ISSN Print: 2664-6781
ISSN Online: 2664-679X
Impact Factor: RJIF 5.32
IJACR 2024; 6(1): 15-22
www.chemistryjournals.net
Received: 19-11-2023
Accepted: 24-12-2023

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Study the effectiveness of paraoxonase-1 and creatine kinase enzymes in acute myocardial infarction patients

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DOI: https://doi.org/10.33545/26646781.2024.v6.i1a.163

Abstract
Myocardial infarction (MI) is a medical emergency, life-threatening, time-sensitive and non-infectious that occurs due to ischemia or stoppage of perfusion caused by pathological changes or abnormalities in the walls of coronary arteries which the coronary arteries cannot supply to part to the heart for long periods, causing damage to the heart tissue and its possible death. The aim of the present study was to the measure concentration of paraoxonase-1 (PON1) enzyme and creatine kinase (CKMB) enzyme in patients with acute myocardial infarction (AMI), acute myocardial infarction with diabetes mellitus (AMI+DM)) and controls, as well identify the association between the parameters that were measured and the increased risk of cardiovascular (CV) risk of MI patients. This study that was done during two months, in Iraq which enrolled 100 sample for persons who met the participation criteria from patients and controls. The statistical evaluation was achieved with the aid of a statistical package for social sciences (SPSS). Where this study found PON1 level raised in the total of patients significantly at (P = 0.001), CKMB concentration increased highly significant in the serum total of patients (P = 0.0003), when compared between patients and healthy and according to T-Test analysis. The conclusion of this study is increased concentration of PON1 and CKMB with statistical differences significant appeared in AMI and (AMI + DM) patients compared to the control group. Correlation analysis revealed no statistically significant correlation between concentrations of the PON1 and CKMB (r = -0.140, P = 0.258).

Keywords: Paraoxonase-1 (PON1), creatine kinase (CKMB), acute myocardial infarction (AMI), (Acute myocardial infarction with diabetes mellitus) (AMI+DM)

Introduction
Heart diseases (HDs) are difficult to recognize due to risk factors such as DM, hypertension (HTN), total Cholesterol (TC), abnormal pulse rate and others. Therefore, HDs must be dealt with carefully, because their nature is complex and it is predicted based on symptoms [1]. Heart consists of three coronary arteries [2], the coronary arteries main (left and right) that branch into smaller arteries [3]. The left coronary artery divides into the left anterior descending artery, which is the largest coronary artery [4]. coronary heart disease (CHD), It is one of the most common heart diseases it is the result of atherosclerosis (AS) changes in the vessels supplying the heart and describes a range of clinical disorders from asymptomatic AS and stable angina pectoris to acute coronary syndrome(ACS) that is classified as elevated MI (STEMI) and non-elevated MI (NSTEMI) and unstable angina pectoris [5] and sudden coronary death(SCD) [6], It is one of the most dangerous results of coronary Artery [5], arrhythmia and heart failure(HF) [7]. CHD is characterized by a complete violation of the heart's blood supply, because of a damage [8] or narrowing coronary arteries [7] and it's the largest cause of death, disease and disability. Rarely a single aetiology is found in the majority of elderly affected [9]. The AS or thromboembolism for left anterior descending artery cause MI involving large areas of the anterior, septal, and apical portions of the heart [4]. Studies have reported that arterial blockage is accompanied by blood vessels inflammation. Once the blood vessel wall is damaged, immune cells collect at the site of infection and produce pro-inflammatory cytokines that activate circulating white blood cells that will engage more immune cells that cause fat accumulation and gradually blockage of the artery, because these areas are smooth for the development of clots, which It clogs the important arteries of the heart, causing MI or stroke [10]. It has been proven that many chemotherapy agents cause CHD, and CV complications during chemotherapy, and

radiotherapy became an increasing problem [11] also, it was found that kounis syndrome is an allergic reaction or hypersensitivity leads to coronary spasm and ACS [12].

