Original
ISSN 2413-0516

Relationship of Midkine in Myocardial Infarction Patients and Some Biochemical Parameters

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(Submitted: 23 March 2022 – Revised version received: 09 April 2022 – Accepted: 28 April 2022 – Published Online: 26 August 2022)

Abstract

Objectives: This study aims to estimate the concentrations of MK, hs-CRP, TnI, AST, ALT and ALP in serum for MI in comparison to wholesome controls, in an effort to check the quantity of this impact at the pathological condition, in addition to understanding the position of MK in MI sufferers and its relationship to liver function tests and may be used as biochemical markers to decide the severity of MI in sufferers.

Methods: The studying include the investigation of midkine (MK), High-sensitivity C-reactive protein (hs-CRP), Troponin I (TnI), aspartate aminotransferase (AST) and alanine aminotransferase (ALT) and alkaline phosphatase (ALP) levels in myocardial infarction (MI) patients. The study includes (84) samples: 34 of myocardial infarction patients (19 male and 15 female) and 50 sample of apparently healthy as control group (25 male and 25 female). Samples were collected during the period from Jan. 2021 to July 2021 from in-patients of Cardiac Surgery Center admitted at Ibn Sina Teaching Hospital and Mosul General Hospital, Mosul, Iraq with matching age ranged between 26–86 years. The clinical diagnosis in each case is made according to a cardiovascular specialist.

Results: The results showed that there was a significant increase in MK, TnI, GOT, GPT and ALP for all studied groups (males and females) of MI patients compared with control groups, and there was no any a significant in hs-CRP. Beside of, showed significant positive correlation between MK with BMI, hs-CRP, TnI, AST, ALT and ALP in control and patients group. Whereas there were no any correlation between MK with age, in patients and control under study.

Conclusion: The study indicated that the MK increased in patients with myocardial infarction, and it's increased in males more than female patients, and that may act as a good markers for diagnosis of myocardial infarction disease.

Keywords: Myocardial infarction, Midkine, hs-CRP, AST, ALT, ALP

Introduction

A major threat to human health, myocardial infarction (MI) is one of the leading causes of death in the world.[1] It is characterized by high morbidity and mortality. Atherosclerosis, a chronic inflammatory disease characterized by the development of fibrofatty plaques, is the pathophysiological cause of MI.[2]

The term MI refers to a heart attack that occurs when blood flow to a particular area of the heart is disrupted and the heart muscle is harmed due to a lack of oxygen. And owing to an unsteady accumulation of plaques, white blood cells, cholesterol, and fat, one of the coronary arteries that delivers blood to the heart develops a blockage. Acute Myocardial Infarction, or AMI, is the term used when the incident becomes severe. Chest discomfort that radiates to the left arm or side of the neck, shortness of breath, perspiration, nausea, vomiting, an irregular heartbeat, anxiety, exhaustion, and other symptoms are all signs of MI.[3,4] The term "silent MI" refers to the approximately 64% of MI patients do not experience chest discomfort.[5] MI is caused by a number of factors, including older age, cigarette use high concentration of cholesterol and fat levels, diabetes, obesity, inactivity, chronic renal disease, hypertension, high levels of bad cholesterol LDL (low density lipoprotein), excessive alcohol intake and use of cocaine and amphetamines.[6,7]

When the present oxygen needs of the myocardium are not met by oxygen supply, MI results. The coronary perfusion is absolutely necessary for the heart's continual delivery of oxygen because it is an obligatory aerobic organ. Normal myocardium does not become ischemic when oxygen intake is raised (as happens during maximal exercise testing) because the myocardial oxygen demand and supply are fulfilled during normal physiology. Even in the absence of overt coronary artery disease, MI is a frequent finding in failing hearts, perhaps as a result of structural or functional changes to the coronary circulation. Ischemia is a self-perpetuating disease that adversely affects prognosis and permanently compromises heart function. Therefore, a more complete and in-depth comprehension of MI pathogenesis in heart failure will probably result in much better results for these patients.[8]

