angina vs. Post MI	0.364		0.664		0.004	
MI vs. Post MI	0.188		0.496		0.038	

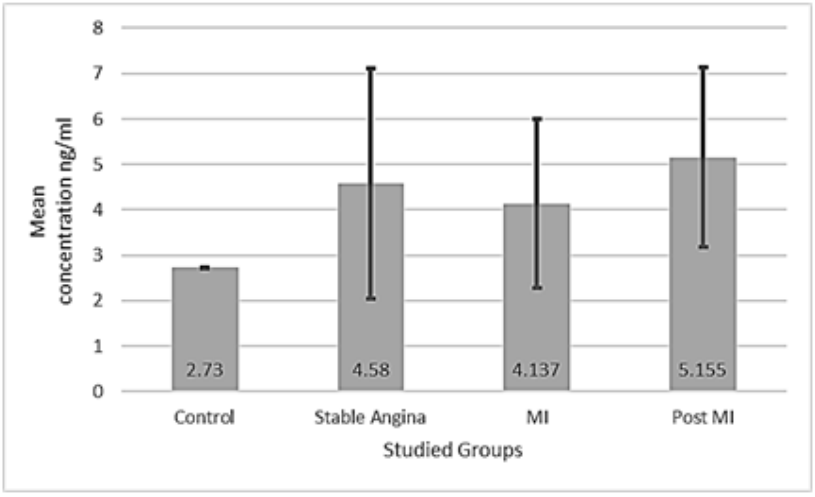

Fig. 1. Cyclooxgenase-2 levels in the different studied groups: Cyclooxygenase-2 levels were (2.73 ± 0.001) in control group, (4.58 ± 2.530) in stable angina group, (4.137±1.863) in MI and (5.155±1.971) in post MI group. The significant P value < 0.05.MI;Myocardial Infarction

Table 3. Routine parameters' results among studied groups in compare to control

Routine test	Unit	Control mean ± SD	Stable Angina mean ± SD	MI mean ± SD	Post MI mean ± SD
TROP-T	µg/L	0.200 ± 0.000	6.700 ± 1.785	15.953 ± 4.250	10.475 ± 1.431
CKMB	µg/L	1.969 ± 0.398	19.210 ± 5.000	61.309 ± 8.363	26.519 ± 6.206
CRP	mg/L	2.069 ± 0.302	6.104 ± 1.097	19.081 ± 2.892	28.669 ± 25.211
CHOLEST	mmol/L	3.744 ± 0.282	39.564 ± 112.099	5.251 ± 0.059	4.597 ± 0.295
LDL	mmol/L	4.708 ± 0.387	3.238 ± 0.064	3.286 ± 0.076	4.077 ± 0.034
GLUCOSE	mmol/L	5.102 ± 0.054	6.562 ± 0.444	10.574 ± 0.207	11.258 ± 0.225
CK	IU/L	229.107 ± 43.859	116.346 ± 8.912	822.467 ± 46.628	717.533 ± 143.662
ALT	U/L	44.877 ± 4.430	36.846 ± 1.562	58.400 ± 5.987	62.640 ± 1.165
AST	U/L	38.757 ± 4.719	27.871 ± 3.974	166.800 ± 16.517	140.740 ± 21.044
LD	U/L	148.929 ± 0.783	270.308 ± 16.385	564.333 ± 51.403	412.467 ± 49.051
NA	mmol/L	139.857 ± 0.038	139.231 ± 0.740	137.800 ± 0.214	136.867 ± 0.570
K	mmol/L	4.193 ± 0.052	4.231 ± 0.019	3.947 ± 0.014	3.947 ± 0.039
Urea	mmol/L	4.671 ± 0.382	5.223 ± 0.327	6.467 ± 0.285	9.667 ± 1.621
HDL)	mmol/L	1.317 ± 0.156	1.225 ± 0.207	1.060 ± 0.072	0.765 ± 0.015
Creatinine	mmol/L	88.143 ± 7.254	107.846 ± 5.839	82.467 ± 6.539	116.533 ± 14.842

