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Original Article

Study of the association of the novel cardiac biomarkers copeptin, MR-proANP, and MR-proADM with coronary artery disease and risk of type 2 diabetes mellitus in a Chinese Han population: a case-control study

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Abstract: Background: C-terminal provasopressin (copeptin), midregional pro-atrial natriuretic peptide (MR-proANP), and midregional pro-adrenomedullin (MR-proADM) are novel cardiac biomarkers associated with patients' prognosis in heart failure, stable ischemic disease, and acute coronary syndrome. We aimed to evaluate the inner correlation between these 3 biomarkers, their association with clinical phenotypes of coronary artery disease (CAD), and the risk of type 2 diabetes mellitus (T2DM) in the Chinese Han population. Methods: The study included 262 patients with CAD, including 27 with old myocardial infarction, 55 with acute myocardial infarction, and 180 with stable CAD. Controls included 130 subjects without CAD. Pearson's correlation coefficient r was calculated to test the associations between the 3 biomarkers and the main continuous variables. Multivariable logistic regression analysis was performed to identify the predictive factors of T2DM. Results: Patients with CAD and non-CAD controls had similar values of copeptin, MR-proANP, and MR-proADM. Compared with non-CAD controls, stable angina pectoris, or old myocardial infarction, those with acute myocardial infarction had the highest levels of copeptin (P=0.030); the group with old myocardial infarction had the highest and the group with acute myocardial infarction had the lowest MR-proANP (P=0.007). There were no significant differences with regards to MR-proADM among the 4 groups (P=0.118). Copeptin, MR-proANP, and MR-proADM were positively correlated with each other, and MR-proANP was positively correlated with hemoglobin and total bilirubin. Compared with subjects without T2DM, those with T2DM had higher values of copeptin and lower values of MR-proADM (all P<0.05). Patients with and without T2DM had comparable levels of MR-proANP. Multivariable regression analysis identified copeptin as a risk predictor (OR: 1.107, 95% CI: 1.017-1.205, P=0.018) and MR-proADM as a protective factor (OR: 0.940, 95% CI: 0.902-0.980, P=0.003) of T2DM. Conclusions: Copeptin and MR-proANP are associated with clinical phenotypes of CAD. Copeptin is a risk factor and MR-proADM a protective factor of T2DM in the Chinese Han population.

Keywords: Coronary artery disease (CAD), type 2 diabetes mellitus (T2DM), cardiovascular risk, biomarkers, copeptin, MR-proANP, MR-proADM, risk assessment

Introduction

Though great progress has been made in the prevention and treatment of cardiovascular diseases (CVDs), coronary artery disease (CAD) is still the leading cause of mortality and morbidity in both developing and developed countries. In particular, the prevalence of CAD has increased with the aging population in the past 20-30 years in China, the largest developing country in the world [1, 2]. Patients with CAD are at greater risk for a subsequent acute myocardial infarction (AMI) and sudden cardiac death; therefore, the identification of sensitive and specific biomarkers of unstable CAD could obviously help in detecting these vulnerable patients earlier so they can be treated with guideline-recommended medications or inter-

ventions to decrease the subsequent cardiovascular risks [3-10].

Fortunately, more novel biomarkers are emerging for the earlier diagnosis of acute coronary syndrome (ACS), including copeptin, MR-proANP, and MR-proADM [3-5]. Moreover, it has been proven that aggressive use of evidence-based prevention strategies for CVD can add millions of quality-adjusted life-years to the adult population in America and lengthen the average lifespan by at least 1.3 years [11].

Despite the above-mentioned progress in early risk stratification and therapy choices among patients with ACS and stable CAD, shortcomings and discrepancies still remain between different populations in the use of these novel biomarkers for earlier diagnosis and risk assessment [12-16]. Even so, among these 3 novel biomarkers, copeptin is evaluated more often than the other 2, and its negative predictive value has been well verified when combined with cardiac troponin T [16-18]. Moreover, MR-proANP and MR-proADM are predictors of adverse cardiac events in patients with type 2 diabetes mellitus (T2DM) [19].

Despite advances in early risk stratification and accurate diagnosis, it is unknown whether these 3 markers are internally related or associated with clinical phenotypes of CAD and risk of T2DM to an identical extent. Therefore, this study was performed to determine the associations between the 3 biomarkers, copeptin, MR-proANP, and MR-proADM, and clinical phenotypes of CAD and risk of T2DM in Chinese Han patients with CAD.