Acute Myocardial Infarction

The MI is a medical emergency[13] life-threatening, time-sensitive [14], and non-infectious that occurs due to ischemia or stoppage of perfusion caused by pathological changes or abnormalities in the walls of coronary arteries [15] which the coronary arteries cannot supply to part of the heart for long periods, causing damage to the heart tissue and its possible death [13]. Sudden occlusion occurs due to AS plaque [16] causing reduced force of heart contraction. If the thrombus ruptures before complete necrosis for the distal tissue will occur MI [15]. Approximately 90% of the consequences of MI caused by a acute clot that prevents atherosclerosis of the coronary arteries [17] the heart muscle becomes inflamed and necrotic at the point of blockage, you will the damaged area rapidly loses its ability to contract and conduct electrical impulses and depletes the supply of O_2 this damage is irreversible and the area of necrosis is eventually replaced by fibrous scar tissue [16]. MI is clinically defined as myocardial injury detected by cardiac biomarkers with evidence of acute cardiac ischemia as changes in the electrocardiogram (ECG) such as the appearance of pathological Q waves [18]. Complete obstruction of coronary artery is the main mechanism of MI [8]. MI causes cardiac remodeling, which are changes in heart size, shape, and function, it is a group of pathophysiological changes including electrophysiological changes, ventricular dilatation, myocyte hypertrophy, and interstitial fibrosis [19]. Most information on prevention, diagnosis, and treatment is still based on studies conducted predominantly in males, although predictive risk factors differ between the sexes [20]. The five common symptoms for MI, are chest pain or discomfort, shortness of breath, pain or discomfort in the arms or shoulders, feeling weak, dizzy or faint, and jaw, neck, or back pain [21]. MI can occur in menopause, family history of (HTN and DM) has a significant contribution, where smoking, obesity and dyslipidemia are modifiable factors, non-modifiable factors are age, sex, genetics [15], age for males over 40, females over 50 years of age, excessive alcohol consumption, high TC, chronic high stress, previous MI and arrhythmia [22]. Diagnosis and treatment of patients depends on the precise classification of the infarction [14] and AMI is divided into modes with respect to period, treatment, and prognosis [20]. ACS is characterized by a sudden decrease in cardiac blood flow and can be diagnosed and categorized into STEMI and NSTEMI based on ECG [23] and generally infarcts are classified on the basis of microscopic size or location (anterior, lateral, inferior, etc.), in the pathological context, an acute, curable or healed infarction should be used [14]. The fourth global definition of disease of MI emphasized the difference between AMI and cardiac injury, where divided MI into five types [23]. The incidence of AMI in the age group (40-60) year is (8) times higher than in persons of younger age [24]. Percutaneous coronary intervention (PCI) is a strategy preferred reperfusion for STEMI patients. The 2013 STEMI guidelines recommend that hospitals capable of performing PCI treat patients within (90 minute) of contact with the medical system [25].