The primary property of midkine (MK) was later thought to coordinate embryonic development.[9] The majority of MK research focused on its role in malignant diseases and suggested a negative impact on the host.[10] A significant portion of the MK literature has demonstrated its capacity to promote inflammatory reactions.[11] Several recent studies have also shown that MK is a key regulator of angiogenesis and cardiac problems in patients with cardiovascular disease.[4] Surgical techniques to open clogged arteries may become a traditional method, and could be replaced by new non-surgical treatment methods for patients with ischemic diseases through the use of MK, which may be primarily related to atherosclerosis, for example within the heart.[12]

This study aims to estimate the concentrations of MK, hs-CRP, TnI, AST, ALT and ALP in serum for MI in comparison to wholesome controls, in an effort to check the quantity of this impact at the pathological condition, in addition to understanding the position of MK in MI sufferers and its relationship to liver function tests and may be used as biochemical markers to decide the severity of MI in sufferers.

Materials and Methods

We measured the concentrations of MK, hs-CRP, TnI, AST, ALT and ALP in blood samples for 84 samples divided into

(34) samples of MI patients (19 male and 15 female) and control group consists of 50 apparently healthy individuals (25 male and 25 female) with negative results for cardiovascular diseases, or chronic diseases, and their age were matched with the MI patients and ranged between 26–86 years, and they have no history of any disease. Samples were collected during the period from Jan. 2021 to July 2021 from patients in the Cardiac Surgery Center and inpatients at Ibn Sina Teaching Hospital and Mosul General Hospital, Nineveh Health Directorates/Mosul - Iraq. The clinical diagnosis in each case is made according to a cardiovascular specialist.

Ten mL of blood and allow to clot, serum was separated by using speed at (4000 × g) for ten mints, divided into (3) sections and kept frozen at (–20°C) until analysis.

The activities of AST, ALT, and ALP were determined from the myocardial and renal tissue using the assay Journal Pre-proof 10 kit, which was purchased from Randox Laboratory Ltd. (Co. Antrim, UK). ELIZA technique is used to quantify midkine, hs-CRP, and TnI using kits tested in accordance to the manufactured procedure (Bioassay technology Laboratory, Shanghai, China) MK Cat. No. E1633Hu, hs-CRP Cat. No. E1805, and TnI Cat. No. E1270. The statistical analysis was performed using SPSS software. Each indicator's average value and standard deviation were determined, and the *P*-value thresholds of Significant at ($P \leq 0.05$), **Significant at ($P \leq 0.001$), and ***Significant at ($P \leq 0.0001$) were used to indicate statistical significance.

Results

Tables 1, 2 and 3 showed a description of healthy and MI patients groups (Males and Females groups), which indicated to non-significant for age and body mass index (BMI) for all groups, males and females.

The results shown in Tables 4, 5 indicated that there is a significant increase in the levels of MK in the serum of MI patients when compared with the healthy group at $P < 0.0001$ and for all and male patients group, but in Table 6 female groups show that there is a significant increase in the levels of MK in MI patients when compared at $P < 0.05$ and there was no evidence of a significant increase in the levels of hs-CRP in the serum of MI patients when compared to the healthy group for all patients, male and female groups, while there is a significant increase in TnI in the serum of MI patients compared with the group of healthy at $P \leq 0.0001$ for all and male groups was observed. In addition, Table 6 shows that there is a significant increase in TnI in the serum of MI patients compared with the group of healthy at $P \leq 0.05$ for female groups.

