

# Quantitative Coronary Angiographic Studies of Patients With Angina Pectoris and Impaired Glucose Tolerance

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**OBJECTIVE** — We investigated the morphological characteristics of coronary arteries in patients with impaired glucose tolerance (IGT) using computer-assisted quantitative coronary angiography. IGT is an independent risk factor for cardiovascular disease. However, the morphological changes developing in the coronary arteries of patients with IGT remain unknown.

**RESEARCH DESIGN AND METHODS** — A total of 534 patients with angina pectoris were studied. Of these, 144 patients were being treated for diabetes. The remaining 390 patients were classified as follows depending on the results of a 75-g oral glucose tolerance test: normal glucose tolerance (NGT) ( $n = 117$ ), impaired fasting glucose ( $n = 3$ ), IGT ( $n = 136$ ), and diabetes pattern (preclinical diabetes) ( $n = 134$ ). The diameters of the middle section of all major coronary artery segments were measured and averaged to determine the averaged vessel diameter (AVD). We defined segments of a diameter of  $\leq 1.5$  mm as diseased lesions and determined the averaged lesion length (ALL).

**RESULTS** — AVD and ALL were significantly different among patients with IGT and those with NGT. Patients with diabetes (preclinical and/or treated) had smaller AVD and longer ALL than those with IGT. By multivariate analysis, postprandial glucose levels were shown to be independently associated with an AVD  $< 3.0$  mm and an ALL  $> 20$  mm.

**CONCLUSIONS** — Diffuse coronary artery narrowing develops not only in patients with diabetes but also in those with IGT. This morphological change is associated with postprandial hyperglycemia.

*Diabetes Care* 28:2217–2222, 2005

Impaired glucose tolerance (IGT) has been regarded as intermediate between normal glucose tolerance (NGT) and overt diabetes. Recently, evidence has been accumulating that IGT may play a pathological role as one aspect of the metabolic syndrome. Epidemiological studies, i.e., the Funagata and DECODE (Diabetes Epidemiology: Collaborative

Analysis of Diagnostic Criteria in Europe) studies (1,2), indicated that IGT characterized as postprandial hyperglycemia is an independent risk factor for cardiovascular disease. However, it is not known whether morphological changes develop in the coronary arteries of patients with IGT, as in those of diabetic patients for whom small vessel diameter and long le-

sion length (diffuse narrowing) are found in multiple vessels (3,4). In the present study, we assessed coronary angiographic features in patients with IGT by using computer-assisted quantitative analysis.

## RESEARCH DESIGN AND METHODS

From April 2000 to June 2002, 1,529 patients were hospitalized due to nonischemic and ischemic heart disease in our facility of the National Cardiovascular Center, a tertiary referral hospital in the northern district of Osaka, Japan. We obtained informed consent and performed quantitative coronary angiography (QCA) in patients with recurrent chest pain associated with electrocardiographic and/or echocardiographic evidence of myocardial ischemia and without contraindications to the administration of iodinated contrast agent (e.g., predialysis state of renal failure). Thus, a total of 914 patients who had organic stenosis were diagnosed with angina pectoris. Of these patients, the 112 patients who previously underwent coronary artery bypass surgery and the 126 patients with chronic total occlusion were excluded because of difficulty of QCA analysis. Among the remaining 676 patients, 144 patients in whom diabetes had previously been diagnosed and who were being treated by diet therapy alone ( $n = 48$ ), oral hypoglycemic agents ( $n = 70$ ), or insulin ( $n = 26$ ) were defined as the treated diabetes group. The average duration of diabetes in this patient group was 17 years. Also, a 75-g oral glucose tolerance test (OGTT) was refused or could not be performed in some very old or severely ill patients who underwent urgent coronary artery bypass surgery, required mechanical circulatory support, or had refractory infectious diseases ( $n = 142$ ). Finally, 390 patients with angina pectoris underwent a 75-g OGTT and were divided into the following four groups: 117 patients with normal glucose tolerance (NGT), 3 patients with impaired fasting glucose (IFG), 136 patients with IGT, and 134 patients who showed diabetes pattern (preclinical diabetes).