Diabetes Mellitus

The diabetes mellitus (DM) is classified into three types according to etiology and clinical presentation diabetes mellitus type (1 and 2) (DMT1), (DMT2), gestational diabetes, and subtypes are monogenetic and secondary DM [26], because of the ambiguities that arose after the discovery of subtypes, for that the classification included new names, which are DM type 1, 2 and 3 [27]. DM is a chronic metabolic disorder [26] involve either a disturbance in insulin secretion, or action, or both [27], It is a multifactorial disease that includes hyperglycemia and insulin resistance [28]. which can lead to direct and indirect effects on large and minute blood vessels [29], complications of large blood vessels lead to (2-4) times the risk of cardiovascular disease (CVD) [26]. The risk factors are advanced age, duration of DM, insulin use, CHD, elevated serum creatinine [30], poor glucose control, smoking, HTN, dyslipidemia and CVD [29]. The risk of CVD in patients with DM is increased due to the association between insufficient insulin action and the various mechanisms of AS that occur in DM. The mechanism that increases CV damage in DM is oxidative stress. Chronic hyperglycemia leads to endothelial or mitochondrial dysfunction, metabolic disturbances, and damage to the extracellular matrix causes a functional deterioration of the heart called cardiopathy [28]. In DM a whole cascade of pathological interactions appears in the endothelium of blood vessels caused by glucose toxicity, excessive action of to stimulate HTN, thrombotic activators and the intensification of oxidative stress leading to endothelial dysfunction (ED), The damaged endothelium itself causes DM and inflammatory factors [31]. The anatomical substrate of inflammation in DM is the endothelium of blood vessels. The deficiency of the enzyme lipoprotein lipase enhances the production of very low density lipoprotein cholesterol (VLDLs) enriched with cholesterol esters, LDL enriched in triglycerides (TGs) and increases small dense Low Density Lipoprotein cholesterol) (sdLDL-c) and reactive oxygen species(ROS).The overproduction of ROS eventually leads to a severe decrease in the bioavailability of nitric oxide(NO), especially in endothelial cells. Oxidation of high Density Lipoproteins (HDLs) by ROS reduces their anti-inflammatory capacity and reverse cholesterol transporter (RCT). Insulin causes increased blood flow and glucose availability in skeletal muscle and additional vasodilation, depending on NO. Hyperinsulinemia can promote cardiac hypertrophy and a significant increase in left ventricular mass with an anti proteolytic effect on the heart [32]. It was observed that the presence of DM doubles the risk of CVD in men and triples it (3) times in women [33]. The risk of developing MI among DM patients is equivalent to that of normal people with a previous history of MI [34]. In 2017, DM was estimated to affect 452 million patients worldwide, a number that is expected to rise to 693 million by 2045 [35].

Paraoxonase-1

Paraoxonases are a family of three specific enzymes: PON1, PON2 and PON3. PON1 is the most studied among them and is not necessarily the most important, that PON2 is the oldest of them, from which it arose PON3 and then PON1 [36]. PON a polygenic family of lipolactonases, their genes are located next to each other on human chromosome 7 [37] and their protein structure is similar, the name paraoxonase is due to the its ability to hydrolyze the compound (diethyl p-nitrophenyl phosphate), which is a metabolite from oxon, parathion organophosphate. PON1 is a Ca-dependent glycoprotein with a molecular weight of (43KDa) and composed of (355 amino acid) and has a structure consisting

of six helical sheets with a central tunnel containing two Ca^{2+} to (7.4Å) apart. The ion in the bottom of the tunnel is structural and gives a conformational stability. The ion present in the cavity of the active site has a catalytic function by locating the substrate and activating the ester bonds for substrate the helixes 1(H1), 2(H2) participate in the PON1-HDL reaction, loop 1(L1) is the cap of the active site and the extended helix 3(H3) called loop 2(L2) participates in substrate recognition [38]. The PON1 genes contain many polymorphisms in the gene coding region [39]. Its enzymatic activity depends on the substrate varies with different backgrounds [40]. CHD has been shown to be closely related to a wide range of genetic variants. One of the major biomarkers of AS is the PON1 gene [41]. PON1 is synthesized in the liver and binds to HDL-c before it is released into the blood, and smaller amounts are made by the kidneys and colon, where a small amount binds to VLDL-c and postprandial chylomicrons [38] and it is found to a lesser extent in LDLs. PON1 possesses three enzymatic activities: lactonase, arylsterase, and paraoxonase. PON1 polymorphisms play an important role in drug metabolism and prevention of CVD and neuro-degeneration [36]. PON1 is plays a role in the regulation of RCT ,anti (oxidation, inflammation, urination, coagulation, DM, microbes and AS) and vasodilation [42]. PON1 hydrolytic enzyme [39] because PON1 and (PONAryl) are believed to have the ability to degrade organophosphates and aromatic carboxylic esters and protects HDL-c and LDL-c from H_2O_2 and its antioxidant effects as it slows down the oxidation of LDL-c [43] through the hydrolysis for fatty acids oxidized, phospholipids, TC and hydroperoxides triglycerides [38]. The arylsterase activity of PON1 is involved in the detoxification of lipid peroxides that is associated with endothelial dysfunction of blood vessels and CHD [40]. In DM may occur complications in CV due to inhibition and disturbance of stability of PON1, PON1 may be affected by binding to HDL-c resulting in decreased efficiency in its antioxidant and H_2O_2 properties [38].

