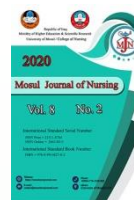




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Evaluating The Activity Of Paraoxonase 1 In Myocardial Infarction

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Abstract

Background and objective: Little is known about paraoxonase1 (PON1) activity and its relation to Coronary Artery Disease (CAD). This study aimed to assess the association of serum PON1 activity with myocardial infarction and to found out its possible relationship with serum High density lipoprotein (HDL-C) in patients with MI. This study had also examined age, gender, lipid profile and evaluate of PON1 activity by changing the parameters as a risk factor.

Methods: This case-control study was carried out at the College of Medicine-Hawler Medical University, from 18th February 2019 to 18th September 2020. Blood specimens were obtained from MI patients in Hawler Cardiac center. A total number of 176 participants were enrolled in this study grouped into 120 patients with MI (36 females and 84 males) diagnosed by consultants and 56 subjects healthy controls (30 females and 26 males). Measurements of serum (PON1, Troponin and lipid profile) were determined in both MI patients and control group. Statistically SPSS version package 20 is used.

Results: The results revealed significant decrease in serum PON1 activity in patients with MI (3.07 ± 0.18 ng/ml) comparing with controls serum PON1 activity (4.79 ± 0.27 ng/ml) ($P < 0.01$). The levels of serum Total cholesterol, Triglycerides, LDL-C and Troponin in patients with MI were significantly higher ($P < 0.01$) when compared to controls. According to gender it was 36(30%) in females, in males 84(70%).

Conclusion: The study concluded that patients with MI had low serum PON1 activity.

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Key words: PON1, MI, lipid profile, Troponin I.

Introduction

The reduction of serum arylesterase and paraoxonase activities in humans, which are measures of paraoxonase-1 [PON-1] function, have been associated with higher risk of atherosclerosis and systemic oxidative stress. The measurement of distinct PON-1 activities has not been utilized in clinical prognostic. Moreover, genetic determinatives of PON-1 activities remain unknown (Tang et al., 2012). Based on its key function in lipoprotein catabolism pathways, human paraoxonase 1 (PON1), which is a calcium-dependent lipoprotein with high-density associated with ester hydrolase, has been increasingly regarded as an effective factor in coronary heart disease (CHD) (Wang et al., 2012).

Coronary Artery Disease (CAD) is the main cause of morbidity and mortality all over the world. Serum paraoxonase which has antiatherogenic features is a lipoprotein (HDL)-bound enzyme with high density. Oxidative stress contributes a major role in atherosclerotic process (Saxena et al., 2011).

Atherosclerotic CAD contains a wide range of clinical entities including asymptomatic subclinical atherosclerosis along with its clinical complications, such as myocardial infarction (MI), angina pectoris, and sudden cardiac death. CAD is the major cause of mortality among industrialized societies. The heterogeneity of

clinical CAD in one hand, and the underlying multi-decade complex pathophysiological processes with genetic and environmental interactions, in the other hand, makes it difficult and costly to understand the genetic architecture of CAD and MI (Dai et al., 2016).

The paraoxonase (PON) 1 located on the high-density lipoprotein (HDL) is the main cause of its antioxidant activity. Moreover, trial studies have shown the protecting potential of PON1 against atherogenesis. The HDL has longer effects on reduction of low-density lipoprotein (LDL) lipid peroxidation compared to antioxidant vitamins, thus, could be more protective. Recently, a number of important progresses have occurred in the context of PON research (Mackness et al., 2004). For example, our understanding of basic biochemical function of PON1 and the possible modulators of its activity has considerably improved. Low activity of serum PON1 is clearly associated with coronary heart disease (CHD). However, the evaluation of the relationships between low serum PON1 and CHD has shown that the activity of low serum PON1 activity could be an autonomous predictor of new CHD cases (Kim et al., 2013).

According to a meta-analysis, PON1 polymorphisms which are highly active in lipid peroxide hydrolysis are associated with decreased CHD risk. This likely underestimates the real contribution of PON1 in CHD, since

these polymorphisms accounts for a small portion of the PON1 activity variations. However, they are important due to the fact that genetic influences are not confounded by other factors connected to both the CHD and diminished PON1 activity (Luo et al., 2018).

