Mediating Effect of C-reactive Protein and Aspartate Aminotransferase on Diabetes Mellitus and Myocardial Infarction Risk

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Abstract

Background: The relationship between diabetes and myocardial infarction has always been the focus of research, but it is not clear whether the DM-MI association is direct or mediated by other factors. Our hypothesis is that part of the risk of MI in DM patients may be mediated by CRP and AST. We examined this hypothesis in the mediation analysis and tried to assess the extent to which CRP and AST could explain the MI risk caused by DM.

Methods: This case-control study was conducted on 130 patients with MI and 130 patients with no-MI. We compared the relevant biochemical indicators of MI and no-MI patients, and applied mediation analysis to test the association of CRP and AST with DM-MI Potential adjustment effect.

Results: The study found that individuals who suffered MI were more likely to have DM as compared with Non-MI (OR = 2.117, 95%CI = 1.130-4.195, *P* = 0.020), and CRP and AST are positively correlated with the occurrence of MI, For every unit increase in CRP and AST levels, the risk level of MI Significantly increased by 1%, 3.1% respectively. The direct effect of DM and MI is 0.847, the mediating effect of CRP is 7.69% of the total effect, and the mediating effect of AST is 52.79% of the total effect. The mediation effect of the CRP-AST path is 0.386, accounting for 12.36% of the total effect. In the mediation model we verified, CRP and AST play a part of the mediation effect between DM with MI, and the total mediation effect accounts for 72.84%.

Conclusions: CRP and AST play an important role in the risk of DM-induced MI. This provides evidence for the mechanism and is of great significance for the exploration of therapeutic targets.

Background

Globally, Myocardial infarction (MI) has become the leading contributor to the burden of disease as assessed on the basis of disability-adjusted life-years[1], and MI accounts for about one million deaths in China annually[2]. There are many reasons for inducing MI, with environmental exposure, genetic risk factors and chronic disease interaction all affecting the risk[3]. Identifying the interaction of other diseases on MI may help to understand the related mechanisms of MI and prevent the development of the disease.

MI represents a typical sterile inflammation, which leads to rapid influx of inflammatory cells into the ischemic area, release of inflammatory cytokines, platelet activation and leukocytosis[4]. C-reactive protein (CRP) is a routinely detected biomarker at admission, and is considered to be the most typical marker for systemic inflammation in patients with acute coronary symptoms (ACS)[5]. The circulating concentration of CRP begins to elevate within 24 hours after acute myocardial infarction (AMI)[6]. The prognostic impact of elevated CRP at baseline was most evident during the first 6 months after MI[7]. Previous epidemiological studies found that c-reactive protein (CRP) value can often be used as predictors of myocardial infarction[8]. Aspartate aminotransferase (AST) is mainly derived from the heart; although, a significant portion is derived from other tissues, such as liver, red blood cells, and muscle. AST levels have been tested routinely in clinical practice for decades, Several studies have emphasized that liver insufficiency is a common accompaniment for patients with cardiovascular disease, and even examined the predictive value of transaminase on the morbidity and mortality of patients with cardiovascular disease[9, 10]. However, since most of these studies are on patients with chronic heart failure, only a few studies are on patients with significant MI. According to recent evidence, transaminase AST may represent predictive markers for patient outcome after AMI[11].

There is a close relationship between diabetes and cardiovascular disease. MI is a serious consequence of metabolic risk factors such as diabetes mellitus (DM)[12]. DM increases the incidence of MI and increases the risk of MI -induced mortality in diabetic subjects compared to non-diabetic subjects[13], According to statistics, the risk of acute myocardial infarction in patients with type 2 diabetes is 6 to 10 times higher than that of the entire population[14]. Diabetes is a metabolic disease with complex mechanisms. Studies have shown that CRP value and AST value are also associated with diabetes[15, 16]. Diabetic MI is a more severe inflammatory condition compared with non-diabetic MI, and the damage to liver function is more serious[17]. However, these studies did not consider the intermediate CRP and AST-related pathway on the process underlying a DM-MI association, and, little is known about the relationship between the levels of admission CRP and AST and myocardial infarction after the stratification of diabetes status (yes/no).

