Abnormal glucose regulation in Chinese patients with coronary artery disease

A cross-sectional study

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Abstract

The purpose of this study was to investigate the prevalence of abnormal glucose regulation (AGR) in patients with established coronary artery disease (CAD), and the association of AGR and acute coronary events in Chinese patients.

A total of 3441 hospitalized patients with established diagnosis of CAD were recruited from 41 centers in 25 cities of China. Oral glucose tolerance test (OGTT) was performed in 2112 patients without known diabetes. Acute coronary events were recorded for the patients.

AGR was detected in 1880 (89%) patients in the OGTT cohort, with 1265 (59.9%) diagnosed with impaired glucose tolerance, 363 (17.2%) diagnosed with diabetes, and 30 (1.4%) diagnosed with isolated impaired fasting glucose. The overall proportion of patients diagnosed with diabetes increased from 30.7% (n = 930) at baseline to 42.6% (n = 1298) following the OGTT analysis. In total 85% (n = 3047) patients in the study was diagnosed with AGR. Multivariate analysis showed that AGR was independently associated with acute coronary events, after adjusting for the traditional risk factors including age, smoking, hypertension, and hyperlipidemia.

The prevalence of AGR is increasing in Chinese patients with CAD, as compared with previous report. AGR was independently associated with acute coronary events. Prospective studies are warranted to evaluate the benefit of intervening prediabetes in adult patients with CAD.

Abbreviations: ACS = acute coronary syndrome, AGR = abnormal glucose regulation, CAD = coronary artery disease, CGI = combined glucose tolerance, DM = diabetes mellitus, IGT = impaired glucose tolerance, I-IFG = isolated impaired fasting glucose, I-IGT = isolated impaired glucose tolerance, OGTT = oral glucose tolerance test, OR = odds ratio, PCI = percutaneous coronary intervention.

Keywords: abnormal glucose regulation, acute coronary events, coronary artery disease

1. Introduction

Coronary artery disease (CAD) is the leading cause of death worldwide.[1] Type 2 diabetes is a major risk factor for CAD, and patients with type 2 diabetes have twice the annual mortality rate owing to CAD of non-diabetic individuals. Furthermore, the incidence and severity of CAD events are higher in diabetic patients.[2] On the other hand, abnormal glucose tolerance was almost twice as common among patients with acute myocardial infarction as in matched controls.[3] It has been recently confirmed that the period of time prior to the development of diabetes, when patients have impaired glucose tolerance (IGT),

may also predispose them to increased cardiovascular risk,[4,5] suggesting abnormal glucose regulation (AGR) is a continuous risk factor for CAD.

Cumulating studies reported a higher prevalence of AGR in patients with CAD comparing with general population. The Euro Heart Survey showed that two-thirds of patients with CAD have comorbidity of AGR.[6] A study in United States reported the prevalence of 30.7% for diabetes and 10% for prediabetes in adult patients with CAD.[7] China Heart Survey, published in 2006, reported a higher prevalence of 76.9% for AGR, as compared with studies based on western populations.[8] Although the prevalence of AGR in Chinese general population is increasing rapidly,[9,10] it is yet unclear how the prevalence in Chinese patient with CAD has evolved in recent years.

The main purpose of this study was to investigate the prevalence of AGR in patients with established CAD, and the association of AGR and acute coronary events in Chinese patients.

2. Methods

2.1. Patients and data collection

The study is a multicenter cross-sectional study involving 41 cardiac centers in 19 cities of China. Hospitalized patients with established diagnosis of CAD were recruited from August 2007 to May 2011. The hospital admissions were labeled as acute or scheduled. All patients were assessed, investigated and treated at

the discretion of the physicians in charge according to their usual institutional practice. Patients with type 1 diabetes were excluded.

Data were collected by a case record form, which included demographic data, medical history, and diagnosis of CAD as well as glucometabolic abnormalities. Blood pressure, lipid levels, smoking status, and current medication were also recorded.