Free radicals of oxygen have been increasingly used to describe injuries in ischemic heart. The relation of high serum uric acid concentration with raised cardiovascular risk have been identified, nevertheless its effect on acute myocardial infarction (MI) remains unclear. Some recent study attempted to find the role of zinc in oxidative stress and tissue injuries. Increased oxidative stress is associated with glutathione peroxidase, superoxide dismutase levels, raised MDA and decreased zinc. Thus, MI changes according to oxidative stress, irrespective of gender (Madole et al., 2015).

When there is no insulin, regular physical activity facilitates the glucose entrance into the cell through influencing several signaling pathways. Also, regular exercise results in improvement of lipid profile and increased PON-1 activity. The interaction of PON-1 with High-density lipoprotein (HDL) in the presence of calcium results in prohibition of low-density lipoprotein (LDL) oxidation, hydrolyzation of free radicals, inhibition of hemoglobin glycation and maintenance of homocysteine structure in the blood. Additionally, decreased PON-1 activity is positively related to the risk of cardiovascular diseases, dyslipidemia, gastric

cancer, renal failure, insulin resistance, and Alzheimer's disease (Fatolahi et al., 2017).

The present study aims to illustrate the current contradiction between PON1 activity and CHD susceptibility. Moreover, the arylesterase activities, paraoxonase1 and other parameters associated with oxidative stress are investigated in patients with myocardial infarction.

Methodology

The subject of our study were grouped into two categories :

- A. MI patients (Group I): A case-control study conducted on hundred and twenty patients with myocardial infarction(MI), who attended to Hawler Cardiac center who were diagnosed with MI.
- B. Healthy controls (Group II): Fifty six selected subjects served as control, all were healthy volunteers and had no evidence for any blood diseases.

The present study which included data collections, examination of patients and performance of the laboratory investigation biochemical analysis was carried out from 18 February 2019 to 24 September 2020, by collaboration between Aryo laborating, Hawler cardiac center and research medical center.

A total of 176 blood samples were collected from 120 MI patients and 56 healthy controles. Blood samples were collected from patients and controls. The collected samples were centrifuged

at (3500 rpm) for 10 minutes at RT. The separated serum was used for measurements of lipid profile (S.T.cholesterol, S.HDL, S.LDL and S.TG), serum troponin and serum paraoxonase1(PON1).

Data Analysis

Statistical analysis of the results was performed using SPSS (Statistical Package for Social Sciences) version 20 software. Results were expressed as Mean±SE. Differences between (MI) patients and controls were assessed using independent T-test. Statistical significance level was informed at a two-tailed (P value≤0.05).

Results

The results presented in this study were based on analysis of two study groups, 120 MI patients which include 36 females (30%) and 84 males (70%). The age range was 19 to 76 years, and 56

control group included 30 females (53.6%) and 26 males (46.4%). The minimum age was 19 years while the maximum age was 76 years (table 1). The mean age of females and males in MI patients were (57.44±1.81) years and (56.03±1.18) years respectively. Over all ages of both sexes enrolled in MI patients were (56.45±0.98) years. The mean age of females and males in control groups were (37.86±0.98) years, (36.38±1.18) years and (37.17±0.76) years for both females and males subject. The mean BMI of female, male and both female and male in MI patients were (29.14±0.53), (28.75±0.44) and (28.87±0.35) respectively. Whereas the mean BMI of control study were (26.64±0.39, 25.7±0.5 and 26.20±0.31) respectively in female, male and both sexes (Table 1).

Table 1: Comparing the relative frequency of age and gender between patients with MI and control groups

Group	Gender	No. of subjects	Age (years)	BMI (kg/m ²)	%
			Mean±SE	Mean±SE	
Patients with MI	Female	36	57.44±1.81	29.14±0.53	30
	Male	84	56.03±1.18	28.75±0.44	70
	Both	120	56.45±0.98	28.87±0.35	100
Control	Female	30	37.86±0.98	26.64±0.39	53.6
	Male	26	36.38±1.18	25.7±0.5	46.4
	Both	56	37.17±0.76	26.20±0.31	100

Lipid profile results in control and MI patients

The lipid profile results of the comparison between patients with MI and controls are expressed in mean $\pm$ SE as shown in (Table 2).

Serum Cholesterol

The result of the serum cholesterol are presented in table 2. The Mean $\pm$ SE value for serum cholesterol were (149.01 $\pm$ 3.71 mg/dl) and (171.75 $\pm$ 4.46 mg/dl) in control subjects and MI patients respectively. The data analysis indicated a statistically significant increase ($P<0.01$) in mean concentration of cholesterol in serum of patients with MI in comparison with control healthy subjects.