In this study, we sought to quantify the mediating role of CRP and AST in the association between the DM and MI in a Southern Chinese Han cohort. Secondly, we aimed to detect the predictive value of serum CRP and AST levels in patients with DM and MI during hospitalization, and the impact of related biochemical indicators on MI.

Methods

Study population

This is a case-control study that included 130 newly diagnosed MI and 130 coronary artery disease (CAD)-free controls who were living in Hefei and undergoing cardiac catheterization at the Fourth Affiliated Hospital of Anhui Medical University. All individuals were mainly Han Chinese from South China. Information on social demographic characteristics (such as gender and age), cigarette smoking and drinking habits were collected through questionnaires during recruitment. Two experienced cardiologists checked the medical records of all participants to confirm their clinical characteristics. According to ACCF/AHA criteria, MI was defined based on clinical symptoms, positive cardiac enzymes and typical electrocardiographic(ECG) changes[18, 19]. The diagnosis of DM the diagnostic criteria for diabetes recommended by the American Diabetes Association[20].

The case group and control group Exclusion criteria included (1) patients without Biochemical laboratory results, (2) those with prior atherosclerotic CVD (e.g., CAD, MI or peripheral vascular disease), (3) those with congenital heart disease, pulmonary heart disease, cardiomyopathy, valvular heart disease, (4) those with malignant tumors, (5) those with decreased liver function. The study was approved by the ethics committee of The Fourth Affiliated Hospital of Anhui Medical University and complied with the principles outlined in the Declaration of Helsinki.

Laboratory Data

Hypertension was defined as a systolic blood pressure ≥ 140 mmHg, a diastolic blood pressure 90 mmHg, or the use of antihypertensive drugs. DM was defined as a fasting blood glucose 7.0 mmol/L, or the use of glucose lowering medication[21].

Peripheral blood samples were obtained at the time of admission and the following were tested: CRP, creatinine, K^+, Na^+, Cl^-, Blood urea nitrogen (BUN). Total cholesterol(TC), triglyceride(TG), glucose, ALT, AST were measured after 12-hours fasting following admission. All blood samples were analyzed in the certified laboratory department of The Fourth Affiliated Hospital of Anhui Medical University. Serum CRP concentrations were quantified from Orion

Diagnostica Oy by immunoturbidimetry. The measuring range is 0.25-10 mg/l. Enzymatic methods were used to measure TG and TC concentrations. The intra- and inter-assay coefficients of variation are within the acceptable range pre-specified by the manufacturer.

Statistical Analysis

After testing for normality by the Kolmogorov-Smirnov test, the data were presented as Median (Q1, Q3). Categorical variables were summarized by using frequencies and percentages. Nonparametric tests (Mann-Whitney U) was used to compare numerical variables between the two groups. Chi-square test was performed to compare categorical variables, and Spearman correlation was used to analyze the relationship between biochemical indicators. A multivariate logistic regression model was used to estimate the odds ratio (OR) and 95% confidence interval (CIs) of DM and biochemical indicators. The model includes covariates related to MI: age, gender, drinking and smoking habits, and hypertension.

Mediation analysis was used to evaluate the mediation effect of CRP and AST between DM and MI. The mediation effect was tested with the PROCESS macro of SPSS[22]. In order to evaluate the mediating effect, the following four aspects must be analyzed: 1) Analyze the influence of the independent variable on the dependent variable; 2) Analyze the influence of the independent variable on the intermediate variable; 3) Analyze the influence of the independent variable and the intermediate variable on the dependent variable; 4) Analyze the impact between the two mediating variables. Since the intermediary variables CRP and AST to be verified in this study are continuous variables, we use bootstrap method to analyze the intermediary effect, and bootstrap sampling is selected 5000 times. In the verified mediation model, the bootstrap 95% confidence interval of the mediation variable does not include 0, which is considered to be the existence of a mediation effect. Proportion mediated was calculated as the ratio between the indirect effect and the total effect.

SPSS (Statistical Product and Service Solutions) 22.0 statistical software package and Stata 15.0 were used to analyze the data, and $P < 0.05$ was considered statistically significant.

