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ORIGINAL ARTICLE

Coronary angiographic studies of impaired glucose regulation and coronary artery disease in Chinese nondiabetic subjects

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Abstract To investigate the prevalence and the extent of coronary artery disease (CAD) in nondiabetic Chinese patients with different categories of impaired glucose regulation (IGR): isolated impaired fasting glucose (I-IFG); isolated impaired glucose tolerance (I-IGT); and combined IFG and IGT (CGI). A total of 556 nondiabetic subjects who had undergone coronary angiography were included in this study. Subjects were classified according to the 75-g oral glucose tolerance test result: normal glucose tolerance (NGT) ($n = 278$), I-IFG ($n = 52$), I-IGT ($n = 128$), CGI ($n = 98$). Significant CAD is defined as the presence of one or more coronary vessels with the lumeninal reduction in diameter to $\geq$50% in a given subject. The severity and extent of coronary atherosclerosis are defined by the Gensini score, the worst artery score, and the number of diseased vessels with significant coronary stenosis (number of diseased vessels). The prevalence of significant CAD in I-IFG and I-IGT groups were similar (67.3%, $P = 0.207$; 67.4%, $P = 0.068$, respectively) but both were higher comparing with NGT group (57.9%), however, it was considerably higher in CGI group (85.9%, $P < 0.001$). The Gensini score, worst artery score, and number of diseased vessels were similar in NGT, I-IFG, and I-IGT groups, but all significantly increased in CGI group after adjustment for other traditional factors (all $P < 0.001$). Logistic regression analyses reveal fasting glucose but not 2-h glucose as a significant determinant in Gensini score, worst artery score, and number of diseased vessels. The prevalence and the extent of CAD did not differ significantly among subjects with NGT, I-IFG, and I-IGT, but increased significantly in those with CGI. Fasting glucose was more strongly associated with angiographically characterized coronary artery stenosis than 2-h glucose.

Keywords Isolated impaired fasting glucose · Isolated impaired glucose tolerance · Combined glucose intolerance · Coronary artery disease · Coronary angiography

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Abbreviations

IGR	Impaired glucose regulation
CAD	Coronary artery disease
NGT	Normal glucose tolerance
I-IFG	Isolated impaired fasting glucose
I-IGT	Isolated impaired glucose tolerance
CGI	Combined impaired fasting glucose and impaired glucose tolerance
OR	Odds ratio
CI	Confidence interval
HOMA-IR	Homeostasis model assessment of insulin resistance

Introduction

Increased blood glucose levels among patients with diabetes mellitus (DM) is associated with increasing risk of CAD [1, 2]. Numerous studies have examined whether elevated blood glucose levels in the nondiabetic range are associated with increased risk of CAD, but results have been controversial [3–5]. A meta-analysis of all available data to 2003 concluded that elevated blood glucose level is in fact a risk factor of cardiovascular diseases among individuals without DM [3], but again other studies showed the lack of association between impaired glucose regulation (IGR) and coronary atherosclerosis or CAD outcomes [4, 5]. Several important questions about the glycemia–CAD relationship remain unclear. First, whether IGR has any impact on CAD? Second, if IGR is associated with the risk of CAD, is there any difference of possible impacts between IFG and IGT on CAD, although current evidence indicates that IGT entails greater risk of CAD [6, 7]? Third, it needs to be determined whether hyperglycemia is a risk marker of CAD independent of other metabolic abnormalities, as well as which methods of glucose assessment (fasting or postchallenge glucose level) may have greater influence are still unknown [8, 9].

Therefore, we aimed to investigate the association of IGR with angiographically determined CAD in Chinese nondiabetic subjects. We compared the severity and the extent of coronary atherosclerosis in subjects with NGT, I-IFG, (I-IGT and CGI). Such comparisons could be more likely to reveal possible differences in the etiology and the risks for CAD associated with fasting and postchallenge glucose hyperglycemia.