The study complied with the Declaration of Helsinki and was approved by the Peking University First Hospital Ethics Committee. All participants signed informed consent statements.

2.2. Definition
2.2.1. Characteristics of admission.
Acute admissions were defined as nonscheduled admissions due to or partially due to acute coronary syndrome (ACS). Scheduled admissions were scheduled admissions for diagnostic procedures, treatment adjustments, or scheduled interventions related to CAD.

2.2.2. Cardiovascular diagnosis.
The criteria to diagnose CAD included history of myocardial infarction (including past myocardial infarction and acute myocardial infarction); CAD diagnosed by coronary angiography (revealing stenosis >50% of the lumen diameter in any major coronary artery); history of percutaneous coronary intervention (PCI) or coronary artery bypass graft; typical angina symptom, with ECG showing transient ST depression of 0.05 to 0.1 mv or T wave inversion, or abnormal stress test. ACS included unstable angina pectoris, acute ST-segment elevation myocardial infarction, and acute non-ST-segment elevation myocardial infarction.

2.2.3. Glucometabolic state measurements.
Diabetes mellitus (DM) was defined according to the WHO classification.[11] All patients without previously known diabetes underwent a standard oral glucose tolerance tests (OGTT) (75 g anhydrous glucose in 250–300 mL water)[11] as soon as they were in a stable condition. For patients with ACS, OGTT was performed 1 week after the event. Glucose levels in venous plasma were measured at the start of the OGTT (0 minute) and at 2-hour post-load (2 hours).

Classification of glucometabolic state was made based on OGTT results when performed and was divided into the following 5 categories: normal glucose regulation (Normal): OGTT (0 minute) <6.1 mmol/L and OGTT (2 hours) <7.8 mmol/L; isolated impaired fasting glucose (I-IFG): OGTT (0 minute) ≥6.1 but <7.0 mmol/L, and OGTT (2 hours) <7.8 mmol/L; isolated impaired glucose tolerance (I-IGT): OGTT (0 minute) <6.1 mmol/L, and OGTT (2 hours) ≥7.8 mmol/L but <11.1 mmol/L; combined glucose tolerance (CGI): OGTT (0 minute) ≥6.1 mmol/L but <7.0 mmol/L and OGTT (2 hours) ≥7.8 mmol/L but <11.1 mmol/L; DM: OGTT (0 minute) ≥7.0 mmol/L, or OGTT (2 hours) ≥11.1 mmol/L. In the current study, prediabetes refers to both IFG, and IGT whereas AGR includes prediabetes and diabetes.

2.3. Statistical analysis
Continuous variables were expressed as the mean ± standard deviation. The variable normality was determined using the Kolmogorov–Smirnov normality test. The differences in normally distributed continuous variables between groups were examined by t test, whereas the Mann–Whitney's U test was used to determine the significance in 2-group non-normally distributed continuous variables. The differences in categorical variables between groups were tested by the χ^2 test. Predictors of acute coronary events were evaluated in all treated patients using logistic regression, and results were expressed as odds ratios (ORs) with 95% confidence intervals (CIs) and P values. All candidate predictors were evaluated using univariate test. If the P value was <.1, this predictor was allowed to enter multivariable models. In addition to this, we forced age and gender into multivariable models. Data were analyzed using the SPSS statistical software, version 20.0 (SPSS Inc, Chicago, IL), with the exception of the Kruskal–Wallis test and the Dunn's post hoc analysis, which was performed using the Graphpad Prism software version 5.0 (GraphPad Software Inc, San Diego, CA). Results with $P < .05$ (2-tailed) were considered statistically significant.