Serum TG

The Mean $\pm$ SE values for TGs were (117.82 $\pm$ 3.91 mg/dl) and (185.4 $\pm$ 10.44 mg/dl) in control healthy subjects (group 1) and MI patients (group 2) respectively. In comparison between healthy individuals and MI patient, a statistical significant differences ($P,0.01$) in serum TGs was observed as shown in (Table 2).

Serum HDL

The results of serum HDL are shown in table 2. The Mean $\pm$ SE value of serum HDL were

(44.25 $\pm$ 1.88 mg/dl) and (39.1 $\pm$ 0.85 mg/dl) in control group and MI patients respectively. A statistical significant decrease ($P<0.05$) level of serum HDL was observed in MI patients in comparison with control group.

Serum LDL

The Mean $\pm$ SE values of serum LDL-C were (73.67 $\pm$ 2.61 mg/dl) and (96.45 $\pm$ 3.55 mg/dl) in control groups and MI patient groups respectively. The result of the existing study clearly showed a statistically significant increase in the level of serum LDL-C in comparison between control groups and MI patient groups (Table 2).

Serum VLDL

The data obtained indicate that the Mean $\pm$ SE for serum VLDL-C were (23.56 $\pm$ 0.78 mg/dl) and (37.08 $\pm$ 2.08 mg/dl) in control subjects and MI patients respectively. In the present study, the results indicate statistical significant differences ($P<0.01$) in serum VLDL-C between both groups (Table 2).

Table 2: The changes in serum lipid profile parameters in control and MI patients

Biochemical parameters (mg/dl)	Control			MI			Statistical evaluation P value
	No.	Mean±SE	Range	No.	Mean±SE	Range	
T. Cholesterol	56	149.01±3.71	101-200	120	171.75±4.46	78-283	P<0.01
TG-C	56	117.82±3.91	48-159	120	185.4±10.44	45-838	P<0.01
HDL-C	56	44.25±1.88	30-79	120	39.1±0.85	20-71	P<0.05
LDL-C	56	73.67±2.61	42-121	120	96.45±3.55	25-173	P<0.01
VLDL-C	56	23.56±0.78	9.6-31.8	120	37.08±2.08	9-167.6	P<0.01

Serum PON1

The Mean±SE values for serum PON 1 level were (4.79±0.27 ng/ml) and (3.07±0.18 ng/ml) in control subjects and MI patients respectively.

The mean concentration of serum control PON 1

level was significantly lower than in MI patients (P<0.01) when compared to the control people (Table 3).

Table 3: Comparison of paraoxonase 1 in control and MI patients

Antioxidant parameter s ng/ml	Control			MI			Statistical evaluation P value
	No.	Mean±SE	Range	No.	Mean±SE	Range	
Paraoxonase 1	56	4.79±0.27	1.26-9.20	120	3.07±0.18	0.13-7.82	P<0.01

Troponin (cardiac biomarker)

Table 4 shows as the Mean±SE values of serum Troponin level were (2.81±0.16 ng/ml) in control subjects, in comparison to (1139.61±190.33 ng/ml) in MI patients. A

statistical significant increase (P<0.01) level of serum Troponin was observed in MI patients when compared to control group.

Table 4: Comparison of Troponin as cardiac enzyme between control and MI patients

Cardiac enzyme ng/ml	Control			MI			Statistical evaluation P value
	No.	Mean±SE	Range	No.	Mean±SE	Range	
Troponin	56	2.81±0.16	2-5.99	120	1139.61±190.33	3.76-9100	P<0.01

Discussion

Accurate detection of MI needs an inter-professional healthcare team consisting of professionals including physicians, nurses, and laboratory technologists. In this regard, different

clinical examinations should be introduced properly. The results of the present study showed that over two-thirds of the patients with MI were men. In line with this finding, Yang et

al reported that MI incidence is higher in men than in women; however, some risk factors are more highly accompanied by with MI in women compared to men. With an increase in age, the association between sex and MI was more limited; however, women still had higher risks of developing MI (Yang et al., 2012).

In addition, the female participants had higher mean age and BMI than the men. Similar results were reported by Yang et al who showed that the females were older than the males, which indicates healthy life pattern and the rather normal coronary artery in females than in males of the same age (Yang et al., 2012). Decreased hospitalization due to MI and patient ages shows improvement in treating coronary artery disease during this period. On the contrary, Yeh et al indicated that the age of MI was similar within the 10-year period (Yeh et al., 2010).