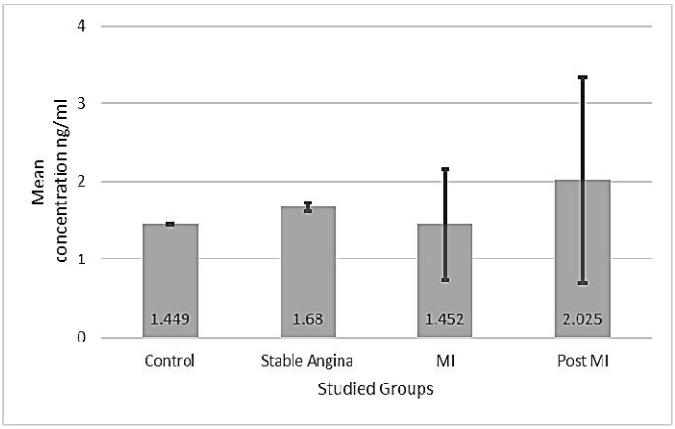

Fig. 2. Mmp-2 level in the different studied group: Matrix metalloproteinas-2 levels were (1.449 ± 0.001) in control group, (1.68 ± 0.0536) in stable angina group, (1.452±0.713) in MI and (2.025± 1.319) in post MI group. MI;Myocardial Infarction

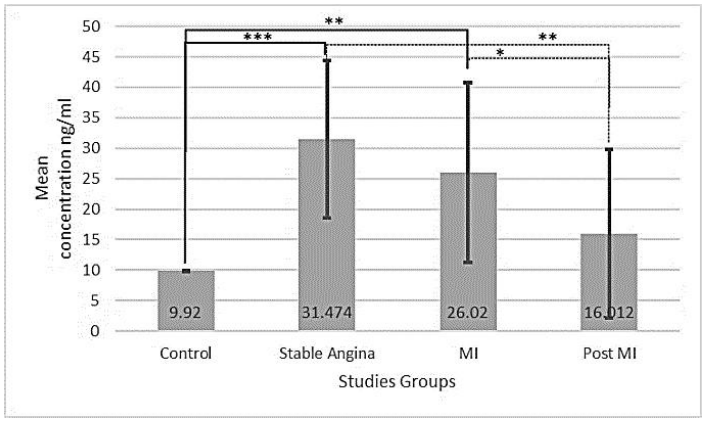

Fig. 3. MMP-9 Levels in the different studied groups: Matrix metalloproteinas-9 levels were (9.92 ± 0.001) in control group, (31.474 ± 12.95) in stable angina group, (26.02± 14.792) in MI, and (16.012± 13.852) in post MI group. The significant P value; * :P ≤ 0.05, ** :P ≤ 0.01, *** :P ≤ 0.001, MI;Myocardial Infarction angina and post MI group (Fig. 4).

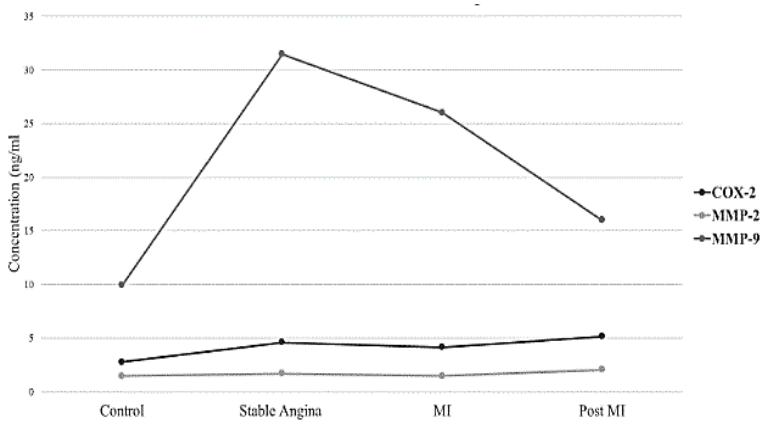

Fig. 4. COX-2, MMP-2 and MMP-9 levels' comparison between studied groups. MI;Myocardial Infarction