Results

Clinical characteristics

Clinical characteristics are summarized in Table 1. There were no significant differences among the four groups of our study with respect to genders, age, or BMI; however, the waist–hip ratios in I-IGT and CGI subjects were significantly higher than in subjects with NGT and I-IFG. The lipid profiles were similar among the four groups, except that triglyceride level was higher in CGI group than in NGT group ($P < 0.001$).

As traditional risk factors for CAD, smoking habit (current smokers) and family history of CAD were similar among the four groups; however, compared with NGT, the prevalence of hypertension was significantly higher in I-IGT group ($P < 0.001$) (Table 1).

Glucose metabolism

As expected, fasting glucose levels in I-IFG and CGI groups were significantly higher than in NGT and I-IGT groups (all $P < 0.001$), but it was comparatively higher in CGI than in I-IFG ($P = 0.044$). In contrast, 2-h glucose levels were higher in I-IGT and CGI groups than in NGT and I-IFG groups (all $P < 0.001$), and with no difference between I-IGT and CGI groups ($P = 0.183$). The average level of glycemia as measured by glycated hemoglobin did not differ significantly between NGT and I-IGT groups, but was significantly increased in I-IFG and CGI groups, with the latter having the highest insulin resistance, calculated by homeostasis model assessment of insulin resistance (HOMA-IR), was significantly higher in I-IFG, I-IGT and CGI groups than in NGT (compared with NGT, $P = 0.002$; $P < 0.001$; $P < 0.001$, respectively) (Table 1).

The prevalence of significant CAD

Three hundred and sixty-eight patients had angiographically diagnosed significant CAD (coronary stenosis with lumeninal diameter reduction to ≥50%) (65.9% of subjects). The prevalence of significant CAD did not differ significantly among subjects with NGT, I-IFG, and I-IGT (57.9 vs. 67.3%; $P = 0.207$; 67.7%; $P = 0.068$, respectively), however, it was significantly higher in those with CGI (85.9%; $P < 0.001$) when compared with those NGT subjects.

The risk factors for significant CAD prevalence were obtained through logistic regression analysis (Table 2). Compared with the NGT group, the CGI group demonstrated significantly higher CAD prevalence after controlling for other risk factors including age, gender, BMI, WHR, smoking, hypertension, and serum lipid (adjusted OR, 2.11 [1.26–3.55], $P = 0.005$). The ORs for subjects with I-IFG and I-IGT were not significantly different from controls (adjusted ORs, 1.34 [0.42–4.30], $P = 0.614$; 1.22 [0.80–1.86], $P = 0.351$, respectively).

Fasting glucose as continuous variables, as well as age and male gender were significantly associated with the prevalence of significant CAD (1.48 [1.01–2.16], $P = 0.043$; 0.24 [0.11–0.55], $P = 0.001$; 1.09 [1.05–1.13], $P < 0.001$, respectively); however, no significant association of 2-h glucose with CAD prevalence was observed ($P = 0.205$).

The extent and severity of coronary atherosclerosis

The extent of CAD (defined by number of diseased vessels) was not statistically different in subjects with I-IFG or I-IGT (0.78 ± 0.99, $P = 0.052$; 0.80 ± 0.97, $P = 0.159$, respectively), but was significantly higher in subjects with

