Patients Undergoing Coronary Artery Bypass Graft Surgery Are at High Risk of Impaired Glucose Tolerance and Diabetes Mellitus During the First Postoperative Year

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This study demonstrates that patients who have undergone coronary artery bypass graft (CABG) surgery have a high prevalence of abnormal glucose tolerance 3 months and 1 year later. Although only 6% were known to have diabetes mellitus (DM) preoperatively, a further 4% were classified DM at two oral glucose tolerance tests (OGTTs) over the subsequent year and a further 18% were classified as having impaired glucose tolerance (IGT) at 12 months. Reproducibility of the 120-minute plasma glucose level in the 75-g OGTT was estimated from a repeat test performed within 10 days. The coefficient of variation (CV) of 120-minute glucose was between 14% and 18%. The observed changes in class of glucose tolerance observed at OGTTs repeated 6 and 12 months after surgery differed from the predicted changes based purely on the estimated variability of 120-minute glucose measurement. There was evidence of regression to the mean for the IGT group. However, there was also evidence of deteriorating glucose tolerance in some subjects. Between 4% and 9% of those with IGT 3 months after CABG surgery developed DM by 12 months, and 26 (13%) of those with initially normal glucose tolerance (NGT) developed IGT. Insulin and glucose responses in the OGTT and estimates of insulin resistance and β-cell function from fasting samples show that insulin resistance was the principal abnormality in IGT subjects, whereas in DM subjects, both insulin resistance and β-cell dysfunction contributed. Analysis of preoperative patient characteristics showed that the presence of either a systolic blood pressure of 140 mm Hg or body mass index (BMI) of more than 25 kg/m^2 identified 51% of the subjects who would at 1 year after surgery include all those who would be classified DM and 67% of those who would have IGT. Further analyses including insulin levels identified groups at particularly high risk of DM, but no combination of readily available preoperative measures identified all those destined to be classified IGT.

ABNORMAL GLUCOSE tolerance is predictive of coronary heart disease events.[1-5] The association is not confined to those with diabetes mellitus (DM) but includes those with impaired glucose tolerance (IGT).[4,5] In patients undergoing coronary artery bypass graft (CABG) surgery, treated DM is associated with more diffuse coronary artery disease and with a poorer long-term result from surgery.[6,7] Whether IGT and "biochemical" DM diagnosed by screening of asymptomatic individuals have similar implications is not known. Nor is it known what the risk of progression is from normal glucose tolerance (NGT) to IGT or from IGT to DM in this population. This is the first report describing, in an unselected group of CABG patients, the prevalence and natural history of IGT and DM diagnosed by repeated oral glucose tolerance tests (OGTTs) according to modern criteria.[8,9]

SUBJECTS AND METHODS

The patients were a series of 353 consecutive patients (297 male) undergoing elective CABG surgery over a 15-month period. All were treated at the Freeman Hospital, Newcastle-upon-Tyne, UK. Preoperative and first-year postoperative follow-up data are presented.

Before surgery, venous blood was drawn after an overnight fast for measurement of fasting glucose and insulin levels, together with other lipid and glycemic measures. Three months after surgery, all surviving subjects were invited to undergo an OGTT. A diet sheet was given to subjects to ensure that a minimum of 150 g carbohydrate was consumed on each of the 3 days immediately preceding the OGTT. Subjects attended after a 10- to 12-hour overnight fast. A flexible venous cannula (Braunula; Braun, Melsungen, Germany) was placed in a forearm vein, and a venous blood sample was drawn for lipid and glucose measurements. Subjects were seated for the remainder of the test. A half-hour after cannulation, a further blood sample was drawn, and the OGTT commenced with the ingestion of a drink containing 75 g glucose monohydrate over 4 minutes. Further samples for glucose and insulin measurement were drawn at 30, 60, and 120 minutes. OGTT results were classified according to World Health Organization criteria using the fasting and 2-hour plasma glucose value.[9] A repeat OGTT was performed within 10 days for 49 of the subjects initially classified IGT, 14 subjects initially classified DM, and 18 subjects initially classified NGT, to calculate the coefficient of variation (CV) of the OGTT. Any subject with abnormal glucose tolerance at 3 months had an additional OGTT performed at 6 months after surgery. A further OGTT was performed in 283 survivors at 12 months after surgery. For OGTTs repeated after 10 days at 3 months after surgery and performed at 6 months and 12 months after surgery, blood samples were obtained at 10, 20, 30, 45, 60, and 120 minutes after glucose was ingested. Not all subjects with known DM (diagnosed preoperatively) had serial OGTTs, but all had fasting plasma glucose and serum insulin measurements.