3. Results

3.1. General data of the patients
A total of 3441 patients were enrolled, out of whom 394 were excluded due to protocol violations. The current database comprised 3047 patients, of whom 1043 (34.2%) were acute hospital admissions and 2004 (65.8%) were scheduled hospital admission (Fig. 1). In the 3047 patients, 2157 were male, and 890 were female, with an age of 62.51 ± 11.04 years. The diagnosis of CAD was summarized as following: acute myocardial infarction (n=953, 34.3%), past myocardial infarction (n=600, 21.7%), CAD proved by coronary angiograph (n=2150, 72.0%), classic angina symptom with ECG changes, (n=565, 16.3%), coronary intervention (PCI or CABG) (1360, 47.5%).

3.2. Glucometabolic state
In the entire cohort, 935 (30.7%) patients had a diagnosis of DM established prior to inclusion. An OGTT was performed in the remaining 2112 (69.3%) patients. According to the results of OGTT, 449 (21.3%), 27 (1.3%), 1163 (55.1%), 110 (5.2%), and 363 (17.2%) patients were classified as normal, I-IFG, I-IGT, CGI, and diabetes, respectively.

AGR was detected in 1663 (78.7%) patients in the OGTT cohort, with more than a half diagnosed with I-IGT, and nearly 20% diagnosed with diabetes. There was no significant difference
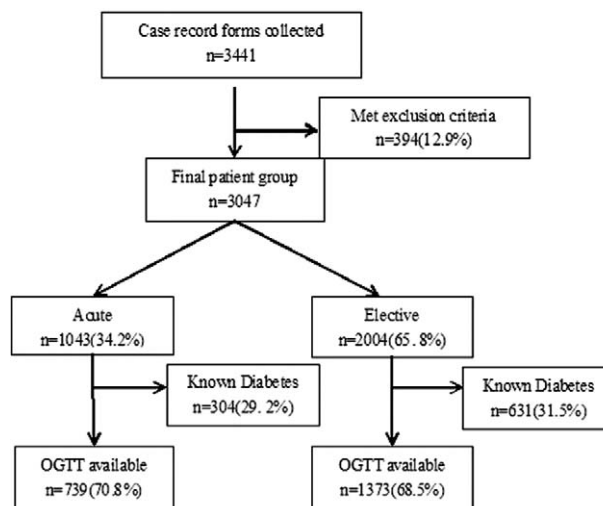

Figure 1. Flowchart of patients recruitment.

in fasting glucose or post-load 2 hours glucose between male and female, or among the different admission groups (Table 1). Patients more than 65 years old had a greater post-load 2 hours glucose level than the other age groups.

In total 85% (n=3047) patients in the study was diagnosed with AGR. The overall proportion of patients diagnosed with diabetes increased from 30.7% (n=935) at baseline to 42.6% (n=1298) following the OGTT analysis.

3.3. Association between acute coronary events and different types of AGR

Among the total cohort of patients (n=3047), there were 540 patients with ACS, including 30, 0, 333, 29, and 148 patients in the normal, I-IFG, I-IGT, CGI, and DM group, respectively. When analyzing the association between acute coronary events and different types of AGR, because the sample size of I-IFG is too small, we integrated the I-IFG and I-IGT patients into 1 group.

All candidate parameters enter the multivariate analysis were listed in Table 2. AGR was independently associated with acute coronary events, after adjusting for the traditional risk factors, including age, smoking, hypertension, and hyperlipidemia.

4. Discussion

Several studies have demonstrated a high prevalence of AGR in patients with CAD. Euro Heart Survey published in 2004 enrolled 4961 patients with CAD from 110 centers in 25 countries.[6] Of the 1920 patients without known diabetes who underwent OGTT, 37% was diagnosed of prediabetes and 18% was diagnosed of diabetes. China Heart Survey published in 2006 recruited 3513 patients from 52 centers, and was the first large clinical survey regarding the glucometabolic state in Chinese patients with CAD.[8] Of the 2263 patients in China Heart Survey without known diabetes who underwent OGTT, 26.9% had newly diagnosed diabetes and 37.3% had prediabetes, and the overall proportion patients. In the current study, 85.1% of patients were diagnosed with AGR, which was much higher than that in China Heart Survey in 2006. It was probably due to the rapid increase in the prevalence of AGR in Chinese general population.[9,10] In a recent study using HbA1c and America

Table 1

Results of OGTT.