Methods

Study subjects

This was a hospital-based case-control study. From January 2013 to December 2015, 392 consecutive patients were enrolled from the Department of Cardiology, Shanghai Jiaotong University Affiliated Sixth People's Hospital East Campus, China. The study included 262 patients with CAD; 27 of these had old myocardial infarction (OMI), 55 had acute myocardial infarction (AMI), and 180 had stable CAD. CAD was defined as stenosis (≥50%) in at least one of the 3 main coronary arteries or their major branches assessed by coronary angiography (CAG) or a history of myocardial infarction (MI) defined according to World Health Organization criteria. Stable and unstable CAD, AMI, and OMI were defined according to available guidelines [20-22]. Controls included 130 subjects without CAD. The exclusion criteria included congenital heart disease, severe liver or kidney disease, a contraindication for the use of iodinated contrast, and noncoronary artery thrombotic disease. The Medical Ethics Committee of Shanghai Jiaotong University Affiliated Sixth People's Hospital East approved this study [NO. 2016-006]. Each patient gave his/her written informed consent before the study began. The main authors had access to information that could identify individual participants during and after data collection.

Coronary angiography and stenosis determination

All participants underwent elective CAG during hospitalization for concern of CAD. Two cardiologists evaluated the degree of stenosis in the 3 main coronary arteries and their main side branches, respectively, with their consensus as the final results.

Clinical parameters and risk factors

Clinical data including age, sex, heart rate, systolic and diastolic blood pressure, alcohol consumption, and risk factors including hypertension, T2DM, and smoking status were collected. Fasting blood sugar (FBS), hemoglobin, uric acid, creatinine, total and direct bilirubin, and plasma concentrations of total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) were determined with an automatic chemistry analyzer (Synchron Clinical System LX20, Beckman Coulter, CA, USA). The methods used to determine hypertension, T2DM, and smoking status have been previously described [23].

Detection of concentration of copeptin, MR-proANP, MR-proADM

Venous blood samples were collected immediately after hospitalization, and plasma concentrations of copeptin, MR-proANP, and MR-proADM were determined in May 2016 using ELISA

Table 1. Summary of baseline characteristics between patients with CAD and non-CAD controls

	Non-CAD controls (n=130)	CAD patients (n=262)	P
Age, years	59.93±12.08	67.67±11.00	0.000
Copeptin, pmol/L	2.23±1.42	3.23±2.05	0.073
MR-proANP, pg/mL	175.57±55.21	172.58±59.35	0.899
MR-proADM, pg/mL	9.37 ±3.20	11.60±4.51	0.111
Weight, kg	66.25±13.18	57.63±12.86	0.011
SBP, mmHg	134.55±16.28	136.16±18.10	0.401
DBP, mmHg	81.91±10.26	79.12±10.67	0.014
HR, bpm	74.52±15.78	73.82±12.75	0.642
Total bilirubin, μmol/L	12.11±6.18	12.40±6.28	0.699
Direct bilirubin, μmol/L	4.22±2.35	4.27±1.72	0.814
Hemoglobin, g/L	137.30±17.59	133.03±17.58	0.025
Uric acid, mmol/L	294.08±97.31	324.83±105.12	0.005
Creatinine, μmol/L	69.67±23.44	94.28±36.24	0.000
Male, n (%)	52 (40.0)	164 (62.6)	0.000
Smoking, n (%)	22 (16.9)	94 (35.9)	0.000
Alcohol consumption, n (%)	6 (4.6)	34 (13.0)	0.010
Hypertension, n (%)	77 (59.2)	195 (74.4)	0.002
T2DM, n (%)	17 (13.0)	80 (30.5)	0.000

Data are expressed as the number of individuals (percentage in parentheses) or the mean ± SD, as appropriate. Abbreviations: AMI, acute myocardial infarction; CAD, coronary artery disease; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; HR, heart rate; LDL-C, low-density lipoprotein cholesterol; OMI, old myocardial infarction; SAP, stable angina pectoris; SBP, systolic blood pressure; T2DM, type 2 diabetes mellitus; TC, total cholesterol; TG, triglyceride.

kits (Shanghai Jianglai Co. Ltd. China), according to the manufacturer's instructions.