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Received for publication 24 February 2005 and accepted in revised form 6 June 2005.

**Abbreviations:** ALL, averaged lesion length; AVD, averaged vessel diameter; FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test; QCA, quantitative coronary angiography.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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Table 1—Patient characteristics

	NGT	IGT	Preclinical diabetes	Treated diabetes
n	117	136	134	144
Age (years)	68 ± 10	68 ± 10	69 ± 10	70 ± 8
Male	97 (83)	113 (83)	111 (83)	106 (74)
BMI (kg/m <sup>2</sup> )	22.9 ± 2.8*	23.8 ± 2.7	24.0 ± 3.4	23.4 ± 3.1
Unstable angina pectoris	36 (31)	50 (37)	53 (39)	58 (40)
Coronary risk factors				
Hypertension	80 (68)	105 (77)	108 (81)	113 (79)
Hypercholesterolemia	80 (68)	101 (74)	97 (72)	105 (73)
Smoking	38 (33)	45 (33)	40 (30)	39 (27)
Family history of CAD	26 (22)	37 (27)	22 (16)	27 (19)
Serum creatinine ≥177 μmol/l	4 (3)	1 (1)	4 (3)	15 (11)*†
Peripheral vascular disease	9 (8)	12 (9)	22 (17)	19 (13)
Stroke	27 (23)	23 (17)	28 (21)	31 (22)
Previous MI	26 (22)	20 (15)	14 (11)	31 (22)†
Previous PCI	55 (47)	64 (47)	64 (48)	67 (46)
PCI	78 (91)	98 (72)	83 (62)	104 (72)
Stent	66 (73)	78 (80)	58 (69)	79 (76)
Glycemic status				
Fasting glucose (mmol/l)	5.02 ± 0.43	5.11 ± 0.49	6.05 ± 1.44	7.26 ± 2.00*†
Postprandial glucose (mmol/l)	6.16 ± 1.24*	9.42 ± 1.09	12.95 ± 1.87*	12.16 ± 3.41*
A1C (%)	5.3 ± 0.4	5.5 ± 0.4	6.1 ± 0.9*	7.3 ± 1.2*
Lipid profile				
Total cholesterol (mmol/l)	4.93 ± 0.88	4.93 ± 0.91	5.03 ± 0.94	4.79 ± 0.89
Triglycerides (mmol/l)	2.78 ± 1.56*†‡	3.29 ± 1.54	3.48 ± 2.09	3.53 ± 1.99
HDL cholesterol (mmol/l)	1.21 ± 0.35*†‡	1.07 ± 0.32	1.06 ± 0.29	1.03 ± 0.29
LDL cholesterol (mmol/l)	3.18 ± 0.75	3.19 ± 0.86	3.27 ± 0.86	3.06 ± 0.82
Medical treatment				
Aspirin	112 (96)	119 (88)	119 (89)	127 (88)
β-Blocker	55 (47)*†‡	95 (70)	94 (70)	87 (60)
Calcium blocker	85 (73)	88 (65)	95 (71)	97 (67)
ACE inhibitor	27 (23)	36 (27)	43 (32)	44 (31)
Statin	54 (46)	63 (46)	67 (50)	63 (44)

Data are means ± SD or n (%). \*P < 0.05 vs. IGT; †P < 0.05 vs. preclinical diabetes; ‡P < 0.05 vs. treated diabetes. CAD, coronary artery disease; MI, myocardial infarction; PCI, percutaneous coronary intervention.