Body mass index (BMI) was calculated (weight in kilograms divided by height in meters squared). Blood pressure was measured using a mercury-in-glass sphygmomanometer. The mean of two measurements made with an interval of 5 minutes after subjects had been seated for more than 30 minutes was used in subsequent analyses. Total cholesterol, triglyceride, and insulin

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concentrations were determined in serum. High-density lipoprotein (HDL) cholesterol concentration was measured in EDTA plasma, and glucose concentration in fluoride-oxalate plasma. Hemoglobin A_1 (Hb_{A1}) was determined using an electroendosmosis method (CV 8.1%). Serum insulin[10] level was measured by radioimmunoassay. Plasma nonesterified fatty acid (NEFA)[11] level was measured using a Cobas BIO (Roche Products Limited, Welyn Garden City, UK) automated enzymatic centrifugal analyzer. Venous plasma glucose was determined using a glucose analyzer (Yellow Springs Instruments, Yellow Springs, OH) after centrifugation of blood collected in fluoride-oxalate tubes. Standard enzymatic methods were used to measure serum levels of cholesterol (cholesterol oxidase, interassay CV 1.5% to 2.2%) and triglycerides (lipase-glycerol kinase, interassay CV 3.0%). HDL cholesterol was isolated from EDTA plasma after precipitation of apolipoprotein B–containing lipoproteins with heparin and manganese and assayed using the cholesterol oxidase method (interassay CV 3.6%).

Statistics

Before analysis, fasting blood glucose, fasting serum insulin, triglyceride, and NEFA distributions were normalized by log transformation. For these variables, the geometric mean ± SD is presented. For other measures, the mean ± SD is presented. Differences between groups were analyzed using one-way ANOVA with Tukey's test to estimate which groups were significantly different. For repeated measures, multivariate ANOVA was used. Pearson correlation coefficients and coefficients of determination were used for linear associations. Slopes of regression lines were compared using the unpaired Student's t test. The area under the curves for determination of incremental glucose and insulin was calculated by Simpson's rule for curves with even numbers of equal-duration time intervals, and by three-eighths rule for curves with odd numbers of equal-duration time intervals. The CV of 120-minute blood glucose in the OGTT was calculated from the formula for duplicates:

$$CV = \frac{\frac{\Sigma (G_1 - G_0)^2}{2n}}{\text{mean}}.$$

G_1 and G_0 are the paired 2-hour glucose measurements from the same in individuals. For subjects with each class of glucose tolerance obtained at the 3-month OGTT, the proportion of subjects expected to have changed glucose tolerance on a subsequent repeat OGTT was calculated by estimating the area in the tail of a standard normal distribution of 120-minute blood glucose with the same mean 120-minute glucose as obtained at the initial 3-month OGTT and the same standard deviation of 120-minute glucose as observed for the 3-month duplicate OGTTs. The expected frequency of OGTT results was then compared with those observed using χ^2 analysis. Pancreatic β-cell function and insulin resistance were calculated from fasting blood glucose and serum insulin concentrations using the computer-solved homeostasis model assessment (HOMA) method described by Matthews et al.[12] Pancreatic β-cell function, expressed as a percentage, equals [(20 · fasting insulin)/fasting plasma glucose] − 3.5. Insulin resistance equals fasting insulin/$22.5e^{-\ln \text{fasting plasma glucose}}$ (expressed as units = mU insulin · kg body weight/l · mg glucose infused · min).