Table 1 Clinical characteristics with respect to the glycemic state

	NGT	I-IFG	I-IGT	CGI	*P*-value
Number (m/f)	278(172/106)	52(34/18)	128(84/44)	98(66/32)	0.751
Age (years)	60.6 ± 9.5	59.3 ± 10.9	65.1 ± 10.9	63.1 ± 9.5	0.351
BMI (kg/m^2)	24.8 ± 3.5	25.5 ± 3.4	25.3 ± 3.4	25.5 ± 3.2	0.056
Waist–hip ratio	0.93 ± 0.01	0.91 ± 0.02	0.95 ± 0.01*	0.95 ± 0.01*	0.016
Coronary risk factors					
Smoking (current smokers)	32.10%	50.0%*$	35.20%	42.90%	0.400
Family history of CAD	15.40%	19.20%	17.20%	20.40%	0.537
Hypertension	57.20%	69.20%	72.7%*	67.30%	0.013
Previous stroke	10.07%	5.77%	9.38%	4.08%	0.264
Prievious MI	13.67%	19.23%	11.72%	22.45%	0.097
PCI	28.06%	32.69%	23.44%	32.65%	0.407
Stent	31.29%	26.92%	25.78%	34.69%	0.235
Glycemic status					
Fasting glucose (mmol/l)	4.73 ± 0.41	5.92 ± 0.33*$	4.78 ± 0.48	6.20 ± 0.38*#$	<0.001
2-h glucose (mmol/l)	5.98 ± 1.02	6.51 ± 0.84	8.97 ± 0.89*#	9.30 ± 0.96*#	<0.001
Glycated hemoglobin (%)	5.89 ± 0.47	6.20 ± 0.46*	6.02 ± 0.51	6.5 ± 0.91*#$	<0.001
Fasting insulin (μm/ml)	9.52 ± 6.48	10.43 ± 6.72	10.45 ± 7.18	12.72 ± 8.30*	0.082
2-h-insulin (μm/ml)	64.12 ± 62.42	63.77 ± 44.38	108.09 ± 79.14*#@	78.10 ± 63.64	<0.001
HOMA-IR	1.95 ± 1.39	2.53 ± 171*$	2.19 ± 1.54*	3.34 ± 2.24*#$	<0.001
Lipid profile					
Triglycerides (mmol/l)	1.75 ± 0.94	1.98 ± 0.77	1.95 ± 1.04	2.26 ± 1.32*	0.005
Total cholesterol (mmol/l)	4.60 ± 1.06	4.63 ± 0.94	4.50 ± 0.97	4.52 ± 1.28	0.819
HDL cholesterol (mmol/l)	1.26 ± 0.44	1.02 ± 0.22	1.24 ± 0.27	1.19 ± 0.30	0.552
LDL cholesterol (mmol/l)	2.67 ± 0.81	2.62 ± 0.65	2.81 ± 1.11	2.68 ± 0.88	0.069
Medical treatment					
Aspirin	53.20%	59.60%	52.70%	55.60%	0.355
β-Blocker	34.30%	44.20%	32.60%	33.30%	0.412
Calcium blocker	9.00%	30.8%*	20.2%*	23.2%*	<0.001
ACE inhibitor	25.90%	48.1%*$	26.40%	35.4%*$	<0.001
Statin	43.90%	50.00%	41.10%	52.50%	0.262

NGT normal glucose tolerance, *I-IFG* isolated impaired fasting glucose, *I-IGT* isolated impaired glucose tolerance, *CGI* combined glucose intolerance (subjects with both IFG and IGT), *BMI* body mass index, *WHR* waist–hip ratio, *CAD* coronary artery disease, *FPG* fasting plasma glucose, *2-h-PG* 2-h-plasma glucose, *HbA1c* glycated hemoglobin, *TG* triglycerides, *TC* total cholesterol, *HDL-c* high-density lipoprotein-cholesterol, *LDL-c* low-density lipoprotein-cholesterol

Coronary risk factors and medical treatment are shown by percentage of positive for these factors. Other data are shown by means ± SD

ANOVA was used for comparisons of multiple group means and the χ^2 test was used to compare frequencies

* $P < 005$ vs. NGT group

\# $P < 005$ vs. I-IFG group

$ $P < 005$ vs. I-IGT group

@ $P < 005$ vs. CGI group

CGI (1.44 ± 1.01, $P = 0.006$) when compared with NGT (0.69 ± 0.96). Moreover, there were no significant differences between subjects with I-IFG and those with I-IGT ($P = 0.345$) (Fig. 1a). Also, the Gensini score and worst artery score did not significantly differ among subjects with NGT, I-IFG, and I-IGT (10.53 ± 15.22 vs. 15.26 ± 18.12, $P = 0.131$; 10.99 ± 14.65, $P = 0.109$ and 5.78 ± 7.47 vs. 7.57 ± 7.12, $P = 0.195$; 5.4 ± 0.7, $P = 0.863$, respectively), but were obviously different when comparing with the subjects with CGI (23.67 ± 21.4, $P < 0.001$; 11.72 ± 10.31, $P < 0.001$, compared with NGT, respectively). What is more, subjects with CGI had significant higher Gensini scores and worst artery scores than those with I-IGT ($P = 0.041$, $P < 0.001$, respectively) (Fig. 1b).