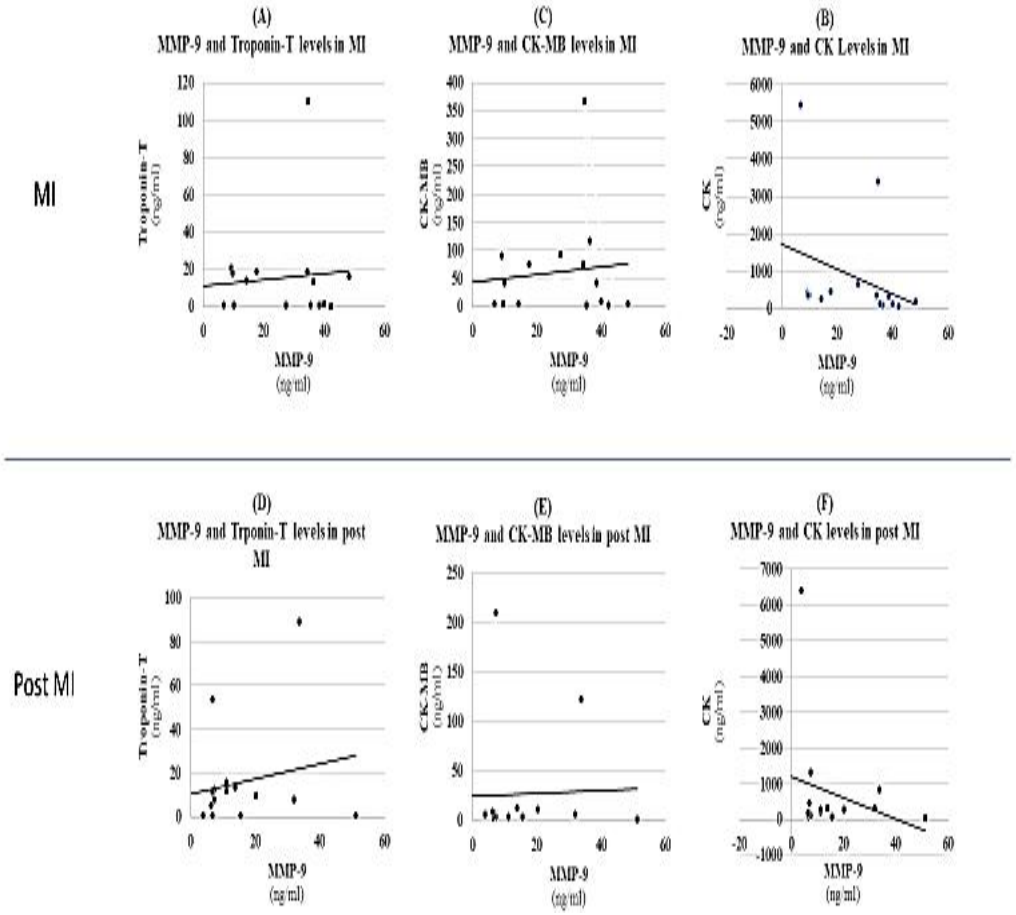

Fig. 5. Correlation study between MMP-9 and cardiac enzymes; CK, CK-MB and troponin in MI and post MI groups

4. DISCUSSION

Our findings indicated that COX-2 level is sustained during all atherosclerosis stages and no significant differences were found between control and studied patient groups in COX-2 level. It was thought that COX-2 may be induced in normal subjects for many reasons. First, to sustain PGI2 level in a baseline in order to maintain vascular homeostasis since it acts as a vasodilator and prevents platelet aggregation. This action is considered as a protective role for COX-2 [13,14]. Second, although COX-2 is an inducible enzyme, it is expressed in normal subjects in both kidney and brain. Third, its secretion is increased as a response to high salt dietary intake and water deprivation [15]. All mentioned reasons could explain why COX-2 is detected in the control group in our study. COX-2 is not detected in foam cells and this suggests that the production of this enzyme is decreased when macrophages are converted to foam cells. Macrophages conversion to foam cells is the main event in plaque formation. This explains the decrease in COX-2 level in MI group compared to stable angina group in our study, since MI is characterized by foam cell accumulation. Although stable angina, MI and post MI subjects were under Aspirin medication, we were still able to detect COX-2 levels in those groups [16]. It has been proved that high level COX-2 induces myocardium protection against reperfusion ischemia, and using COX-2 inhibitors had delayed the healing process for the infracted zone [17–19]. This explains our findings regarding the high levels of COX-2 in post MI than both stable angina and MI, however this was found insignificant statistically. Since COX-2 enhances MMPs production, we have measured both MMP-2 and MMP-9 in control, stable

angina, and MI and post MI patients. No significant differences found between patient groups when compared to normal subjects.

It was demonstrated that no relation exists between MMP-2 and cardiovascular progression [20]. It was postulated that MMP-2 was detected in normal vessels, stable angina and MI and its level in those patients is higher than its levels in normal vessels [21-22]. MMP-2 level is increased in post MI subjects while it exists with lower levels in stable angina and MI groups confirming its protective role in recovery in post MI [23]. Furthermore, Pasterkamp G [24] detected MMP-2 and MMP-9 in the damaged part of heart after 24 hours from manifesting MI. In studies by Noji [25], MMP-2 was found with high level in stable plaque and this is correlated with plaque calcification. On the other hand, MMP-2 was found higher in its level in MI than that in stable angina [25]. It is still not clear when MMP-2 level elevation occurs; while some studies suggested that MMP-2 level raises as soon as MI develops and lasts for 7 days post MI, others suggested that the elevation starts after 1 week from MI and lasts up to 3 weeks in the infraction region [26]. It was postulated that MMP-2 breaks down cell membrane contents and produces chemoattractants that facilitate macrophages migration. Thus, absence of MMP-2 decreases macrophages migration and subsequent plaque rupture. It was demonstrated that tissue inhibitor metalloproteinase-2 (TIMP-2) suppresses plaque rupture and MI development by inhibiting MMP-2 activity. When we measured MMP-9 level in our studied groups, we found that its level is insignificantly higher in stable angina than MI but significantly higher in stable angina than post MI . Moreover, MMP-9 level in MI group was significantly higher than post MI. We found significant differences in stable angina, MI and post MI groups compared to control subjects. MMP-9 levels were significantly higher in both stable angina and MI compared to control group in post MI, MMP-9 level was insignificantly higher than control subjects. MMP-9 is believed to increase the cardiac damage in stable angina and participates in MI development since it enhances ROS production, increases cytokines release and thinning the fibrous cap walls thus enhancing plaque rupture [27].Furthermore, subjects with stable angina has high LDL levels which upregulate MMP-9 expression and production [28]. This explains why MMP- 9 levels was higher in stable angina than MI group in our study. In a study by Chen [26], MMP-9 was detected in the first two hours after MI in the infracted area and after four days in the remote area (non-infracted area). Its level was higher in the infracted region than the remote one [26].