Creatine Kinase isoenzymes MB

The creatine kinase(CK) a two-dimensional enzyme [44] has a critical effect on the transfer of energy from mitochondria to sites of use adenosine triphosphate(ATP) in the brain, skeletal muscles, and heart. In cardiac cells, it is expressed as three identical enzymes: creatine kinases type M and B, and sarcomeric mitochondrial creatine kinase.

$$\text{Creatine} + \text{ATP} \leftrightarrow \text{Phosphocreatine} + \text{ADP} + H^+$$

In patients with MI, ATP and phosphocreatine levels are rapidly depleted resulting in tissue damage and increased CK-MB levels [45]. In stimulated tissues, CK conjugates to ATP-consuming enzymes and performs reverse transmission of the phosphoryl group (P) between phosphocreatine and adenosine diphosphate (ADP) in the presence of Mg ,the CK is also able to act as a cellular metabolic balancer by reducing the rise in intracellular ADP and H^+ which prevents ADP-induced ATPase inactivation and acidification of cells [46]. Myocardial death due to MI leads to the release of many molecules such as CK into the blood. Since CK-MB is the isoform found in cardiac, it is the most specific and accurate for detecting MI among the three isoforms [47], its elevation is relatively specific to myocardial injury especially in patients with ischemic symptoms when skeletal muscle damage is not present, elevated CK-MB can be due to non-cardiogenic causes such as hypothermia [48]. CK-MB is the first visceral biomarker of heart damage identified in 1979 [49] when released into the blood, CK-MB can be divided into two groups, MB1 and MB2, and when AMI occurs, MB2 passes into the blood with a significant change in the (MB2:MB1) ratio. Considered as the (MB2:MB1) ratio ≥1.5 is an indicator of AMI [44]. The sensitivity level of CK-MB in the diagnosis of MI is about 90% [50]. The relative index (CK-MB/total CK × 100) can be used to diagnose MI , if this indicator is 2.5% or higher, then CK-MB has a great potential to launch from the heart. Total levels of CK and CK-MB correlate with infarct size, and CK-MB cannot detect minor damage to the heart [44]. Some studies have shown that asphyxiated newborns have significantly higher CK-MB values than healthy infants in the first 24 hours of life [46]. CK-MB is found in small amounts in skeletal muscle and may be elevated during physical exercise or in certain diseases [51]. CK-MB is not relatively sensitive to detecting small MI and cannot be used for late diagnosis of AMI but can be used to suggest infarct extension if levels rise again after declining [52].