ANOVA adjustment for age, gender, BMI, smoking, hypertension, and serum lipid confirmed that subjects with

Table 2 Estimates of relative risk of the prevalence of significant CAD

	OR	95% CI	*P*-value
Male	0.24	0.11–0.55	0.001
Age	1.09	1.05–1.13	<0.001
BMI	0.93	0.82–1.04	0.179
Waist–hip ratio	2.39	0.01–3.22	0.756
Hypertension	0.64	0.32–1.28	0.271
Smoking	1.43	0.92–2.25	0.114
Triglycerides	0.89	0.64–1.25	0.828
Total cholesterol	1.00	0.71–1.74	0.997
LDL cholesterol	1.06	0.56–1.62	0.908
HDL cholesterol	0.71	0.20–2.55	0.599
Fasting glucose	1.48	1.01–2.16	0.043
2-h Glucose	1.09	0.96–1.23	0.205
Glycated hemoglobin	1.09	0.63–1.88	0.753
HOMA-IR	0.36	0.03–4.11	0.412
I-IFG:NGT[a]	1.34	0.42–4.30	0.614
I-IGT:NGT[a]	1.22	0.80–1.86	0.351
CGI:NGT[a]	2.11	1.26–3.55	0.005

OR odds ratio, *CI* confidence interval, other abbreviations see Table 1

Logistic regression analysis was used to calculate ORs and their 95% CI

[a] Adjusted for gender, age, BMI, waist–hip ratio, hypertension, smoking, triglycerides, total cholesterol, HDL cholesterol, LDL cholesterol

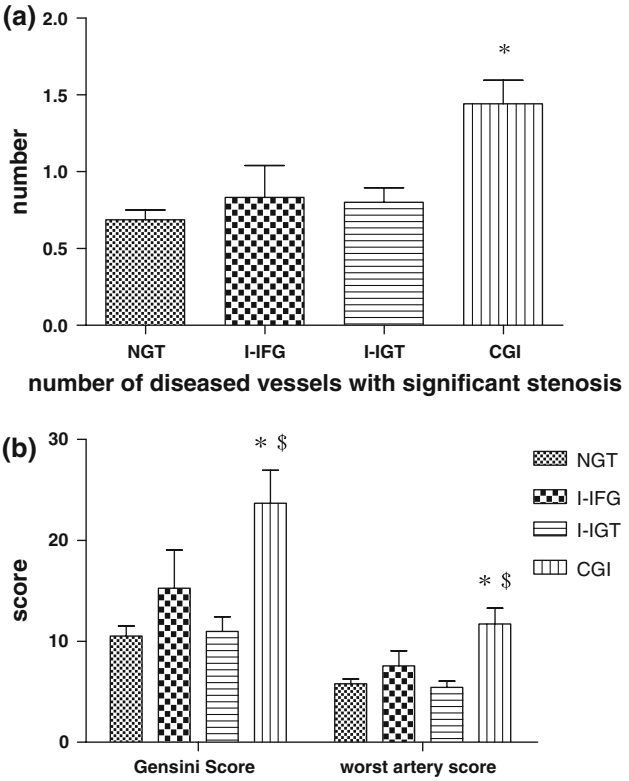

Fig. 1 Comparison of coronary angiography results of extent and severity of coronary atherosclerosis. **a** Comparison of number of diseased vessels with significant stenosis in nondiabetic subjects. **b** Comparison of Gensini score and worst artery score in nondiabetic subjects

CGI had a significantly higher extent of CAD ($P < 0.001$) and an increased CAD severity ($P < 0.05$ for both compared scores) than NGT subjects. There were no statistically significant differences between scores of subjects with NGT, I-IFG, and I-IGT (all $P > 0.05$). After additional adjustment for fasting glucose, the difference of Gensini scores between NGT and CGI groups appeared less significant ($P = 0.040$), and it disappeared between I-IGT and CGI group ($P = 0.079$). After additional adjustment for 2-h glucose, the differences of Gensini scores among NGT, I-IGT, and CGI group remained significant ($P = 0.007$, $P = 0.048$ compared with CGI, respectively).