Statistical analyses

We used SPSS 19.0 software (SPSS, Chicago, IL, USA) for statistical analysis. Normally distributed data were presented as means ± standard deviation. Comparisons between groups were performed using the student *t*-test or one-way ANOVA. The significance of inter-group differences for categorical variables was determined using the chi-square test. Pearson's correlation coefficient r was calculated to test the associations among the variables copeptin, MR-proANP, MR-proADM, age, body mass index, main plasma lipid parameters, uric acid, and creatinine. Multivariable logistic regression analysis was performed to identify potential factors associated with the risk of T2DM. In this process, T2DM was used as the dependent variable, and the independent variables included both categorical and continuous variables. Two-tailed *P* values <0.05 were considered statistically significant.

Results

Comparison of baseline characteristics between CAD patients and non-CAD controls

A total of 392 subjects were enrolled, including 262 with CAD and 130 non-CAD controls. **Table 1** summarizes the basic characteristics of the study subjects. Compared with controls without CAD, patients with CAD had higher values for average age, uric acid, creatinine, lower values of hemoglobin, DBP and weight (all P< 0.05). Furthermore, the group with CAD also had higher ratios of the male sex, T2DM, hypertension, smoking, and alcohol consumption (all P<0.05). In spite of the differences noted above, participants with CAD and non-CAD controls had similar levels of copeptin, MR-proANP, MR-proADM, and total and direct bilirubin levels (all P> 0.05). Furthermore, the 2 groups had similar values for SBP and heart rate (all P>0.05).

Comparison of levels of copeptin, MR-proANP, MR-proADM, among non-CAD controls and 3 groups with different CAD phenotypes

All study subjects were divided into 4 groups as non-CAD controls, SAP, OMI, and AMI. **Table 2** summarizes the average values of these 3 indexes in the 4 groups, respectively. Compared with non-CAD controls, SAP or OMI, those with AMI had the highest levels of copeptin (P=0.030); the group with OMI had the highest and the group with AMI had the lowest MR-proANP (P=0.007). There were no significant differences with regards to MR-proADM among the 4 groups (P=0.118).

Correlation analysis of copeptin, MR-proANP, MR-proADM, and main clinical parameters

Pearson's correlation coefficient r was calculated to test the associations among copeptin, MR-proANP, MR-proADM, and other main continuous parameters. Analysis showed that copeptin, MR-proANP, and MR-proADM were positively correlated with each other (all

Table 2. Comparison of values of copeptin, MR-proANP, MR-proADM among non-CAD controls and 3 groups with different CAD phenotypes

	Controls (n=130)	SAP (n=180)	OMI (n=27)	AMI (n=55)	P
Markers					
Copeptin	2.23±1.42	2.20±1.63	3.30±1.30	7.17±2.23	0.030
MR-proANP	175.57±55.21	169.58±58.42	233.24±86.88	123.44±69.81	0.007
MR-proADM	9.37 ±3.20	9.49±3.34	13.55±3.57	14.29±3.29	0.118

Table 3. Correlation analysis of copeptin, MR-proANP, and MR-proADM and main clinical parameters

	Copeptin	MR-proANP	MR-proADM	Hemoglobin	Total bilirubin
Copeptin, r (p)	--	0.354 (0.000)	0.779 (0.000)	0.037 (0.464)	0.063 (0.216)
MR-proANP, r (p)	0.354 (0.000)	--	0.521 (0.000)	0.100 (0.049)	0.149 (0.003)
MR-proADM, r (p)	0.779 (0.000)	0.521 (0.000)	--	0.065 (0.199)	0.094 (0.062)