Many studies showed that MMP-9 is significantly related to atherosclerosis progression [21].In a study by Loftus [29], its level was higher in MI than stable angina [29].It was found that absence of MMP-9 in post MI facilitated angiogenesis in left ventricle (LV) which highlighted MMP-9 role in breaking down components required for angiogenesis [30]. Angiogenesis is a part of healing process in post MI stage and this is considered as a protection from any further cellular damage and facilitates entrance of bioactive molecules to the injured area to prevent ischemia [31-32]. This explains the detected drop in MMP-9 level in post MI group in our study. Existence of MMP-9 with high levels in post MI was proved to facilitate the recovery process in mice [33]. It was demonstrated that foam cells are the source of MMP-9. Moreover, foam cells amount is correlated with the amount of MMPs and with fibrous cap thinning [34].

MMP-9 expression was increased by two-fold in monocyte derived macrophages which were isolated from MI patients [35]. Indeed, our results support that MMP-9 level is higher in both stable angina and MI groups than in post and control groups. MMP-9 is produced by many cells including fibroblasts, neutrophils, macrophages, monocytes and macrophages/monocytes-derived foam cells. Neutrophils produce MMPs and proteases which in turn activate MMP- 9 [36]. During shear stress, fibroblasts, by the action of cytokines, produces MMP-9 which acts upon collagen decreasing its amount [37]. Certainly, MMP-9 by its role in decreasing collagen layer of the fibrous cap will enhances plaque instability and rupture [38]. Recent studies demonstrated MMP-9 dual role as pro/anti- inflammatory agent before and after MI. In studies by Jong GP in 2006 and in 2012, the level of MMP-9 was detected as soon as the MI developed [34]. We noticed that MMP-9 elevation was positively correlated with Troponin-T level in both MI and post MI.

Indeed, many studies proved the correlation between MMP-9 and Troponin-T levels in MI patients [39]. Similarly, MMP- 9 elevation was positively correlated with CK-MB level in both MI and post MI. In stable angina group, although MMP-9 reached the highest level than other groups, Our findings indicated that MMP-9 can

be used with Troponin-T, CK and CK-MB as confirmatory marker for MI and post MI stagesand can be used as an indicator for the risk of stable angina.

5. CONCLUSION

From the present study we have concluded MMP-9 can be considered as a good marker for confirming the diagnosis of MI and post MI stage as it showed significant elevation in its level in MI and then decrease in post-MI, while both COX-2 and MMP-2 cannot be used as markers for diagnosis of stable angina or MI. Moreover, slightly higher levels of Troponin-T, CK, and CK-MB could be indicators that the patient may be in stable angina, and treatment intervention is required to prevent atherogenesis progress and subsequent complications.. Further studies are needed to confirm our findings regarding the use of estimation of MMP-9 levels along with Troponin-T and CK-MB as markers in MI and post MI stage in case that there will be another method to measure MMP-9 in serum other than ELISA.

6. LIMITATION

The size of patients' groups was small and this is because of difficulty in selecting and obtaining blood samples from the subjects according to exclusion criteria and patients especially post MI group. MMP-9 estimation in serum by ELISA is time consuming and its cost is more than chemiluminescence method used with Troponin-T.

CONSENT

As per international standard or university standard, patient's written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

This protocol was approved by the unit of Biomedical Ethics-Research committee (Reference No.1154–13), Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia.

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This research was approved by registration and national committee of bio and med. Ethics with reference number (1154-13).We would like to thanks Prof. Nabil Al-A'ama for his assistant by facilitating subjects' selection from his cardiac clinic.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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