To further investigate which clinical variables and risk factors were associated with the extent and severity of coronary stenosis, we performed multivariate stepwise regression analyses (Table 3). We found that male gender, age, fasting glucose were independently associated with Gensini score, worst artery score, and number of diseased vessels (all $P < 0.05$). However, 2-h glucose did not enter the regression analyses equations (all $P > 0.05$). In addition, HOMA-IR and glycated hemoglobin were risk factors for worst artery score and number of diseased vessels, respectively (all $P < 0.05$).

Discussion

In this study, we evaluated the prevalence and the extent of coronary artery stenosis of subjects in different categories of IGR using current ADA definitions. We found the prevalence and extent of CAD did not differ significantly among subjects with NGT, I-IFG, and I-IGT; however, it was significantly increased in subjects with CGI. CGI was revealed to be an independent risk factor for angiographically characterized coronary atherosclerosis. Fasting glucose was strongly and independently associated with Gensini score, worst artery score, and number of diseased vessels.

In recent years, IGR has been repeatedly examined as a risk factor for cardiovascular morbidity and mortality [1–4, 6–9], however, there are only few reports [5, 10–13] on the morphologic characteristics of coronary artery in patients with IGR, but with conflicting results. Seibaek et al. and Horimoto et al. [5, 10] reported a lack of association between IGT and severity of stenosis. Other studies, however, suggested [11, 14] that angiographic atherosclerotic changes (smaller vessel diameter and longer lesion length) occurred in coronary arteries in patients with IGT,

Table 3 Multivariate stepwise regression analyses of the extent and severity of coronary atherosclerosis

	Gensini score		Worst artery score		Number of diseased vessels	
	β	*P*-value	β	*P*-value	β	*P*-value
Male	−0.29	<0.001	−0.25	<0.001	−0.26	<0.001
Age	0.12	<0.001	0.1	0.049	0.11	0.021
BMI	−0.14	1.08	−0.1	0.039	−0.15	0.005
Waist–hip ratio	0.01	0.911	−0.05	0.394	0.08	0.161
Smoking	0.09	0.154	0.05	0.311	0.09	0.074
Hypertension	0.03	0.69	0.03	0.588	0.05	0.37
Triglycerides	0.05	0.378	0.02	0.718	0.05	0.379
Total cholesterol	0.06	0.346	0.06	0.232	0.04	0.466
LDL cholesterol	−0.09	0.164	0.02	0.68	0.01	0.842
HDL cholesterol	−0.07	0.392	−0.06	0.232	0.03	0.595
Fating glucose	0.16	0.042	0.2	0.032	0.13	0.011
2-h Glucose	0.05	0.409	0.07	0.206	0.06	0.272
Glycated hemoglobin	0.08	0.209	0.03	0.587	0.11	0.016
HOMA-IR	0.05	0.392	0.19	0.041	0.12	0.05

β standardized coefficients; other abbreviations see Table 1

Multiple stepwise regression was applied to examine the independent risk factors for Gensini score, worst artery score and number of diseased vessels

and once postchallenged diabetes developed, the prevalence and the number of significant stenosis would increase. In the present study, we focus on nondiabetic subjects with different IGR categories. We found that subjects with CGI had higher prevalence of significant CAD, and the extent and severity of coronary atherosclerosis would certainly increase, which was partially in agreement with the results from Kataoka et al. [11] and Saely et al. [14]. However, our study failed to find associations of I-IFG or I-IGT (especially the I-IGT state) with the prevalence and extent of coronary atherosclerosis. This observation, combined with the ARIC study [13] which indicates that neither impaired fasting glucose nor impaired glucose test is associated with an increased risk of all-cause mortality or incident coronary heart diseases after a median follow-up of 6.3 years in fully adjusted models, suggests that in nondiabetic subjects, only the coexistence of impaired fasting glucose state and impaired glucose tolerance state entails risk of CAD.