Relative risk and 95% confidence intervals of the relative risk were also calculated for preoperative variables that might predict postoperative glucose tolerance. Discriminant function analysis was performed against 12-month glucose tolerance (coded 0 = NGT, 1 = IGT, and 2 = DM) based on a selection of preoperative patient variables: log fasting glucose, log fasting insulin, age, BMI, gender (coded 1 = men and 2 = women), HOMA insulin resistance, HOMA β-cell function, systolic blood pressure, log NEFA, and log triglyceride. Analysis was performed either by direct entry or with variables entered to minimize between-group residual variance.

RESULTS

Postoperative Changes in Weight, Blood Pressure, Lipids, and Fasting Glycemia

Three months after CABG, there were significant but relatively small changes in weight and BMI (−3%), total cholesterol (−12%), triglycerides (−17%), low-density lipoprotein (LDL) cholesterol (−18%), and HOMA β-cell function (−12%). There were significant increases in HDL cholesterol (11%), NEFA (24%), and fasting plasma glucose (2%). HbA_1, fasting insulin, and HOMA insulin resistance were unchanged. At 12 months, significant differences from preoperative values persisted for weight, LDL cholesterol, triglycerides (−23%), HDL cholesterol (17%), diastolic blood pressure, and systolic blood pressure. At 12 months, all measures of fasting glycemia were no different from preoperative values (Table 1). Comparing 3-month and 12-month OGTT data, 120-minute insulin and glucose concentrations were unchanged (120-minute glucose: 3-month 6.9 ± 2.2 *v* 12-month 6.7 ± 2.1 mmol/L, P = NS; 120-minute insulin: 3-month 68 ± 48 *v* 12-month 68 ± 57 μU/mL, P = NS). Comparing 3-month and 12-month OGTT data, there were small but significant increases in the area under both glucose (3-month 16.5 ± 3.6 *v* 12-month 16.9 ± 3.9 mmol/L · 120 min, $P < .05$) and insulin (3-month 157 ± 108 *v* 12-month 175 ± 122 μU/mL · 120 min, $P < .005$).

Prevalence of Abnormal Glucose Tolerance 3 and 12 Months After CABG

Three months after surgery, 6% of patients were known to have DM, a further 4% were classified DM at OGTT, and 20% were classified IGT. The overall prevalence of abnormal glucose tolerance was 35% of those studied (those studied being 88% of survivors). At 12 months, the prevalence of DM was unchanged, but a nonsignificant reduction in the prevalence of IGT had occurred (3-month 20.3% *v* 12-month 15.3%, P = NS). Abnormal glucose tolerance was present in 29% of those studied (87% of survivors). No subjects with 120-minute plasma glucose values greater than 7.8 mmol/L and less than 11.1 mmol/L had fasting plasma glucose values greater than 7.8 mmol/L. The 120-minute blood glucose value therefore reflected prevalence of IGT and DM (Table 2). Figure 1 demonstrates that in 261 subjects studied at both 3 and 12 months after CABG, there was no difference in the distribution of 120-minute glucose at 3 and 12 months. In the 272 subjects studied at 12 months (14 of 33 with DM were not retested at 12 months), the distribution of 2-hour plasma glucose was positively skewed with no evidence of bimodality (Fig 2).

Reproducibility of OGTT

The 3-month OGTT was repeated within 10 days in 81 subjects (first-test glucose tolerance results: normal in 18, IGT in 49, and DM in 14). The CVs of duplicate fasting and

Table 1. Changes in Lipid and Glycemic Measures, Blood Pressure, and Weight After CABG