The results in Tables 7, 8 show that there is a significant increase in the levels of AST, ALT and ALP in the serum of myocardial infarction compared with the group of healthy at $P \leq 0.0001$ and $P \leq 0.001$ for all and male groups, and in

Table 1. **Description of healthy and all MI patients groups**

Parameters	Healthy group *N* = 50		Patients group *N* = 34		*P*-value
	Mean	SE	Mean	SE	
Age, (Year)	54.54	1.85	58.88	2.18	0.19
Weight, (kg)	80.82	2.33	84.12	2.69	0.291
Height, (cm)	171.22	1.16	171.3	1.12	0.811
BMI, (kg/m^2)	27.56	0.74	28.77	0.99	0.215

Table 2. **Description of males for healthy and MI patients groups**

Parameters	Healthy group *N* = 25		Patients group *N* = 19		*P*-value
	Mean	SE	Mean	SE	
Age, (Year)	53.68	2.1	58.22	2.65	0.101
Weight, (kg)	84.16	2.85	85.33	3.29	0.833
Height, (cm)	176.1	1.34	173.0	1.18	0.102
BMI, (kg/m^2)	27.16	0.85	28.63	1.22	0.340

Table 3. **Description of females for healthy and MI patients groups**

Parameters	Healthy group *N* = 25		Patients group *N* = 15		*P*-value
	Mean	SE	Mean	SE	
Age, (Year)	57.4	2.89	61.43	2.86	0.087
Weight, (kg)	77.48	3.63	78.43	2.68	0.111
Height, (cm)	166.4	1.33	164.7	1.24	0.408
BMI, (kg/m^2)	27.96	1.24	28.31	1.02	0.19

Table 4. **MK, hs-CRP and TnI in all MI patients group**

Biochemical Parameters	Healthy group *N* = 50		Patients group *N* = 34		*P*-value
	Mean	SE	Mean	SE	
MK, (pg/ml)	159.7	6.1	410.1	24.78	0.0001***
Hs-CRP, (ng/ml)	1.25	0.075	1.13	0.081	0.262
Tn, (pg/ml)	0.06	0.02	9.39	1.39	0.0001***

***Significant at ($P \leq 0.0001$).

Table 5. **MK, hs-CRP and TnI in male MI patients group**

Biochemical Parameters#	Healthy group *N* = 25		Patients group *N* = 19		*P*-value
	Mean	SE	Mean	SE	
MK, (pg/ml)	152.3	5.91	422.7	41.63	0.0001***
Hs-CRP, (ng/ml)	1.288	0.123	1.137	0.086	0.339
Tn, (pg/ml)	0.08	0.054	8.467	1.55	0.0001***

***Significant at ($P \leq 0.0001$).

Table 6. **MK, hs-CRP and TnI in female MI patients group**

Biochemical Parameters	Healthy group *N* = 25		Patients group *N* = 15		*P*-value
	Mean	SE	Mean	SE	
MK, (pg/ml)	167.2	10.81	361.4	13.36	0.008*
Hs-CRP, (ng/ml)	1.212	0.089	1.11	0.22	0.624
Tn, (pg/ml)	0.04	0.016	12.97	2.96	0.005*

*Significant at ($P \leq 0.05$).

Table 7. **AST, ALT and ALP in all MI patients group as compared with healthy group**

Enzyme Activity Levels, (U/L)	Healthy group $N = 50$		Patients group $N = 34$		*P*-value
	Mean	SE	Mean	SE	
AST	13.38	1.10	39.26	4.82	0.0001***
ALT	5.8	0.39	10.03	0.93	0.0001***
ALP	12.02	0.58	20.02	1.84	0.0001***

***Significant at ($P \leq 0.0001$).

Table 8. **AST, ALT and ALP in males MI patients group as compared with healthy group**

Enzyme Activity Levels, (U/L)	Healthy group $N = 25$		Patients group $N = 19$		*P*-value
	Mean	SE	Mean	SE	
AST	13.44	1.51	39.81	5.39	0.0001***
ALT	6.24	0.71	10.78	1.105	0.005*
ALP	12.7	0.83	19.87	1.99	0.001**

*Significant at ($P \leq 0.05$), **Significant at ($P \leq 0.001$), ***Significant at ($P \leq 0.0001$).

Table 9. **AST, ALT and ALP in females MI patients group as compared with Healthy group**

Enzyme Activity Levels, (U/L)	Healthy group $N = 25$		Patients group $N = 15$		*P*-value
	Mean	SE	Mean	SE	
AST	13.32	1.64	37.14	3.62	0.022*
ALT	5.36	0.31	7.14	1.03	0.038*
ALP	11.34	0.82	20.58	2.92	0.014*

*Significant at ($P \leq 0.05$).