Prior studies have demonstrated that the risk of cardiovascular disease is strongly associated with diabetic state or hyperglycemia, except for concomitant risk factors including age, sex, hypertension, obesity, dyslipidemia, and smoking, as seen in DECODE study [15]. Several studies [5, 11, 14, 16] have attempted to find the link between glucose levels as continuous variables and the development of coronary atherosclerosis, and the results were mixed, showing significant independent relationships between postprandial glucose levels and CAD in most [11, 14, 16] but not all studies [5]. Few had shown strong association between fasting glucose and CAD after multivariate adjustment. We also found that age, male gender, blood pressure, smoking habits, fasting glucose, 2-h glucose, glycated hemoglobin, HOMA-IR, higher LDL cholesterol and lower HDL cholesterol were correlated with Gensini score, worst artery score, and number of diseased vessels. Among these parameters, however, we found that fasting glucose levels were independently associated with Gensini score, worst artery score, and number of diseased vessels by multivariate stepwise regression analysis, as shown in Table 3, with no independent association found for 2-h glucose.

Evidence has also been extracted from the results of multivariate analyses of Gensini score among IGR categories. It showed that after additional adjustment for fasting glucose, the difference of Gesini score appeared less significant between NGT and CGI groups, and it disappeared between I-IGT and CGI groups. After adjustment for 2-h glucose, the differences between NGT, I-IGT, and CGI groups remained significant. These data all suggest that fasting glucose is more strongly associated with the severity and extent of CAD than 2-h glucose in nondiabetic subjects, and it may modify substantially the risk for atherosclerosis. Given that fasting glucose was an independent determinant of the risk of CAD in this study, our failure to detect the significant difference between I-IFG group and NGT group is probably due to our relatively small sample size in the I-IFG group.

The primary strengths of this study include standardized glucose and coronary angiography measurements to assess

glycemia and coronary artery atherosclerosis, and extensive CVD risk factor measurements. Several limitations merit discussion, however, first, the studied sample size is small, especially in I-IFG and CGI groups. Second, this study was performed on a selective basis, as subjects were not randomly chosen but enrolled only from hospitals with clusters of high-risk patients. Therefore, the actual prevalence of CAD might be overestimated. Third, the cross-sectional nature of this study exhibited only the association of glucose levels at one time with cardiovascular risks, with no repeated glucose tolerance tests.

In summary, we have shown CGI is a strong and independent risk factor of angiographically characterized coronary atherosclerosis, whereas subjects with I-IFG or I-IGT appear to have no association with the presence and extent of CAD. Fasting glycemia is more strongly associated with angiographically characterized coronary stenosis than 2-h glucose and modify substantially the risk for atherosclerosis.

Subjects and methods

Subjects

Between January 2005 and December 2007, we recruited 1382 Chinese subjects who were diagnosed with acute myocardial infarction or undergoing coronary angiography for the evaluation of CHD at the department of cardiology in Rui-Jin Hospital affiliated to Shanghai Jiao-Tong University School of Medicine. Patients were included for study if they had undergone coronary angiography and no history of hypoglycemic therapy treatment ($n = 763$), and standard 75 g oral glucose tolerance test (OGTT) was performed. Patients who showed absence for OGTT or because of missing clinical information ($n = 77$) and those who were newly diagnosed for diabetics according to the OGTT results ($n = 130$) were excluded. Thus, the final nondiabetic subjects in the study are 556.