Results

The baseline data of the participants included demographic characteristics, laboratory data, Smoking and drinking status, DM and hypertension diagnosis results. The median age of patients with MI and Non-MI were 70 years (56–78) and 71 years (56–78), of which males account for 67.69% of the total. Individuals who suffered MI were more likely to have DM as compared with Non-MI ($P < 0.01$), and MI patients have higher CRP levels ($P < 0.01$). TG concentrations in patients with MI is higher but there is no statistical difference ($P = 0.063$). There was no difference in other demographic characteristics (propensity score matching excluded the influence of smoking, drinking, gender and hypertension) (Table 1).

Table 1
Study population characteristics (N = 260)

Characteristics	MI (n = 130)	Non- MI (n = 130)	*P*-Value
Age [a]	70.00(56.00, 78.00)	71.00(56.00, 78.00)	0.992
Sex (N (%))			1.000
Male	88(50.0)	88(50.0)	
Female	44(50.0)	44(50.0)	
TG [a], mmol/L	1.25(0.90, 1.82)	1.09(0.80, 1.53)	0.063
TC [a], mmol/L	4.05(3.42, 4.81)	4.06(3.35, 4.59)	0.603
CRP [a], mg/L	14.07(3.51, 41.26)	2.07(0.70, 9.31)	0.001
Diabetes (N (%))			0.001
Yes	72(66.7)	36(33.3)	
No	58(38.2)	94(61.8)	
Hypertension (N (%))			1.000
Yes	59(50.0)	59(50.0)	
No	71(50.0)	71(50.0)	
Cigarette smoking (N (%))			0.358
Yes	47(54.0)	40(46.0)	
No	83(48.0)	90(52.0)	
Alcohol consumption (N (%))			0.634
Yes	23(47.0)	26(53.0)	
No	107(50.7)	104(49.3)	

CRP, C-reactive protein ; TG, triglyceride; TC, total cholesterol; [a] Median (Q1 - Q3).

As shown in Table 2, Spearman correlation analysis between biochemical indicators was performed, statistically significant Spearman correlations were identified between some indicators. The degree of association between MI with DM and biochemical indicators was investigated using multinomial logistic regression. After controlling for confounding variables such as age, gender, smoking, drinking, and hypertension, the results are shown in Table 3: Exposure to DM increases the risk of MI (OR = 2.117, 95%CI = 1.130–4.195, *P* = 0.020), CRP, AST, creatinine and TG are all positively correlated with the occurrence of MI. For every unit increase in CRP, AST, creatinine and TG levels, the risk level of MI Significantly increased by 1%, 3.1%, 1.2%, 49.7%, respectively. Other biochemical indicators have no correlation with the risk of MI.

Table 2
Spearman correlation coefficients of biochemical indicators

Biochemical indicators	ALT	AST	BUN	Creatinine	TC	TG	K	Na	Cl
CRP	0.194**	0.242**	0.324**	0.293**	-0.077	-0.046	0.034	-0.247**	-0.219**
ALT		0.672**	0.015	0.075	0.034	0.208**	-0.067	-0.178**	-0.132**
AST			0.090	0.147**	-0.040	-0.007	-0.037	-0.206**	-0.163**
BUN				0.574**	-0.024	-0.130*	0.175**	-0.164**	-0.126*
Creatinine					-0.143*	-0.122	0.193**	-0.129*	-0.062
TC						0.347**	0.004	0.001	-0.037
TG							-0.110	0.106	0.029
K								-0.084	0.059
Na									0.584**

*P< 0.05, *P< 0.01

Table 3
Logistic regression analysis of influencing factors of myocardial infarction

Variable	Multivariate adjusted Model [a]	
	OR (95%CI)	*P*
Diabetes	2.117(1.130, 4.195)	0.020
CRP	1.010(1.000, 1.020)	0.047
ALT	1.001(0.979, 1.024)	0.920
AST	1.031(1.011, 1.052)	0.002
BUN	0.904(0.790, 1.035)	0.143
Creatinine	1.012(1.000, 1.023)	0.043
TC	0.863(0.637, 1.168)	0.339
TG	1.497(1.025, 2.186)	0.037
K	1.151(0.576, 2.299)	0.690
Na	0.935(0.830, 1.053)	0.269
Cl	0.982(0.896, 1.076)	0.701

