Correlation of cardiovascular risk parameters with serum interleukin-6 and C-reactive protein in patients with myocardial infarction

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Abstract

Objective: We aimed to determine the correlation of cardiovascular risk parameters with serum interleukin-6 (IL-6) and high-sensitivity C-reactive protein (hs-CRP) in patients with acute myocardial infarction (AMI). Methods: This cross-sectional study was conducted among patients admitted to the intensive care unit (ICCU) King Abdulaziz University Hospital, Jeddah, from March 2019-February, 2020. Blood samples and other data were collected from 100 adult AMI patients admitted to the ICCU (age, 40–60 years) and from 40 age- and BMI-matched healthy adults. Results: The comparison of median and interquartile range of the IL-6 and hs-CRP levels showed that the median values in the MI group were significantly higher than in the healthy control ($p < 0.001$). Levels of FPG, HbA1c, TG, LDLc were significantly higher, while HDLc was significantly lower in MI patients than control subjects. In the MI group, hs-CRP showed a significant correlation with BMI ($r=0.531$; $p<0.001$), and waist circumference ($r=0.448$; $p<0.001$). With regard to the gender-based comparison, the hs-CRP and IL-6 levels were not significantly different in male and female MI patients (5.90±2.0 vs. 6.80±8.2; $p=0.166$ and 21.23±8.2 vs. 21.06 ±8.7; $p=0.948$, respectively). However, IL6 levels were significantly different between males and females in the control groups (6.64±3.0 vs. 9.74±4.7;$p=0.017$). Conclusion: IL-6 and hs-CRP were significantly higher in MI than the healthy group. No correlation was found with biochemical parameters. Further research is needed to explore the pathways involving these two molecules in the pathogenesis of MI. Keywords: Myocardial infarction, interleukin-6, cardiovascular risk parameters, C-reactive protein, HDL-c

What is already known about this topic?

Among MI patients, inflammatory cytokines such as Interleukin-6 (IL-6) and also its signalling product, C-reactive protein (CRP), are seen in high levels.

The circulating IL-6 levels constitute a substantial pro-atherogenic cytokine, and its level is an independent predictor of cardiovascular mortality.

What does this article add?

Nevertheless, it is not yet clear as to the reason behind elevations in the level of cytokines, either due to obesity or due to localized or generalized inflammation.

IL-6 and hsCRP were notably higher in the MI group compared to healthy control.

Our findings support the assumption that IL-6 and CRP levels do affect cardiovascular risk outcomes.

Introduction

Cardiovascular diseases (CVDs) are the primary cause of death worldwide: it is approximated that 17.5 million people die from CVDs every year, and this makes CVDs accountable for more than one-fourth of the total global deaths.[1] There is a considerable amount of evidence to show that obesity is one of the strongest risk factors associated with the development of MI. Obesity is characterized by inflammation that is related to other disorders, too.[2]Blood vessel inflammation plays a vital role in the initiation of plaques, their progression, and fibrous capture, which causes the formation of local thrombus and leads to hypoxia-related myocardial damage. In MI patients who have thrombus, the infarction-related arteries often exhibit endothelial dysfunction. In such vessels, inflammatory cytokines, such as interleukin-6 (IL-6), and its related signaling protein C-reactive protein (CRP), are found at high levels.[3] Additionally, epidemiological research, as well as meta-analytical studies, have reported a linkage between the IL-6 and CRP levels in heart diseases, even among healthy males and females. Both markers have been linked with an augmented risk of mortality, especially in patients with unstable coronary artery disease (CAD).[4, 5] In particular, circulating IL-6 is considered as an important pro-atherogenic cytokine, and its level is an independent predictor of cardiovascular mortality.[6]

High serum levels of IL-6, as well as other cytokines, are associated with poor clinical outcomes in hospitalized patients who have unstable angina or ST-elevated myocardial infarction (STEMI).[7]Moreover, multiple diseases that commonly lead to death among the elderly might stimulate or sustain a systemic inflammatory state that can be detected via a rise in IL-6 levels and other pro-inflammatory cytokines.[8] In addition, IL-6 is one of the major cytokines involved in the production of acute-phase proteins, which show elevated levels in clinical conditions such as tissue injury caused by infections, tumors, ischemic disorders, and trauma.[9]Exploring the correlation of IL-6 with other important clinical parameters in these pathophysiologic events might shed light on the underlying inflammatory mechanisms and their association with an increased risk of mortality.[9]