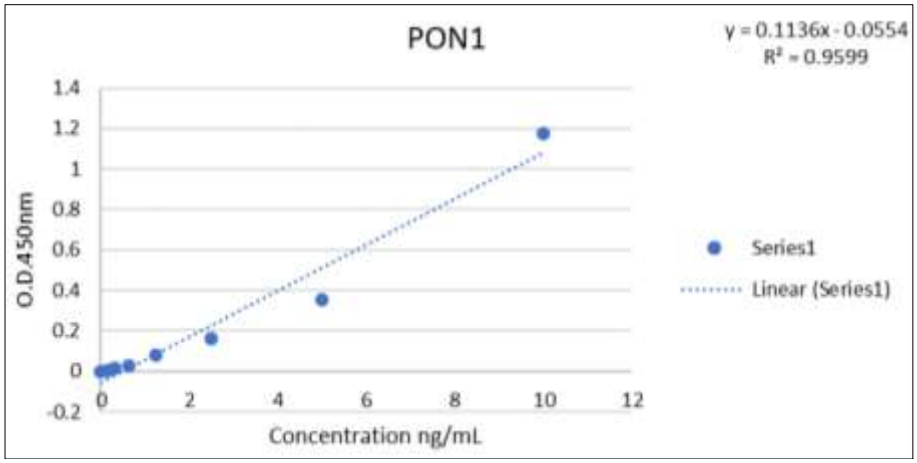
2. Materials and Methods

2.1.Collection and preservation of research samples

Individual information was collected on a questionnaire after obtaining official approval, venous blood samples were drawn blood samples (100 samples) were collected, that included of male sex only from the ages of (40-80) years of smokers and nonsmokers, which included (34) samples for AMI patients, (33) samples for (AMI + DM) patients and (33) samples for healthy people. Patient samples were collected in the period two months in the Internal Resuscitation Division after they were diagnosed by specialized doctors, of those who did not exceed their stagnation a full day of Kirkuk Governorate hospitals/Iraq. AMI patients who underwent drug therapy or coronary artery bypass grafting were excluded. After separating the blood sample and obtaining the serum, it was frozen at a temperature of (-20 ℃) until the variables were measured.

2.2.a. Determination Level of Paraoxonase-1 in Blood Serum

Using Human PON1 (serum paraoxonase/arylesterase 1) enzyme linked immunosorbent assay (ELISA) kit supplied by the korean company (LABISKOMA). The device has been used absorbance microplate reader-ELX800TM – BioTekTM and the automated microplate strip washer-ELX50-BioTek. Absorbance was read at 450nm, and then, the concentration of PON1 was calculated.



Graph 1: Standard titration curve for an enzyme PON1

2.2.b. Determination Level of CK-MB in Blood Serum

The diagnostic kit was used to measure the CKMB enzyme prepared by the chinese company (Shijiazhuang Hipro Biotechnology Co.,ltd).This product is used to determine the activity of creatine kinase (isoenzyme MB) in human serum, it is mainly used for the adjuvant diagnosis of MI, muscular dystrophy and other diseases.

2.3. Statistical Analysis

A statistical analysis program known as the SPSS was used (Tow-Sample T-test or independent samples T-test) by comparing the group patients of AMI and (AMI+DM), both of them separately, with a healthy group, for the extraction the mean, standard deviation (SD), probability level P-value, and correlation analysis.

3. Results

Table 1: Shows the numbers and percentages of infected and healthy people

Patients		AMI		AMI+DM		Control	
No.	%	No.	%	No.	%	No.	%
67	67	34	50.746	33	49.2537	33	33

Table 2: The level of PON1 and CK-MB in the serum of the groups under study

Parameters	P-value		Mean±SD	
	AMI n=34	AMI+DM n=33	Total Patients n=67	Control n=33
PON1	(10.22±1.50)** 0.0002	(9.45±1.70)* 0.038	(9.84±1.63)** 0.001	8.53±1.82
CK-MB	(70.5±14.4)** 0.0003	(50.6±13.1)** 0.0003	(60.7±9.8)** 0.0003	20.5±1.22
**High statistical differences($p \leq 0.01$) *Normal statistical differences($p \leq 0.05$)				

As shown in the table above and Figures (1) and (2), it was found that the level of concentration of PON1 by unit (ng/mL) using the mean standard deviation rises in AMI patients with higher statistical differences appear at the level of probability (P=0.0002) ¸ also rises in (AMI + DM) patients with normal statistical differences appear at (P = 0.038), and it rises in the total of patients significantly higher at (P = 0.001) when compared to the healthy control. CK-MB concentration in units (U/L), using the mean standard deviation. It rises in the sera of both AMI, (AMI + DM) patients and total patients and shows high statistical differences at the level of probability (P = 0.0003) compared to the control group. A negative correlation between the concentration of each (PON1 and CKMB) has no statistical significance (r = -0.140, P = 0.258).