**The 75-g OGTT**

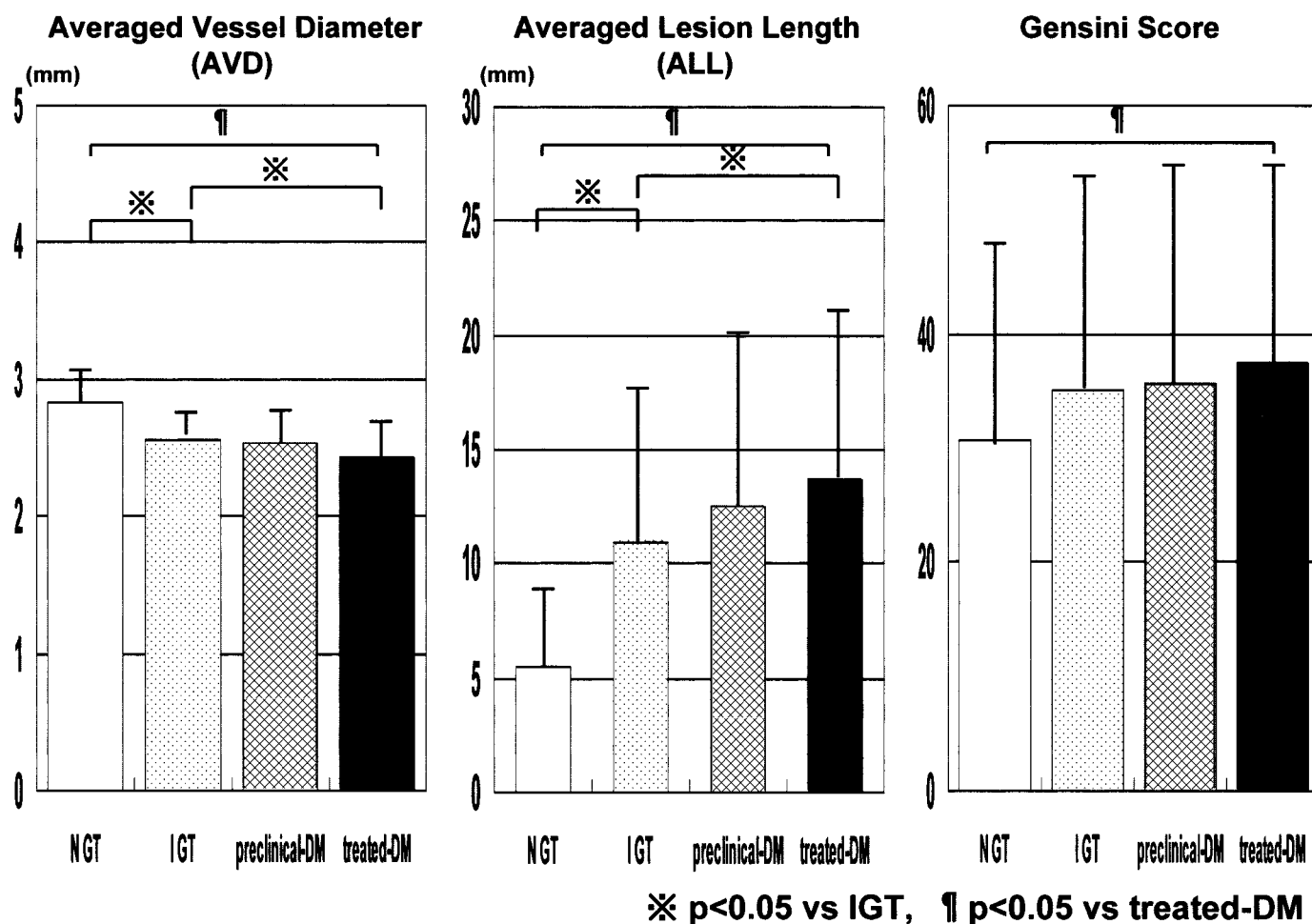
The 75-g OGTT was performed after overnight fasting. Venous blood samples were taken during fasting and at 120 min after the glucose load to measure blood glucose level. The World Health Organization criteria were used for classifying the OGTT results (5) in the present study. The NGT group was defined as having a fasting plasma glucose (FPG) level <6.1 mmol/l and a postprandial glucose level <7.8 mmol/l. The IFG group was defined as having a FPG level ≥6.1 mmol/l but <7.0 mmol/l and a postprandial glucose level <7.8 mmol/l. The IGT group was defined as having a FPG level <7.0 mmol/l and a postprandial glucose level ≥7.8 mmol/l but <11.1 mmol/l. The preclinical diabetes group was defined as

having a FPG level ≥7.0 mmol/l and a postprandial glucose level ≥11.1 mmol/l.