The present study indicated that the serum PON1 level in MI group was lower in comparison with the control group. In this regard, the results by Sökmen et al showed that PON1 concentration and activity are lower in subjects with significant coronary artery disease. They also indicated that PON1 concentration and activity are significantly associated with coronary artery disease assessed by quantitative coronary angiography (Sökmen et al., 2019). Moreover, in their study, Ibanez et al showed that PON1 polymorphisms are independent risk factors for MI patients (Ibanez et al., 2018). This

supports the idea that PON1 associated with HDL-C.

In the present study, the analysis of serum Troponin I in myocardial infarction patients was found to be significantly higher in comparison with the control group. In line with the results of the present study, Park et al indicated that elevated serum concentrations of cardiac Troponin I causes myocardial damage; however, this is not necessarily equals to myocardial infarction. As they reported, it remains for the clinician to distinguish whether an increased cardiac Troponin I concentration is the result of coronary plaque rupture/occlusion or whether it has another cause (Park et al., 2017). However, an increased cardiac Troponin I alone will never cause a clinical diagnosis, although this fact cannot be ignored that cardiac Troponin I measurements have been a precious step forward in identifying high-risk patients with acute coronary syndromes (Baker et al., 2011). It is essential to diagnose acute MI quickly because improved long-term outcomes of heart function can be obtained if the time between symptom onset and reperfusion therapy is appropriately short (Zughaft & Harnek, 2014).

The findings of the present study showed that serum cholesterol level in MI groups was higher in comparison with the control group, which indicates that the occurrence of myocardial infarction is highly associated with the mean concentration of cholesterol. This result was in agreement with those of the study conducted by

Guerin et al who referred to serum cholesterol as an independent risk factor for acute myocardial infarction. They stated that this association is linear, with no threshold level (Guerin et al., 2018). In addition, there is a multiplicative relation between cholesterol and other major risk factors on the relative risk of myocardial infarction. Furthermore, inflammation, insulin resistance, and high serum cholesterol levels are associated with decreased serum paraoxonase 1 activity (Kowalska et al., 2015).

The mean value for TG in MI patients was higher than the control group. Similarly, the results of the study by Soeiro Ade et al revealed that the risk of major cardiovascular events significantly increased in patients with a TG level ≥ 170 mg/dl (Soeiro et al., 2015). This suggests that high TG level is a risk factor for MI, and the higher the TG level is, the greater the risk of MI. Also, serum HDL level among MI patients was lower in comparison with the control group showed in (table 5.2). In this regard, previous studies have shown that the level of serum HDL-C is significantly associated with occurrence of MI. In their study, Ramirez and Hu observed that HDL-C decreased in many patients with acute MI. They also analyzed its role in raised CAD mildly. A brief analysis of its sub-particles indicated that increasing total concentration may not be sufficient to protect MI. However, blood levels of HDL-C < 40 mg/dl might be an influential warning sign for atherosclerotic development. As a result, they suggested that statin treatment should be

employed to prevent increased CAD and MI in such patients (Ramirez & Hu, 2015).

In addition, the level of serum LDL-C in the MI patients was higher in comparison with the control group. However, some studies have revealed inverse associations of LDL-C after MI with all-cause mortality (Cho et al., 2010; Reddy et al., 2015). Moreover, the results of the study by Pokharel et al indicated that the incidence rate was higher in patients with LDL-C < 100 mg/dl than the overall population (Pokharel et al., 2017). In addition, an analysis conducted by Martin et al demonstrated that the dense form of very-low-density lipoprotein cholesterol and higher levels of remnant lipoprotein cholesterol levels as defined by intermediate-density lipoprotein cholesterol in patients with MI were associated with decreased all-cause mortality at 2 years (Martin et al., 2015). The results of the present study demonstrated that there is a significant difference between the MI and control groups in terms of their serum VLDL-C, such that the level of VLDL-C in MI groups was higher in comparison with the control group. This result is in agreement with the results reported by Holmes et al who demonstrated that the cholesterol level in VLDL is positively associated with increased risk of MI (Holmes et al., 2018).

Conclusion

Low serum levels of PON1 were markedly prevalent among patients with MI. The PON1 function is sensitive to oxidative stress and the

physiological function of PON1 seems to degrade oxidized phospholipid in lipoproteins and cell membranes.

The mean serum concentration of SOD, MDA, T. Ch, T. Gs, LDL-C, VLDL-C and Troponin I were significantly higher in patients with MI ($P<0.01$) when compared to control groups. The result of these biomarkers showed reasonable validity for suspected patients with MI.

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