High-sensitivity CRP (hs-CRP) has been shown to be a biomarker for vascular risk in atherothrombosis.[10] hs-CRP has also been shown to be a prognostic marker in acute coronary syndrome patients, but it has poor specificity. In fact, it may be more useful as a prognostic marker when used in combination with IL-6, which has been reported to be a marker of inflammation, localized coronary plaques, and atherosclerotic plaques,[11] and has also been reported to be significantly associated with inflammatory plaques in acute coronary syndrome patients.[12] A combination of clinical parameters, such as CRP, IL-1,and IL-6, has shown promise as a target for anti-inflammatory agents used for atheroprotection.[13] In the context of involvement of IL6 and CRP in the process of MI, this study was designed to determine the correlation of different parameters of cardiovascular risk with serum IL-6 and hsCRP levels in patients with MI.

Methods

This cross-sectional study was conducted among patients admitted to the intensive care unit (ICCU) King Abdulaziz University Hospital, Jeddah, Saudi Arabia from March 2019-February, 2020. The patients were selected with the help of a non-probability convenience sampling technique. Blood samples and other data were collected from 100 adult patients (88 males and 12 females) admitted due to MI (age, 40–60 years) and from 40 healthy adult individuals (24 males and 16 females) who were matched with the patients in terms of their age and BMI and selected from the general population. Patients who had liver diseases, any type of cancer, endocrinal problems, such as thyroid disorders, Cushing syndrome, and others, were excluded. This study received the ethical approval of the ethical committee of KAUH (Ref No. 369-19). Blood samples and other data were collected after the patients' written consent was obtained.

Venous blood (5 ml) was collected in the morning after overnight fasting, and the serum fraction was separated by centrifugation. The separated serum fraction was maintained at -80°C for the measurement of biochemical variables. The serum IL-6 and hs-CRP levels were measured by ELISA kits provided by Bio-Techne (R and D Systems, Minneapolis, Minnesota, USA) and Beijing Mesochem Technology Co. Ltd.(Beijing, China), respectively. Fasting plasma glucose (FPG), HbA1c, total cholesterol, triglyceride, HDLc, and LDLc were also measured using commercially available kits on an auto-analyzer (Roche Modular P-800, Germany).

The serum parameters (quantitative data) are presented as mean and SD, while the qualitative data are reported as frequency and percentage. Shapiro-Wilk test indicated that data was not normally distributed ($p<0.005$). Mann-Whitney U test was used to determine the variance between two groups and Spearman correlation for finding the hs-CRP and IL-6 correlation with the baseline clinical and biochemical characteristics. SPSS version 26.0 was employed for the data analysis. A p-value of less than 0.05 was considered significant.

Results

The comparison of median and interquartile range of the IL-6 and hs-CRP levels showed that the median values in the MI group were notably higher than in the healthy control ($p<0.001$). Levels of FPG, HbA1c, TG, LDLc were significantly higher, while HDLc was significantly lower in MI patients than control subjects (Table 1).

In the MI group, hs-CRP showed a significant correlation with BMI ($r=.531;<.001$)), and waist circumference($r=.448;p<.001$). None of the other baseline clinical or biochemical characteristics were correlated with IL-6 in the MI group or the control group (Table 2).

With regard to the gender-based comparison showed that the hs-CRP and IL-6 and levels were not significantly different in male and female MI patients (5.90 ± 2.0 vs. 6.80 ± 8.2;$p=0.166$ and 21.23 ± 8.2 vs. 21.06 ± 8.7; $p=0.948$, respectively) (Fig 1). However, IL6 levels were significantly different between males and females in the control groups (6.64 ± 3.0 vs. 9.74 ± 4.7;$p=0.017$) (Fig 2).