Based on the OGTT results, subjects were divided into the following groups according to the current ADA criteria [17], with the 2003 modifications [18]: (i) NGT (fasting glucose < 5.6 mmol/l and 2-h glucose < 7.8 mmol/l, $n = 278$), (ii) I-IFG (5.6 mmol/l $\leq$ fasting glucose < 7.0 mmol/l and 2-h glucose < 7.8 mmol/l, $n = 52$); (iii) I-IGT (fasting glucose < 5.6 mmol/l and 7.8 mmol/l $<$ 2-h glucose < 11.1 mmol/l, $n = 128$); and (iv) CGI (5.6 mmol/l $\leq$ fasting glucose < 7.0 mmol/l and $7.8 <$ 2-h glucose < 11.1 mmol/l, $n = 98$).

All subjects gave informed written consent, and the study was approved by the Institutional Review Board of Rui-Jin Hospital.

Methods

Clinical and biochemical measurements

All the patients underwent history screening (date of birth, smoking, alcohol consumption, and medical history). Height and weight (with light clothes and without shoes), waist and hip circumference and seated blood pressure were determined by the same observer. BMI was calculated as weight (kg) divided by the square of height (m).

The 75-g OGTT was performed between 07.00 and 08.00 h after an overnight fasting. Venous blood samples were collected during fasting and at 2-h after glucose loading. Plasma glucose level was measured immediately after blood centrifugation using an enzymatic method (Beckman CX-7 Biochemical Autoanalyser, Brea, CA, USA). Fasting insulin and 2-h insulin levels were measured using a double antibody radioimmunoassay by enzymatic methods (DSL, Webster, Texas, USA). Fasting serum levels of triglycerides and total cholesterol were measured by enzymatic methods (Beckman coulter Inc, Fullerton, CA, USA). High-density lipoprotein-cholesterol and low-density lipoprotein-cholesterol were measured by enzymatic methods (HDL-c, LDL-c Direct, Wake Pure Chemical Industries Ltd. GmbH, Neuss, Germany). Glycated hemoglobin was measured by high performance liquid chromatography using the BioRad Variant Hemoglobin HbA1c assay (Hercules, CA, USA). HOMA-IR was used to estimate insulin resistance (fasting insulin $\times$ fasting glucose)/22.5 [19].

The presence of CAD risk factors was measured. Current cigarette smoking was defined as a daily intake of more than five cigarettes. The diagnosis of obesity was based on the criteria of Asia-Oceania [20], which was defined by BMI $\geq$25 kg/m^2. Hypertension was defined as systolic blood pressure $\geq$140 mmHg, or diastolic blood pressure $\geq$90 mmHg in at least two separate measurements, or a history of hypertension.

Coronary angiography was performed in multiple projections with the Judkins technique. The data were assessed by an experienced cardiologist, who was blind to the glucose tolerance status. Coronary atherosclerosis was diagnosed in the presence of any coronary lumen narrowing at angiography, coronary stenos with lumen narrowing $\geq$50% were considered significant. CAD was defined as the presence of one or more vessels with significant stenosis in a given subject. The extent of coronary atherosclerosis was defined as number of diseased vessels with significant stenosis (number of diseased vessels) in a given subject; the severity of coronary atherosclerosis was defined by the Gensini score [21] and worst artery score, which was defined by the highest score of a single stenosis in a given patient.

Statistical analysis

Data were described as means ± SD for continuous variables or as percentage for categorical variables. Logarithmic transformation was used for HOMA-IR, number of diseased vessels, and Gensini score because of the high degree of skewing. Differences in studied variables were tested for statistical significance with the χ^2 test for categorical variables, with the analysis of variance (ANOVA) for normally distributed continuous variables, and with the Mann–Whitney *U*-tests for non-normally distributed continuous variables. Fisher's least significant difference (LSD) post hoc test was applied for multiple comparisons where appropriate. Logistic regression was used to calculate odds ratios (ORs) and their 95% confidence interval (CI). Multiple stepwise regression analysis was applied to examine the independent risk factors for Gensini score, worst artery score and number of diseased vessels. *P*-values <0.05 were considered significant. All analyses were performed using software package SPSS 11.0 for windows (SPSS Inc., Chicago, IL, USA).

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