Table 4. Summary of baseline characteristics between T2DM and non-T2DM subjects

	Non-T2DM (n=295)	T2DM (n=97)	P
Age, years	63.96±12.22	68.04±10.66	0.003
Copeptin, pmol/L	2.68±1.02	3.16±1.27	0.009
MR-proANP, pg/mL	184.13±44.51	161.48±58.06	0.093
MR-proADM, pg/mL	11.93 ±3.48	7.79±2.57	0.015
Weight, kg	61.12±6.52	58.53±7.09	0.483
SBP, mmHg	135.07±19.96	137.31±17.24	0.281
DBP, mmHg	80.72±10.87	77.98±9.49	0.027
HR, bpm	73.23±13.34	76.51±14.95	0.044
Total bilirubin, μmol/L	12.61±6.25	11.38±6.16	0.091
Direct bilirubin, μmol/L	4.26±1.82	4.25±1.30	0.982
Hemoglobin, g/L	136.50±16.72	128.18±19.07	0.000
Uric acid, mmol/L	313.82.08±100.55	317.09±112.49	0.005
Creatinine, μmol/L	79.68±31.85	105.67±68.07	0.000
TC, mmol/L	4.62±1.76	4.46±1.14	0.403
TG, mmol/L	1.53±0.82	1.98±1.60	0.000
LDL-C, mmol/L	2.59±0.70	2.62±0.79	0.837
HDL-C, mmol/L	1.18±0.25	1.18±0.27	0.942
Male, n (%)	169 (57.3)	47 (48.4)	0.121
Smoking, n (%)	88 (29.8)	28 (28.9)	0.957
Hypertension, n (%)	197 (66.8)	75 (77.3)	0.051
Grouped by CAD or not			0.000
Non-CAD, n (%)	113	17	
SAP, n (%)	131	49	
AMI, n (%)	33	22	
OMI, n (%)	18	9	

See **Table 1** for abbreviations.

P<0.01). Furthermore, MR-proANP was positively correlated with hemoglobin (r=0.1, P=0.049) and total bilirubin (r=0.149, P=0.003). However, there were no other correlations between these 3 indexes and other continuous indexes (**Table 3**).

Comparison of characteristics between T2DM patients and non-T2DM subjects

Compared with non-T2DM subjects, patients with T2DM had higher values of copeptin and average age, uric acid, creatinine, and heart rate (all P<0.05). Furthermore, the group with T2DM had lower values for MR-proADM, hemoglobin, and DBP and a higher ratio of OMI and AMI (all P<0.05). In spite of these differences, subjects with T2DM and non-T2DM had comparable levels of MR-proANP, total and direct bilirubin, TC, LDL-C, and HDL-C (all P>0.05). Moreover, the 2 groups had similar ratios for male sex and smoking (all P>0.05), and a borderline significance for hypertension (P=0.051) (**Table 4**).

Multivariable regression analysis of predictors of T2DM

After adjustment for sex, hypertension, smoking, SBP, DBP, and other continuous parameters, 3 factors were identified as predictors of T2DM. These 3 factors were risk factors copeptin (OR: 1.107, 95% CI: 1.017-1.205, P=0.018) and TG (OR: 1.526,

Table 5. Multivariable regression analysis of predictors of T2DM

Variables	B	P	OR	95% CI
Copeptin	0.102	0.018	1.107	1.017-1.205
MR-proADM	-0.062	0.003	0.940	0.902-0.980
TG	0.423	0.001	1.526	1.193-1.952
Creatinine	0.006	0.057	1.006	1.000-1.011

See **Table 1** for abbreviations.

95% CI: 1.193-1.952, P=0.001), and protective factor MR-proADM (OR: 0.940, 95% CI: 0.902-0.980, P=0.003) (**Table 5**).

Discussion

This study explored the internal correlation among 3 novel cardiac biomarkers, copeptin, MR-proANP, and MR-proADM, and their association with clinical phenotypes of CAD and the risk of T2DM. In addition to the significance of copeptin, MR-proANP, and MR-proADM being verified as internally correlated, copeptin and MR-proANP were found to be associated with clinical phenotypes of CAD. Furthermore, copeptin and MR-proADM were found to be risk and protective predictors of T2DM, respectively, in the Chinese Han patients.

More recently, novel biomarkers of hemodynamic stress have been proven to be useful for the earlier diagnosis of ACS, among which copeptin, MR-proANP, and MR-proADM are especially helpful in early risk stratification, diagnosis, and prognosis prediction [3-5]. Moreover, copeptin levels are associated with infarction size and heart function in ST-elevation myocardial infarction (STEMI) [24]. However, the diagnostic or prognostic value of these biomarkers was not consistent in patients with heart failure (HF) [25] or ACS [12-14, 16, 26].