**Coronary angiography and quantitative analysis**

Selective coronary angiography was performed in multiple projections after administration of intracoronary nitroglycerin (0.125–0.25 mg). Coronary angiographic measurements were performed using computer-assisted quantitative analysis (CMS-QCA version 4.0; MEDIS medical imaging systems, Leiden, the Netherlands). In addition to the Gensini score, which has been validated previously (6), the following parameters were used for the assessment of morphological characteristics in global coronary trees. We measured the diameters of the

middle section in each major coronary artery segment: segments 1, 2, and 3 of the right coronary artery; segments 6, 7, and 8 of the left anterior descending artery; and segments 11 and 13 of the left circumflex artery. For each patient, we calculated the average diameter of these segments, which was defined as averaged vessel diameter (AVD). We also defined segments narrowed to a diameter of ≤1.5 mm as diseased lesions (with the exception of the far distal portion of segments 8 and 13 showing a smooth and regular edge) and determined averaged lesion length (ALL). The data from QCA were assessed by an experienced cardiologist (I.M.), who was blind to the glucose tolerance status. The interobserver correlation coefficient and the percent error were



**Figure 1**—Comparison of QCA results of AVD, ALL, and Gensini score among the four groups. DM, diabetes.

0.99 and  $7.3 \pm 4.9\%$  for AVD and 0.93 and  $7.4 \pm 5.9\%$  for ALL. The intraobserver correlation coefficient and the percent error were 0.93 and  $3.6 \pm 2.2\%$  for AVD and 0.98 and  $3.9 \pm 2.6\%$  for ALL.

### Study design

All the patients underwent history screening, a physical examination and angiographic and laboratory analyses including HbA<sub>1c</sub> (A1C), total cholesterol, triglyceride, HDL cholesterol, LDL cholesterol, and creatinine levels. In addition, patients were assessed for the prevalence of coronary risk factors, i.e., hypertension, hyperlipidemia, smoking habits, and family history, and for the presence of diabetes complications, i.e., nephropathy, a history of myocardial and cerebral infarction, and the presence of arteriosclerotic obliteration. BMI was calculated as the weight in kilograms divided by the square of height in meters (2). Blood glucose levels measured 2 h after breakfast or the

75-g OGTT were defined as those in the postprandial state in the present study. Among the four groups (NGT, IGT, preclinical diabetes, and treated diabetes), ANOVA was performed followed by Bonferroni post hoc testing. For univariate analysis, the following clinical variables and risk factors were regarded as covariates: age, sex, glycemic status (fasting, postprandial glucose level, and A1C level), lipid profiles (total cholesterol, triglyceride, HDL cholesterol, and LDL cholesterol levels), creatinine level, BMI, and the use of cardiovascular medications. On the basis of the results of univariate analysis, we performed multivariate logistic regression analysis to investigate the independent predictors of small AVD ( $<3.0$  mm) and long ALL ( $>20$  mm). A  $P$  value of  $<0.05$  was considered to indicate statistical significance. All analyses were performed using Stat-View software, version 5.0 (SAS Institute, Cary, NC).

**RESULTS**—Clinical characteristics are summarized in Table 1. Most of the parameters, with the exception of BMI, triglyceride and HDL cholesterol levels, and the prevalence of  $\beta$ -blocker treatment, were not different between the IGT and NGT groups. The prevalence of renal failure (serum creatinine level  $\geq 177$   $\mu\text{mol/l}$ ) was higher in the treated diabetes group than in the IGT group.

### Glucose metabolism

As shown in Table 1, the fasting glucose and A1C levels were similar between the NGT and IGT groups. However, the postprandial glucose level was significantly different between the NGT and IGT groups ( $P < 0.05$ ). All of these parameters relating to glucose metabolism were significantly higher in the preclinical and treated diabetes groups than in the IGT group ( $P < 0.05$ ).