	N	Fasting glucose, mmol/L	Post-load 2-hour glucose, mmol/L
Total	2112	5.35 ± 1.28	9.32 ± 2.75
Gender			
Male	1576	5.33 ± 1.24	9.28 ± 2.69
Female	536	5.41 ± 1.37	9.46 ± 2.90
P		.2619	.5379
Admission			
Acute	739	5.43 ± 1.60	9.35 ± 2.73
Scheduled	1373	5.31 ± 1.06	9.31 ± 2.76
P		.8165	.626
Age,* y			
18–44	149	5.17 ± 1.21	8.70 ± 2.75
45–64	1108	5.31 ± 1.20	9.22 ± 2.70
≥65	855	5.42 ± 1.39	9.56 ± 2.80
P		0.0125	0.0002

OGTT = oral glucose tolerance test.
* Kruskal–Wallis test was used for multiple group comparison.

Table 2

Predictors of acute coronary events.

Predictors	P	OR (95% CI)
Age (increased by 1 y)	.097	0.992 (0.983–1.001)
Gender	.345	1.128 (0.897–1.446)
Smoking	.000	2.369 (1.841–3.048)
Hyperlipidemia	.206	1.232 (0.891–1.704)
Hypertension	.832	0.973 (0.753–1.257)
Glucometabolic state	.000	
Normal	Reference	
I-IFG or I-IGT	.001	3.989 (2.644–6.016)
CGI	.000	3.452 (1.926–6.188)
DM	.022	1.952 (1.292–2.950)

CGI = combined glucose tolerance, CI = confidence interval, DM = diabetes mellitus, I-IFG = isolated impaired fasting glucose, I-IGT = isolated impaired glucose tolerance, OR = odds ratio.

Diabetes Association standards to diagnosis, the prevalence of prediabetes reached as high as 50.1% in Chinese general population.[12] This study suggested the prevalence of AGR in Chinese patients with CAD is increasing possibly faster than that in general population.

The main finding of the current study was that in addition to diabetes, IGR including I-IFG or I-IGT, and CGI were independently associated with acute coronary events, after adjusting for the traditional risk factors including age, smoking, hypertension, and hyperlipidemia. It was found by Bartnik et al that abnormal glucose tolerance is a strong risk factor for future cardiovascular events after myocardial infarction.[13] The study by Petursson et al found that with increasing severity of AGR, there is an increasing risk of new cardiovascular events after CABG, and AGR is prevalent and predicts a poor outcome after CABG.[14] Our study further extended this finding with larger sample size and broad disease spectrum of CAD. It was suggested AGR, by its multiple interactions with inflammatory response, pro-oxidative stress and not the least pro-coagulatory properties, may play an important role for promoting CAD.[14] Therefore, these results highlighted the importance of early intervention in patients with not only diabetes, but also impaired glucose regulation, is crucial for preventing the development and progression of CAD. Although early intervention of prediabetes in general population had demonstrated cardiovascular benefits,[15,16] it is still unknown whether intervention of prediabetes in patients already diagnosed with CAD would have similar benefits.

There were several limitations of our study. First, this study is a cross-sectional one; therefore, we are not able to investigate the role of AGR on the long-term outcome of these patients. Second, about 10% of the patients were excluded at the recruiting stage due to protocol violation, selection bias cannot be fully avoided. This may lead to the limited ability of an extrapolation of the results to larger context. Third, we did not have the data of insulin measurements and homeostasis model assessment.

In conclusion, the prevalence of AGR is increasing in Chinese patients with CAD. AGR was independently associated with acute coronary events. Prospective studies are warranted to evaluate the benefit of intervening prediabetes in adult patients with CAD.

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