Discussion

Even though MI has been associated with both hsCRP as well as IL-6, albeit to a lesser extent, it has been challenging to establish the direct role of inflammatory cytokines in MI. Nonetheless, a few studies have implicated the IL-6 pathway in the pathogenesis of MI and other heart diseases. According to the present study results, both the IL6 and CRP levels were higher in MI patients than in healthy controls. Additionally, CRP was significantly correlated with BMI and waist circumference. Few studies have also demonstrated that CRP and IL-6 are significantly associated with adverse cardiovascular events.[14-16] For example, aChinese study demonstrated a significant correlation between both IL-6 and hsCRP and CVD risk factors and mortality.[17] In line with our study, Lai et al. reported that the serum IL-6 concentrations in coronary disease patients were substantially high ($p<0.001$) in contrast to those in the control group.[14] Another study reported that the IL-6 levels were positively correlated to the risk factors for CVD that cause inflammation and plaque formation, and therefore, IL-6 and CRP can be used as indicators of the prognosis of adverse cardiac events.[15] In another study, Velásquezet al. reported that CRP and IL-6 had a significant association with hypertension, diabetes, smoking, BMI, and age. The study concluded that elevations in IL-6 levels were associated with the risk of MI.[16]

In a study on 44 STEMI patients, Wilkowska et al. reported elevated levels of IL-6 in all the patients and observed that the IL-6 levels were higher among depressed MI subjects than among non-depressed MI subjects.[18] In another study in the STEMI population, the circulating levels of CRP and IL-6 were found to be increased, especially in patients with a high peak of troponin T.[19] Although the biochemical parameters were deranged in MI patients, these parameters were not significantly correlated with IL-6 and CRP.

A study on 73 patients with acute MI (AMI) reported elevated IL-6 levels in CAD patients than in the controls; further, the study concluded that both the IL-6 and CRP levels were associated with AMI and cardiac injury.[20] In our MI patients, too, the CRP levels were elevated compared with the controls ($p<0.05$) and were preceded by an increase in IL-6 levels. Additionally, another study on the association of CRP and IL-6 levels with the risk of death and cardiovascular events in atrial fibrillation patients reported that the IL-6 level was significantly correlated with vascular death, major bleeding, i.e., hemorrhagic stroke, and thromboembolic outcomes, while CRP was significantly associated with MI.[21]

IL-6 has been reported to be more strongly correlated with the risk of cardiovascular mortality than CRP.[22] Elevated IL-6 level is an important biomarker and powerful predictor for long-term assessment of cardiovas-

cular mortality risk in STEMI patients.[23] This is because serum IL-6 is the main stimulator for acute phase hepatic response, which is linked with an increase in blood viscosity as well as platelet count and activity. Further, IL-6 slows down lipoprotein lipase activity as well as its levels in plasma, thereby leading to an increase in the uptake of lipid through macrophages.[24] In addition to this, circulating IL-6 stimulates the hypothalamic-pituitary-adrenal axis, and the triggering of this axis is significantly correlated with central obesity, insulin resistance, and hypertension, all of which are risk factors for cardiovascular mortality.[25] We also observed that age in the control group was negatively correlated with IL6, but there is no specific explanation for this correlation.

The findings discussed in this study support the assumption that IL-6 and CRP levels are involved in the MI, but their correlation with cardiovascular biochemical risk factors is not found. It seems that IL6 and CRP are not involved in AMI's mechanism via biochemical factors, but these might play a pathogenic role in AMI by some other mechanism.

Limitations of the study

This study is not immune to observer or selection bias. In particular, as the study was carried out at a single center, the results might not be representative of the whole Saudi population. Likewise, the number of patients and controls in each group was not equal, and this might have led to a bias. Additional multi-centered studies with larger sample sizes would be useful for achieving better and more accurate results.

Conclusion

IL-6 and hsCRP were significantly higher in MI than the healthy group. No Correlation was found with biochemical parameters. Further multi-centered studies on a larger scale are needed that would be insightful in terms of gaining better and improved knowledge and more accurate data.

Author Contributions

Ranya Alawy Ghamri: Data collection, drafting and critical revision of the article

Mukhtiar Baig: Study design, and data analysis/interpretation

Kamal Alghalayini : Approval of article

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Table 1: Comparison of the demographic and clinical characteristics of patients and healthy control subjects

Variables	Control group (n = 40)	Control group (n = 40)	Patients (n = 100)	Patients (n = 100)	P-value
	Median	IQR	Median	IQR	
Age (y)	53	8.5	53	12	0.894
BP systolic (mm Hg)	124	16.5	123.5	23	0.852
BP diastolic (mm Hg)	78.5	8.5	75	16	0.209
BMI (kg/m^2)	27.01	4.69	27.42	6.95	0.852