Table 2—Univariate and multivariate analyses

	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
Predictors for small vessel diameter (AVD <3.0 mm)				
Age	1.035 (1.008–1.064)	0.0117	1.028 (0.999–1.056)	0.055
Female sex	3.293 (1.288–8.419)	0.0128	2.916 (1.118–7.608)	0.0287
Fasting glucose	1.005 (0.995–1.015)	0.3712		
Postprandial glucose	1.008 (1.004–1.013)	0.0007	1.008 (1.003–1.013)	0.0016
A1C	1.181 (0.922–1.513)	0.1874		
Total cholesterol	1.001 (0.994–1.009)	0.7682		
HDL cholesterol	1.009 (0.987–1.032)	0.4166		
LDL cholesterol	0.998 (0.990–1.006)	0.6129		
Creatinine	1.145 (1.030–1.273)	0.0125	1.171 (1.031–1.331)	0.0155
Hypertension	0.883 (0.471–1.655)	0.6977		
Smoking habit	0.843 (0.486–1.461)	0.5425		
Predictors for long lesion length (ALL >20 mm)				
Age	1.041 (1.010–1.073)	0.0091	1.040 (1.007–1.074)	0.0187
Female sex	2.040 (1.115–3.735)	0.0208	2.051 (1.021–4.120)	0.0434
Fasting glucose	1.010 (1.002–1.018)	0.0106	1.002 (0.991–1.013)	0.3780
Postprandial glucose	1.009 (1.005–1.014)	<0.0001	1.009 (1.002–1.015)	0.0059
A1C	1.398 (1.148–1.703)	0.0009	1.211 (0.928–1.579)	0.1584
Total cholesterol	1.000 (0.992–1.008)	0.9550		
HDL cholesterol	0.969 (0.944–0.995)	0.0206	0.969 (0.943–0.997)	0.0296
LDL cholesterol	1.005 (0.997–1.014)	0.2346		
Creatinine	1.021 (0.885–1.178)	0.7762		
Hypertension	1.317 (0.660–2.628)	0.4347		
Smoking habit	0.510 (0.257–1.012)	0.0540		

### QCA

The results of QCA are summarized in Fig. 1. In the IGT group, smaller AVD and longer ALL were found than in the NGT group ( $P < 0.05$ ). These angiographic changes were more prominent in the treated diabetes group ( $P < 0.05$ ). When assessed by the Gensini score, statistics reached significance only between the NGT and the treated diabetes groups.

### Univariate and multivariate analyses

We found that the angiographic characteristics of the IGT and diabetes groups were small AVD and long ALL. Therefore, to investigate which clinical variables and risk factors were associated with these morphological changes in the coronary artery, we performed univariate and multivariate analyses (Table 2). Age, female sex, and postprandial glucose and creatinine levels were significant predictors of small AVD (<3.0 mm) by univariate analysis. By multivariate analysis, female sex and postprandial glucose and creatinine levels were independent predictors. In addition, age, female sex and fasting and postprandial glucose levels, A1C, and lower HDL cholesterol levels were signif-

icant predictors of long ALL (>20 mm) by univariate analysis. Among these parameters, age, female sex, and postprandial glucose and lower HDL cholesterol levels were independent predictors by multivariate analysis.

**CONCLUSIONS**— The major findings of the present study using computer-assisted QCA analysis are that the morphological changes of small vessel diameter and diffuse vessel narrowing developed not only in the diabetes groups but also in the IGT group. Furthermore, these changes were associated with postprandial hyperglycemia.

### High prevalence of IGT in patients with coronary artery disease

A previous study reported a high prevalence of abnormal glucose tolerance (IGT 35% and diabetes 31%) in 181 patients with acute myocardial infarction (6). In the present study of patients with angina pectoris, the prevalences of IGT and diabetes (preclinical and treated) were 24.9 and 52.5%, respectively. Also, FPG and A1C levels were similar between the IGT and NGT groups. These findings indicate

that IGT plays a pathological role and its diagnosis based on a 75-g OGTT is important in patients with coronary artery diseases.