OR, odds ratio; CI, confidence interval;

[a] Adjusted for maternal age, sex, hypertension, cigarette smoking, alcohol consumption

Mediation analysis was performed to test whether the observed associations between DM and MI could be explained by biochemical indicators, so we adopted the SPSS macro program (PROCESS) to test the mediating effect of CRP and AST between DM and MI. Model 6 is used to calculate the indirect effects explained by CRP and AST and the direct effects applied through DM. The results are shown in Table 4: The direct effect of DM and MI is 0.847, the mediating effect of CRP is 0.240, and the mediating effect of CRP is 7.69% of the total effect; the mediating effect of AST is 1.647, and the mediating effect of AST is 52.79% of the total effect. Since the path between CRP and AST is significant ($P < 0.05$), it indicates the existence of chain mediation. The mediation effect is multiple mediation effects (Fig. 1 for the mediation effect test model). The mediation effect of the CRP-AST path is 0.386, accounting for 12.36% of the total effect. In the mediation model we verified, there are significant statistical differences between direct and indirect effects. CRP and AST play a part of the mediation effect between DM with MI, and the total mediation effect accounts for 72.84%.

Table 4
Mediation analysis of the association between diabetes mellitus and myocardial infarction risk mediated by CRP and AST

	Step1-a	Step2-b	Step3-c'	Mediation effect	Mediation effect percentage(%)
CRP	25.314 (11.655, 38.973)**	0.010 (0.001, 0.018)*	0.847 (0.232, 1.463) **	0.240 (0.053, 0.623)	7.69%
AST	53.054 (7.209, 98.899)*	0.031 (0.013, 0.049)**	0.847 (0.232, 1.463)**	1.647 (0.004, 2.090)	52.79%
CRP-AST	25.314 (11.655, 38.973)**	0.031 (0.013, 0.049)**	0.847 (0.232, 1.463)**	0.386 (0.004, 2.090)	12.36%

Note: Step1-a refer to the effect of the independent variable on the mediated variable; Step2-b refer to the effect of the mediated variable on the dependent variable; Step3-c' refer to the effect of direct effect of the independent variable on the dependent variable. $^{**}p < 0.01$, $^{*}p < 0.05$.

Discussion

In this latest study based on the Southern Chinese cohort, we used the mediation model to check whether CRP and AST act as mediators in the association between DM and MI. Both CRP and AST are significantly related to MI, and DM has a highly significant direct impact on MI risk. The results show that most of the effects of DM are mediated through CRP and AST, and this indirect effect of CRP and AST accounts for about two-thirds of the risk of MI caused by DM.

Advanced statistical models may be important for accurately assessing the impact of multifactorial diseases, including the interactions between diseases and the regulatory effects of intermediate mediators on diseases. Mediation analysis is a promising method, which has been widely used in social science research and psychological research in the past[23], and can be used to determine possible mechanisms that mediate influencing factors-disease associations. It can flexibly explain the extent to which the influence of independent variables on the results can be mediated by potential potential intermediaries. It can also assess potential biases caused by exposure-mediation interactions, which are difficult to resolve with traditional methods. Serum CRP and AST values are independent predictors of mortality in patients with MI and have predictive value for the occurrence of MI. However, there are limited studies on the relationship between CRP and AST and MI patients after

stratification by DM status (yes/no). Previous studies have showed that the increase in CRP value at admission is a risk sign of MI in DM patients[24], and the relationship between AST and MI has always been concerned[25]. In the current study, CRP value and AST value are predictors of MI in diabetic and non-diabetic patients. In addition, our research further illustrates the mediating effect of CRP and AST between DM and MI.

CRP is mainly secreted by the liver and responds very quickly to infections, inflammatory diseases and tissue ischemia. The influence of inflammation on cardiovascular events has always been a key issue in clinical research. In the Canakinumab Anti-inflammatory Thrombosis Outcome Study (CANTOS), it was found that treatment with canakinumab (a monoclonal antibody that selectively neutralizes interleukin-1β) resulted in fewer cardiovascular events than placebo[26], patients with the greatest decrease in CRP levels experienced the greatest decrease in major cardiovascular events[27], and our study also found that the CRP value of no-MI patients is lower than that of MI patients, indicating that CRP may be the target of this benefit[28]. A cross-sectional study showed that AST was positively correlated with the risk and severity of early coronary heart disease, suggesting that these enzymes can be used as surrogate markers of cardiovascular risk[29]. Studies have shown that AST is related to the risk of myocardial infarction, the reduction of AST level can reduce the initial infarct size and fundamentally change the inflammatory response pattern of damaged myocardium[30]. The results of this study are the same as ours, AST is positively correlated with the risk of MI.