Copeptin, MR-proANP, and MR-proADM act more often as biomarkers of myocardial stress and structural changes, and it is reasonable to observe their elevations in the early stage of AMI. In the present study, although CAD patients and non-CAD controls had similar levels of copeptin, MR-proANP, and MR-proADM, compared with that in non-CAD controls and SAP, those with AMI had the highest levels of copeptin; the OMI group had the highest and the AMI group had the lowest MR-proANP. Even in the large sample study by O'Donoghue et al [26], after adjustment for coexisting variables and using a dichotomous cut point, it was MR-proANP, not copeptin or MR-proADM, that was significantly associated with a higher risk of cardiovascular death or HF. In spite of the available data, the optimal multimarker strategy for CAD diagnosis and prognosis prediction remains undefined.

In our study, Pearson's correlation coefficient r was calculated to test the associations among copeptin, MR-proANP, MR-proADM, and other main continuous parameters. The results showed that copeptin, MR-proANP, and MR-proADM were positively correlated with each other, which was consistent with results previously reported [26]. More interestingly, in this study, we found that MR-proANP was positively correlated with both hemoglobin and total bilirubin, which partially supports the findings of Maier et al [19]. Serum bilirubin and heme oxygenase were found to be internally correlated and elevated in AMI but not in non-AMI patients, which might reflect formation of high collateral flow [27]. However, inconsistent results also exist. In the study by Acet et al, results show that higher total bilirubin predicts poor infarct-related artery patency [28]. Furthermore, in another small sample study, total bilirubin was found to be decreased in AMI patients [29]. The real relationship between MR-proANP, hemoglobin, and bilirubin or its mechanism warrants further research.

In assessment of future risk of cardiovascular events, T2DM is recognized as equivalent to CAD. T2DM is associated with increased 12-month major adverse cardiovascular events in AMI patients with lower values of left ventricular ejection fraction (LVEF <40%) [30]. In this study, compared with non-T2DM subjects, T2DM patients had higher values of copeptin and heart rate levels, a higher ratio of OMI and AMI as well as lower levels of MR-proADM, hemoglobin, and DBP. Altered heart rate variability during daily life is linked to insulin resistance [31]. Higher heart rate partially reflects diabetic cardiovascular autonomic neuropathy, which is closely associated with T2DM and could lead to increased risk of AMI, in-hospital mortality, reduced LVEF, and sudden cardiac death [32-34]. A recent study also shows that, compared with neonates delivered from moth-

ers with type 1 or gestational diabetes, those born to mothers with T2DM have the lowest levels of MR-proANP [35]. In the present study, patients with and without T2DM had similar levels of MR-proANP. After adjustment for coexisting factors, copeptin and TG were identified as risk predictors and MR-proADM as a protective factor of T2DM. Our study results partially support the association between hypertriglyceridemia, insulin resistance, and T2DM [36]. With regards to the emerging prevalence of T2DM, these novel findings might have important values for clinical practice.

This study has both strengths and limitations. First of all, the relatively small study sample and one time point detection of these 3 cardiac markers might limit the power of the study; secondly, because this is a hospital-based case-control study and all subjects were enrolled from one tertiary hospital, the study population does not represent the general population. Even so, the strength of our study is that all subjects underwent elective CAG and thus all had a definite and accurate diagnosis, which enhances the quality of the study design. Finally, we did not evaluate the relation between these indexes and LVEF values, and our study also lacks causal evidence and long-term follow-up data, which restrict the interpretation of these results.

Conclusions

We have reported, for the first time, that besides being internally related, copeptin and MR-proANP are associated with clinical phenotypes of CAD. Furthermore, copeptin is a risk factor and MR-proADM a protective factor for T2DM in the Chinese Han population studied. These findings reveal novel evidence linking CAD and T2DM and offer additional value for our daily practice.

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Disclosure of conflict of interest

None.

Abbreviations

ACS, acute coronary syndrome; AMI, acute myocardial infarction; CAD, coronary artery disease; CAG, coronary angiography; CVDs, cardiovascular diseases; DBP, diastolic blood pressure; FBS, fasting blood sugar; HDL-C, high-density lipoprotein cholesterol; HR, heart rate; LDL-C, low-density lipoprotein cholesterol; MR-proADM, midregional pro-adrenomedullin; MR-proANP, midregional pro-atrial natriuretic peptide; OMI, old myocardial infarction; SAP, stable angina pectoris; SBP, systolic blood pressure; SD, standard deviation; T2DM, type 2 diabetes mellitus; TC, total cholesterol; TG, triglyceride.

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