### Angiographic characteristics in patients with IGT

Although IGT is a risk factor not only for the development of diabetes but also for cardiovascular morbidity and mortality (1,7–10), there have been few reports of the angiographic characteristics in patients with IGT. In a previous study of 99 patients with coronary artery disease (11), abnormal glucose tolerance (IGT and diabetes) was found in 37 patients, for whom the degree of coronary atherosclerosis, assessed by a hand-held caliper method, was the same as that for patients with NGT. Another study (12) was performed using 466 patients who were undergoing coronary angiography, including patients with chest pain syndrome (10%) and those with nonischemic cardiac disease (21%). QCA analysis could not reveal differences between the NGT group ( $n = 291$ ) and the IFG group ( $n = 82$ ), which would be due to the high percentage of patients without

significant coronary artery narrowings (67–73%) in these two groups. Therefore, in the present study, we focused on patients both with angina pectoris and with angiographically documented coronary artery narrowings.

QCA analysis has the advantage of being more accurate and reproducible than visual hand-held caliper measurements (13–16). However, in particular patients with diffuse narrowings it is difficult to identify a reference segment against which diseased lesions can be compared. In these patients, there is the possibility of underestimating the severity of vascular disease when it is assessed by “percent” diameter of stenosis. In fact, as shown in Fig. 1, this could happen with the measurement of Gensini score, which enabled us to detect changes in patients with IGT. In the present study, we defined segments narrowed to a diameter of  $\leq 1.5$  mm as diseased lesions in the major proximal segment of coronary trees. Although further modification of methodology to consider left main coronary artery lesions is needed, the present study using QCA analysis, which assesses absolute values, is a novel method to assess pathological changes of diffuse and small coronary lesions.

We found that there were significant differences in AVD and ALL between the NGT and IGT groups, indicating that angiographic atherosclerotic changes (smaller vessel diameter and longer lesion length) develop in coronary arteries in patients with IGT. The degree of changes found in patients with IGT was similar to that in patients with preclinical diabetes but was less than that in treated diabetic patients in whom FPG and A1C levels were markedly elevated.

### Postprandial hyperglycemia as an important determinant for coronary atherosclerosis

As seen in previous epidemiological studies, such as the DECODE study (2), the risk of cardiovascular disease is strongly associated with postprandial hyperglycemia. In the present study, multivariate analysis showed that the postprandial glucose level was an independent predictor for both small AVD ( $< 3.0$  mm) and long ALL ( $> 20$  mm) (17–22), indicating that postprandial hyperglycemia is strongly associated with diffuse and small coronary artery narrowing in patients with abnormal glucose tolerance.

Hyperglycemia promotes atherogenesis by several possible mechanisms, including increased generation of free radicals (oxidative stress), decreased production of nitric oxide, activation of the polyol pathway and the diacylglycerol-protein kinase C system, and increases in nonenzymatic glycation products and the glycosylation of certain proteins (23–28). A recent *in vivo* study (29) demonstrated that inflammatory cytokine levels were more affected by oscillatory than continuous hyperglycemia and that this inflammatory response to hyperglycemic spikes was attenuated by antioxidants. These findings may explain, in part, why acute hyperglycemia occurring postprandially could produce cardiovascular damage.

### Limitation

Because this is a retrospective clinical investigation, we acknowledge the possibility of a selection bias for some patients. Also, a statistical association does not prove that the risk factor directly promotes coronary artery atherosclerosis. Thus, in addition to measurements of potential confounders (e.g., fat distribution, physical fitness, or inflammation), prospective studies of an interventional nature will be required to determine whether postprandial hyperglycemia has a causal role in development of coronary artery disease.

In summary, the present study using quantitative angiographic analysis demonstrates that postprandial hyperglycemia is associated with the development of diffuse coronary artery narrowings in patients with angina pectoris.

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