We found that DM, CRP, and AST have a significant correlation in MI risk, which is consistent with the mediating effect of CRP and AST between DM and MI. However, we also found that creatinine is also significantly related to the risk of MI. Although the chance of discovery cannot be ruled out, a previous study found that compared with DM patients with increased serum creatinine during follow-up, DM patients with increased serum creatinine The risk of MI is increased[31], and this result is consistent with our findings. However, we did not find that creatinine has a mediating effect between DM and MI. This may be because creatinine affects the occurrence of MI risk through other channels, and ethnic differences also have a certain impact on the results. The results of the correlation analysis between TG and MI risk are also consistent with previously reported, that the increase in serum TG level causes an increase in MI risk[32], but we also found that there was no significant difference in TG levels between MI and no-MI patients ($P > 0.05$), and TG had no mediating effect between DM and MI.

AST plays the main mediating effect in the DM-MI association, and the DM-MI mediating effect mediated by CRP only accounts for 7.69%. Although the DM-MI association is not mainly mediated by CRP, it can significantly enhance the mediating effect of AST in the presence of CRP, which is reflected by the synergy of CRP and AST in the risk of DM-MI. The mechanism by which DM increases the risk of MI is still unknown. It may be through inflammation to increase the risk of MI. This is due to the high expression of CRP leading to greater inflammation and the myocardial inflammation induced by AST. A previous report supports our view, which shows that high expression of inflammatory factors in diabetic patients is significantly associated with an increased risk of MI[33].

To our knowledge, this is the first study to use mediation analysis to study the mechanism of DM-induced MI in a case-control study. The advantage of our research lies in the use of intermediary analysis beyond traditional analysis, which can provide more causal explanations for the interaction between disease and disease for specific hypotheses, and mediation analysis is a powerful tool to disentangle direct and indirect effects, which can provide insights on mechanisms[34]. The existence of chain intermediary explains the interaction between the factors that affect the disease, which is more comprehensive for the discovery of the mechanism. We performed coronary angiography on all participants to avoid misclassification of asymptomatic CAD and other heart diseases that may show symptoms similar to MI (such as pericarditis and cardiomyopathy).

There are several limitations to this study. First, we only studied some biochemical indicators and traditional cardiovascular risk factors, and smoking and drinking status are self-reported, which may be misclassified due to memory errors, and exposure through passive smoking is not included in the model, which may affect the results to a certain extent[35]. Therefore, the influence of unmeasured mediator-outcome confounding factors or the interaction between exposure factors and intermediary can not be ruled out. These may play a role effect in the research. Some other influencing factors (such as obesity, environmental factors, eating habits, etc.) may also affect the development of DM-MI in the same direction, which would result in changes in the degree of direct effect and indirect effects. CRP and AST only represent part of the mediating effects, which may include more complex mediating effects and unresearched regulatory effects. Therefore, it may overestimate the mediating effect of CRP and AST on the association of DM-MI, and the discovery of more mediators associated with DM-MI is of great significance for improving the predictive ability of CRP and AST and as a reference for the treatment of diseases. Finally, the study mainly included individuals of Han ethnicity in South China, so it is not clear whether these findings can be generalized to other populations.

Conclusions

In summary, we found that CRP and AST seem to be an important way for DM to induce the risk of MI, and CRP and AST can explain the association between DM-MI to a greater extent. Mediation analysis provides new insights that affect the interaction between diseases, and may be important for both disease research and treatment targets. Further research will provide more insights into the interaction mechanism of these two common chronic diseases and may help explain our findings.