Variables	Control group (n = 40)	Control group (n = 40)	Patients (n = 100)	Patients (n = 100)	P-value
Waist circumference (cm)	94	9.5	94	22	0.979
FPG (mmol/L)	5.14	0.36	5.5	1.25	<0.001
HbA1c (%)	4.99	0.4	5.9	1.79	<0.001
TC (mmol/l)	4.23	1.07	4.32	1.7	0.575
TG (mmol/l)	1.24	0.73	1.97	1.01	<0.001
HDLc(mmol/l)	1.09	0.31	0.84	0.25	<0.001
LDLc(mmol/l)	3.01	1.08	3.26	1.14	0.007
hs-CRP (mg/l)	0.52	1.04	6.16	2.91	<0.001
IL6 (pg/ml)	7.74	7.35	19.39	15.72	<0.001

“BMI = body mass index, FPG = fasting plasma glucose, HBA1c = hemoglobin A1c, TC = total cholesterol, LDL-C = low-density lipoprotein cholesterol, HDL-C = high-density lipoprotein cholesterol, hs-CRP = high-sensitivity C-reactive protein, IL-6 = interleukin-6 “

Table 2: Correlation of hs-CRP and IL6 with baseline clinical and biochemical characteristics

Variables	Hs-CRP (pg/ml)	Hs-CRP (pg/ml)	IL6 (ng/ml)	IL6 (ng/ml)
	Control (n = 40)	Patients (n = 100)	Control (n = 40)	Patients (n = 100)
	r (p-value)	r (p-value)	r (p-value)	r (p-value)
Age (y)	-.099(.545)	.010(.923)	-.368*(.020)	.046(.651)
BP systolic (mm Hg)	-.084(.606)	.033(.744)	-.025(.881)	-.081(.425)
BP diastolic (mm Hg)	-.076(.641)	.105(.297)	.057(.726)	-.034(.740)
BMI (kg/m^2)	.129(.429)	.531** (.000)	.070(.668)	.012(.908)
Waist circumference (cm)	.103(.528)	.448**(.000)	.081(.617)	.010(.925)
FPG (mmol/L)	-.125(.444)	.043(.671)	-.232(.150)	-.047(.646)
HbA1c (%)	.140(.389)	.092(.361)	-.053(.746)	-.022(.829)
TC (mmol/l)	-.005(.975)	.055(.587)	-.017(.915)	-.047(.641)
TG (mmol/l)	.283(.077)	.075(.461)	.102(.530)	-.012(.909)
HDLc(mmol/l)	.076(.643)	.153(.127)	-.162(.319)	.040(.694)
LDLc(mmol/l)	-.032(.842)	-.005(.957)	.293(.066)	.028(.779)
Hs-CRP (mg/l)	1.000	1.000	.232(.150)	-.013(.898)
IL-6 (pg/ml)	.232(.150)	-.013(.898)	1.000	1.000

“BMI = body mass index, FPG = fasting plasma glucose, HBA1c = hemoglobin A1C, TC = total cholesterol, LDL-C = low-density lipoprotein cholesterol, HDL-C = high-density lipoprotein cholesterol, hs-CRP = high-sensitivity C-reactive protein, IL-6 = interleukin-6”

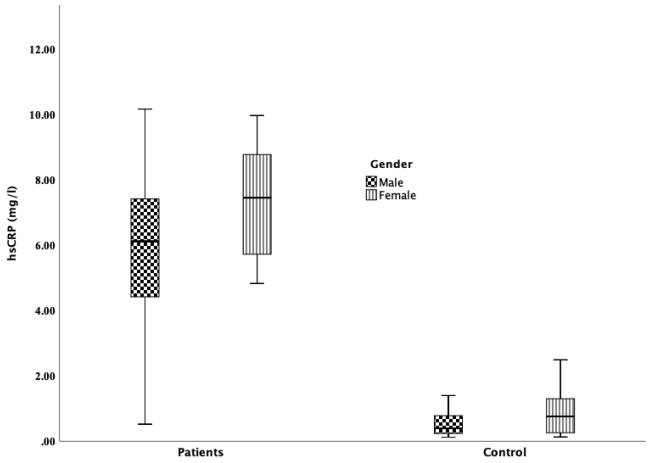

Fig 1 Gender-based comparison of hsCRP among patients and control groups (Clustered Boxplots)

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