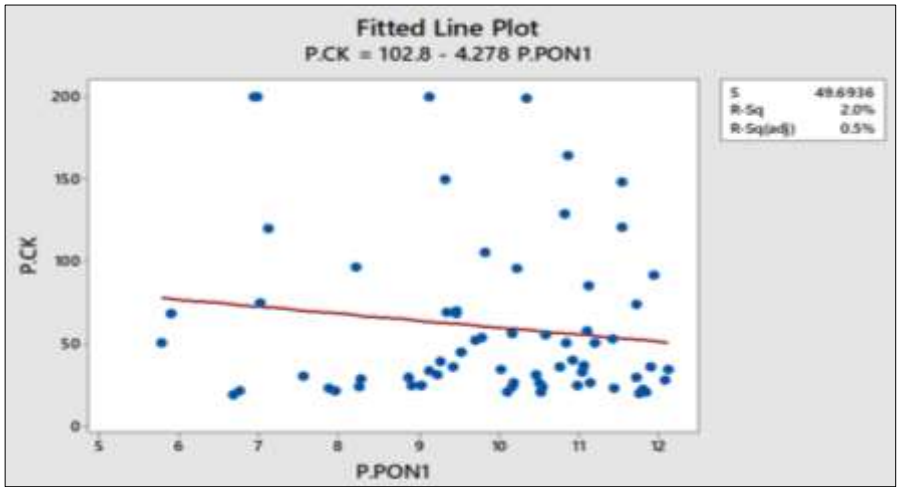


Fig 1: Shows the correlation coefficient between the level of PON1 and CK-MB level

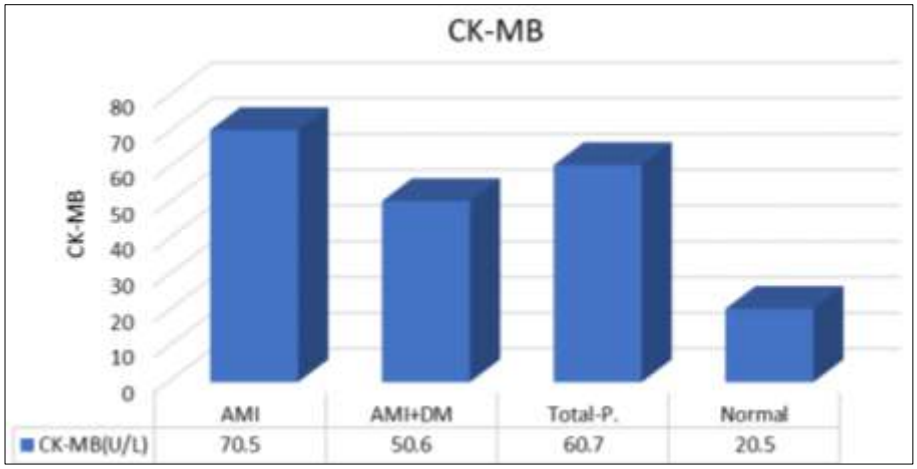


Fig 2: PON1 and CK-MB levels in serum of AMI patients, AMI+DM patients, total patients and healthy group