Table 10. **Linear relationship between MK and some biochemical parameters measured in the control and MI patient groups**

Biochemical Parameters	Midkine (MK), (pg/ml)			
	Control group, $N = 50$		MI Patients, $N = 34$	
	r-value	*P*-value	*r*-value	*P*-value
Age, (Year)	0.370	0.129	0.632	0.085
BMI, (kg/m^2)	0.229	0.173	0.85*	0.034
Hs-CRP, (ng/ml)	0.632*	0.009	0.508*	0.023
TnI, (pg/ml)	0.774*	0.015	0.892*	0.013
AST, (U/l)	0.1*	0.05	0.767	0.028
ALT, (U/l)	0.789*	0.039	0.583*	0.051
ALP, (U/l)	0.314*	0.027	0.530*	0.022

*Significant at ($P \leq 0.05$).

Table 9 female groups show that there is a significant increase in the levels of AST, ALT and ALP in the serum of MI compared with the group of healthy at $P \leq 0.005$.

The present study showed in Table 10 significant positive correlation between MK with BMI, hsCRP, TnI AST, ALT and ALP in control and patients group. Whereas there were no any correlation between MK with age, in patients and control under study.

Discussion

One of the important biomarkers used in clinical diagnosis is medkine. The data of midkine obtained in this study are consistent with the findings of previous studies performed by Woulfe et al.,[13] While treating the heart specifically is a clear therapeutic objective, other essential organs also need to be protected, and MK may be able to help in this regard in addition to repairing brain damage. In rodent models of ischemic myocardial infarct, for instance, Due to its powerful angiogenic and anti-apoptotic effects, MK has been shown to be cardio-protective, resulting in reduced myocardial infarction, thus improved cardiac function, and increased overall survival. Injecting MK intracoronary or intramyocardially enhanced survival, reduced infarct acuity, and decreased apoptosis through to cell survival and angiogenesis.[13,14]

MK also contributes to myocardial infarction, cardiac hypertrophy, and ischemic heart damage. The role of MK in these various pathologies is still up for debate, though, Because MK has positive benefits, such as ischemic heart damage, heart failure, and myocardial infarction by improving cardiac function and antiapoptosis, stimulating angiogenesis, and reducing detrimental remodeling.[15]

The findings of high-sensitivity C-reactive protein (hs-CRP) are in agreement with other studies for other diseases, such as metabolic problems, cerebrovascular illness, and coronary atheroseclerosis.[16-18] C-reactive protein (CRP) damages the vascular endothelium, causing it to malfunction and become more sensitive to proatherogenic stimuli, is also linked to the existence of chronic low-intensity inflammation.[17] Because cardiac imaging techniques cannot assess inflammation-induced vascular changes, biomarkers that can identify these changes are highly valuable.[19,20] Additionally, it is critical to develop procedures for the precise and sensitive identification of people those who are in risk of developing cardiovascular disorders. These requirements could be satisfied by the biomarker of inflammation known as serum high-sensitivity CRP (hs-CRP).

According to the Physician's Health Study findings, people with greater baseline hs-CRP concentrations have a doubled risk of stroke and a tripled risk of MI.[21] In contrast to lipids or homocysteine, the female health research found that hsCRP is a superior predictive predictor for cardiovascular events.[22] Last but not least, Yoshinaga et al. (2017)[23] noted that increased hs-CRP is a significant risk factor for patient death in hospitals.[24]

Troponin I play an important roles in myocardial infarction as a specific biomarker.[4] These findings are consistent with Ammirati et al., (2021)[25] Cardiac special troponin (cTn) are significant Common biomarkers utilized in contemporary clinical Diagnosis to suspected MI, and their altitude is a key feature in the diagnosis of acute MI.[26] The causes of myocardial damage are many, and myocardiocyte apoptosis, with or without obvious indications of necrosis, may cause the release of cTn from injured cells.[27] The two troponin indicators used in clinical practice are troponin I (TnI) and troponin (TnT). Despite the fact that these are two different proteins, they are

both employed because they both represent myocyte damage and have comparable diagnostic accuracy for MI[28] despite the fact that age had no discernible influence on them.[29]