Abbreviations

MI
Myocardial infarction; DM:diabetes mellitus; CRP:C-reactive protein; AST:Aspartate aminotransferase; ALT:Alanine aminotransferase; ACS:acute coronary symptoms; ECG:electrocardiographic; BUN:Blood urea nitrogen; TC:Total cholesterol; TG:triglyceride; CAD:coronary artery disease;

Declarations

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Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on request.

Authors' contributions

HZ, MMJ and HZ made main contribution to design of the study, drafted the manuscript, and performed the statistical analysis and participated. ZPL and QJ performed data collection. SH, CS and LZ helped conduct the

literature review and prepared part of the Discussion section of the text. ZPC, WJ and JFH participated in the design and coordination of the study and participated in the data collection. All authors have read and approved the final manuscript.

Competing Interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

Consent for publication

Not applicable.

Ethics Approval and Consent to Participate

The research protocol has been approved by the Ethics Committee of the Fourth Affiliated Hospital of Anhui Medical University and has followed the specifications of the Declaration of the Helsinki World Association. All patients gave written informed consent.

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Figures

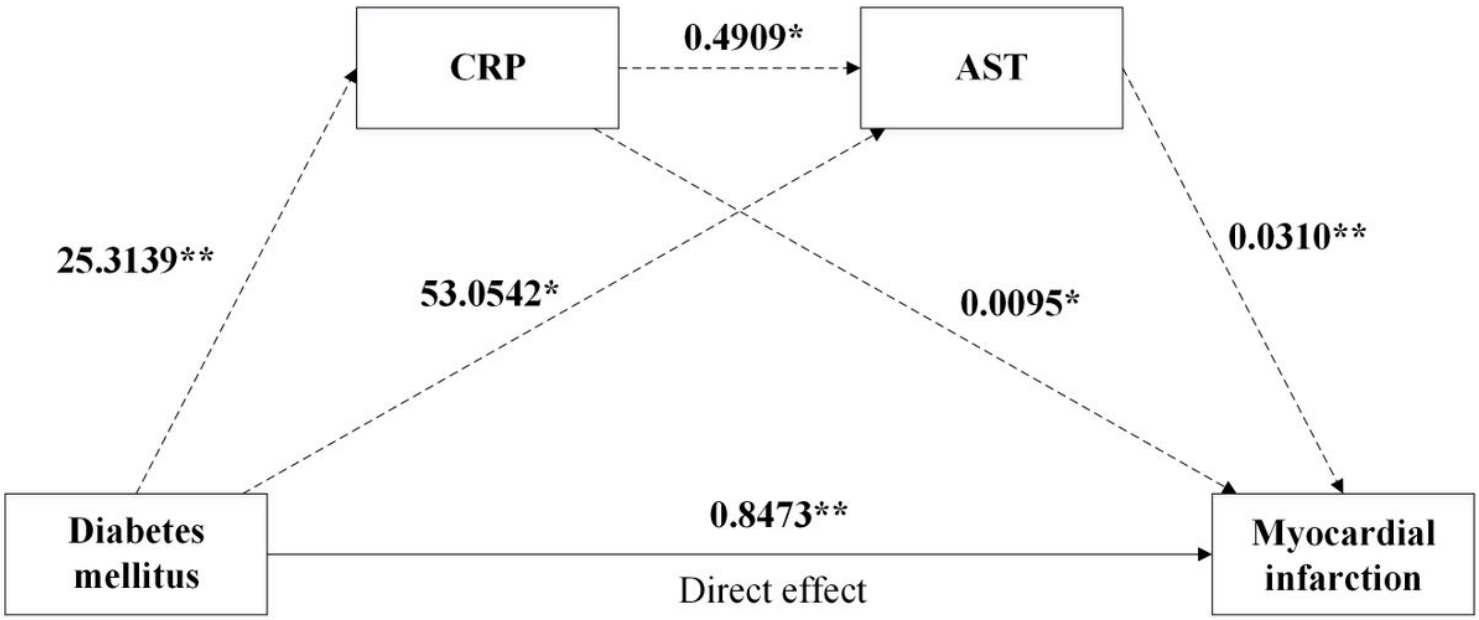

Figure 1

Mediation analysis of the effect of C-reactive protein (CRP) and Aspartate aminotransferase (AST) on the association between diabetes mellitus (DM) and myocardial infarction (MI).