4. Discussions

In this study the level of PON1 concentration was rises in AMI, (AMI + DM) and total patients when compared them with control group ، they are not compatible with both Sowmya Varadhan *et al*., who found a lower level of PON1 in ACS patients as compared to the control group [53], conflict with the study by Lorena Ciumărnean *et al*., which showed decreased activity of PON1 arylsterase in patients with consider as an independent predictor of 1-year survival after AMI [54] and the study by Anna Wysocka *et al*., which found that DM patients with coronary artery disease (CAD) had lower PON1 activity than in DM patients, although similar lipid properties [55], and conflict with the study by Mike Mackness and Eser Sozmen that confirmed that low PON is associated with AS, by comment by them on some of the datas which they called inaccurate from realistic side [56], including that high PON levels are associated with AS and that are supporting the our results and which are showed up in (citation 19) from the study of Yaser Said Cetin *et al*. [57]. PON1 gene contains approximately 200 different single nucleotide polymorphisms [40] that alter the oxidation state of lipoproteins [38], the polymorphism independently affects the enzyme's ability to protect LDL oxidation [40] and affects its hydrolytic activity with natural and synthetic substrates [39]. Its activities show differences between individuals and multiracial due to genetic polymorphism ، even among individuals with the same genotype, its activity may show differences (13-40) times due to external factors, lifestyle, age, different physiology, or diseases that can affect the levels of PON1 [54]. The elucidation of the physiological roles of PON, the active center, and all applications in medical fields depend on its substrates [58] and homocysteine thiolactone is one of its basic internal substrates that can negatively affect protein structure/function through post-translational modification and has recently been shown to be predictive of MI in CAD patients [39]. PON is also known as (aromatic esterase 1) encoded by the PON1 gene. Polymorphisms in the PON1 gene, (L55M and Q192R) on exon (3 and 6) respectively are known to pose a risk for CVD [59]. Oxidative stress is a defect resulting from deficits in defense systems or excessive production of ROS associated with decreased antioxidant activity. This deficiency could be the result of genetic factors, environmental, metabolic imbalance, toxicity or direct attacks by accumulation of free radicals, cause nonspecific and irreversible oxidation of biological molecules thus loss of function and can cause metabolic imbalance who will affect biological molecules in their structures or activities. By physiology neutralization of free radicals is ensured by defense systems enzymatic and non-enzymatic antioxidant. PON plays an important role in equilibrium redox similar, individuals do not have the same antioxidant potential. Is prepared a repair process for each pathological condition as a result, the endogenous defense induces many signaling mechanisms to adapt to the new physiological situation [60]. As our study showed that the level of cardiac creatine kinase was elevated in the all AMI and (AMI + DM), and total patients when compared them with control group. Our study found a significant increase in CK-MB levels in patients with AMI, and this is consistent with the study of Haider Raad Hashim [17], and the study of Salih Hamzah [61] and a study (Mehmet Oguzhan Ay *et al*.) whereas, CK-MB levels were found in the STEMI ($p< 0.001$) and NSTEMI ($p< 0.001$) group of AMI patients significantly higher than the control group [62]. And the results of our study are identical with the study (Dr. Kiran Kumar Akka and Dr. Pampa Reddy), which found a significant increase in the level of CK-MB in patients with DMT2 and MI [63]. While it did not agree with the study (Mingdan Zhu *et al*.), which did not show any significant change in the level of CK-MB in the group MI [64]. when the myocardial membrane loses its integrity due to muscle cell death, the first injuries caused by AMI lead to an increase in the concentration of CK-MB in the surrounding blood to measurable values after approximately 4 or 6 hours. Concentrations can reach peaks of (39-185) ng/mL in the period(18-24) hour [65] since it is cleared from the circulation faster than cTn, this makes it the best biomarker for detecting re-infarction in patients [66]. CK-MB is the most cardiac specific enzyme [67]. Disease states usually result in moderate or extensive tissue damage (depending on the time and severity of disease onset) which eventually leads to the release of enzymes (non-functional enzymes specific to the diseased organ or tissue) into the circulation resulting in an increase in the activity of these enzymes in fluids body [47].

Abbreviations MI, myocardial infarction; PON1**,** paraoxonase-1; AMI, acute myocardial infarction; (AMI+DM), acute myocardial infarction with diabetes mellitus; CV, cardiovascular; SPSS, statistical package for social sciences; HDs, Heart diseases; HTN, hypertension; TC, total Cholesterol; CHD, Coronary Heart Disease; AS, atherosclerosis; ACS, acute coronary syndrome; STEMI, elevated MI; NSTEMI, non-elevated MI; SCD, sudden

coronary death; HF, Heart Failure; ECG, electrocardiogram; DMT1 and DMT2, diabetes Mellitus type (1 and 2); CVD, cardiovascular disease; ED, endothelial dysfunction; VLDLs, very low density lipoproteins; LDL-C, Low-Density Lipoproteins Cholesterol; TGs, triglycerides; sdLDL-C, small dense LDL; ROS, reactive oxygen species; NO, nitric oxide; HDLs, high Density Lipoproteins; RCT, reverse cholesterol transporter; CK, Creatine kinase; ATP, adenosine triphosphate; ADP, adenosine diphosphate; ELISA, Enzyme Linked Immunosorbent Assay; SD, standard deviation; CAD, coronary artery disease.

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