The results of serum cardiac enzyme including AST and ALT activity levels are in consistent with researchers Djakpo et al., (2020)[30] and Shamshirian et al., (2020).[31] Multiple causes might result in increased AST and ALT levels. Elevated AST and ALT have been linked to four separate pathways.[32] First, direct tissue injury (damage to the plasma membrane with protein leakage or cell necrosis produced by a variety of damaging agents or stimuli) or apoptosis are the most prevalent causes of increased activity of aminotransferases, including AST (In conditions of physiological cellular renewal or increased apoptotic stimuli). Reasonably, larger organs with higher AST activity are the primary source of increased AST in circulation. Elevated AST levels are usually associated with inflammatory liver disease (Viral hepatitis), alcoholic liver disease, cirrhosis, cholestasis syndromes, drug toxicity, acute myocardial infarction, septic shock, and skeletal muscle injury/injury. Acute myocardial ischemia or myocardial cell necrosis, which occurs in acute myocardial infarction, is a common cause of increased serum AST activity.[33]

Alkaline phosphatase (ALP) activity level obtained in this study indicate that their outcomes data support the conclusions of prior studies that there is an increase in the activity level of ALP in the serum in MI.[34] As many tissue-specific isozymes as different genes encode the ALP [phosphate-monoester phosphohydrolase; EC 3.1.3.1] enzyme. It is present in a variety of species (bacteria, plants, and mammals) and is capable of catalyzing the hydrolysis of the phosphomonoester R-O-PO3 without regard to identification category "R".[35]

In the emergency room, regular blood tests for liver function, such as serum transaminases and alkaline phosphatase (ALP), are frequently performed. Acute myocardial infarction (MI) patients may have abnormal liver function values without having clinically obvious liver damage.[36] A strong predictor of mortality in the general population, according to recent research, is the nonalcoholic fatty liver disease fibrosis score, which includes serum transaminases.[37,38] In individuals with post-acute coronary syndrome, this score is related to an increased risk of subsequent cardiovascular events.[39] Diagnostic signs include cytosolic enzymes like CK-MB and ALP, which leak from the injured tissue into the circulation when the cell membrane is torn or permeable. Additionally, the serum's level of enzymes is inversely correlated with the quantity of necrotic cells.[40]

The correlations between MK and some biochemical parameters measured in the control and MI patient groups indicate that MK is a crucial regulator of angiogenesis, the formation of new blood vessels and arteriogenesis in pathological vascular conditions, according to recent study. Due to the increasing number of cases of cardiovascular diseases, which is primarily attributed to atherosclerosis and occlusive arterial disease, Blockage in one of the heart's arteries caused by fat accumulation, angiogenesis which is the process by which new blood vessels are created from pre-existing ones through this protein MK can avoid surgeries It is interesting that the sulfate groups have a significant impact on the effects of MK on neuronal survival and outgrowth.[41] As the disease causes an increase in the level of hsCRP, TnI AST, ALT, and ALP with the increase in the levels of MK, an increase in MK is a certain indicator of an increase in the incidence of myocardial infarction and the associated damage to the work and function of the heart muscle. Along with demonstrating that the MK rose along with the BMI, MK may be involved in this process as it is generated and released by adipocytes. MK is related with increased production of inflammatory mediators in adipose tissue, which leads to chronic inflammation.[42,43] As a result, the MK was raised, and a strong positive association was seen between the MK and BMI.

Increase in the level of MK reflects the level of indicators of heart disease from hsCRP and TnI. This is clear evidence and a good indicator that MK can be considered a clear sign of myocardial infarction, which can be added as another guide for a good and early diagnosis of this disease.

Conclusion

The study indicated that the MK increased in patients with myocardial infarction, and it's increased in males more than female patients, and that may good markers to diagnose the myocardial infarction disease.

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