	Preoperative (n = 353)	Postoperative 3 Months (n = 295)	Postoperative 6 Months (n = 281)	Postoperative 12 Months (n = 283)
Weight (kg)	74.7 ± 10.9	72.9 ± 10.9*	73.0 ± 11.2†	74.3 ± 11.5*
BMI (kg/m²)	25.7 ± 2.9	25.1 ± 2.9*	25.3 ± 3.6§	25.8 ± 3.2
Waist-to-hip ratio	—	—	0.93 ± 0.05	0.92 ± 0.05
Systolic BP (mm Hg)	127 ± 18	—	—	137 ± 20*
Diastolic BP (mm Hg)	76 ± 10	—	—	81 ± 12*
Total cholesterol (mmol/L)	6.5 ± 1.3	5.7 ± 1.1*	5.8 ± 1.1*	6.0 ± 1.1
Triglycerides (mmol/L)				
Geometric mean	1.91	1.58	1.58	1.48
Geometric SD	1.20-3.02	1.02-2.45*	0.98-2.57*	0.87-2.51§
HDL cholesterol (mmol/L)	1.01 ± 0.27	1.12 ± 0.25*	1.19 ± 0.28*	1.18 ± 0.28*
LDL cholesterol (mmol/L)¶	4.32 ± 1.16	3.54 ± 0.89*	3.59 ± 0.95*	3.73 ± 0.92‖
NEFA (mmol/L)				
Geometric mean	0.45	0.56	0.49	0.49
Geometric SD	0.28-0.71	0.36-0.87*	0.31-0.78	0.32-0.74
HbA_1 (%)	6.7 ± 1.0	6.4 ± 0.9	6.6 ± 1.1	6.6 ± 1.0
Fasting plasma glucose (mmol/L)				
Geometric mean	5.4	5.5	5.4	5.4
Geometric SD	4.5-6.5	4.7-6.5*	4.6-6.3	4.6-6.3
Fasting insulin (μU/mL)				
Geometric mean	8	7	7	8
Geometric SD	4-16	4-15	4-15	5-17
HOMA β-cell function (%)	34.8 ± 29.0	30.6 ± 23.9‡	30.5 ± 27.2#	33.4 ± 28.5
HOMA insulin resistance (U)	2.65 ± 4.13	2.59 ± 4.10	2.51 ± 3.72	2.62 ± 3.22

*$P < .001$, †$P < .005$, ‡$P < .01$, §$P < .02$, ‖$P < .05$: preoperative value by multivariate ANOVA.
¶Calculated according to Friedewald formula.
#$P = .06$.

120-minute glucose measurements were as follows: for fasting glucose, first-test NGT, CV = 6%; first-test IGT, CV = 6%; and first-test DM, CV = 4%. For 120-minute glucose, first = test NGT, CV = 14%; first-test IGT, CV = 18%; and first-test DM, CV = 16%. The CV of the 120-minute glucose value was unaffected by the interval between the two OGTTs. Comparing 3-month and 12-month 120-minute glucose values, the CV was 12% for those initially NGT, 18% for those initially IGT, and 17% for those initially DM. The relationship between 2-hour plasma glucose in two OGTTs performed within 10 days is shown in Fig 3 (2-hour glucose in test 2 = 0.84 · 2-hour glucose in test 1, $r^2 = .544$). Overall, 48% of repeat OGTTs showed the same class of glucose tolerance as the initial test. Of those initially NGT, 25% of repeat tests were IGT. Of those initially IGT, 61% of repeat tests were NGT and 6% were DM. Of those initially DM, 29% of repeat tests were IGT and 7% were NGT.

Table 2. Glucose Tolerance at 3 and 12 Months After CABG Surgery

Class of Glucose Tolerance	3 Months No.	3 Months %	12 Months No.	12 Months %
NGT	193	54.5	200	56.2
IGT	68	19.3	50	14.2
New DM	13	3.7	13	3.7
Known DM	21	5.9	20	5.7
Dead	18	5.1	27	7.6
Missing	40	11.5	43	12.6

Changes in Glucose Tolerance

Figure 2 shows the distribution of 120-minute plasma glucose values at 12 months after CABG according to the class of glucose tolerance at 3 months. Of those who were IGT at 3 months, the 120-minute plasma glucose in the 12-month OGTT varied between 3.1 and 12.8 mmol/L. Results of repeated OGTTs over the first 12 postoperative months are shown (Table 3) for those subjects who were either IGT or DM at 3 months. Included in the table are the expected frequencies of each class of glucose tolerance based on the expected proportion of the population contained in the tail of the standard normal distribution beyond a given cutoff point of glucose tolerance for a group with the same mean 120-minute plasma glucose value in the 3-month OGTT and with the same standard deviation of Δ120-minute glucose in comparing the two 3-month OGTTs (10 days apart). There are significant differences between observed and expected frequencies of glucose tolerance at the 3-month repeat, 6-month, and 12-month OGTTs for those IGT at 3 months, with an excess of NGT for those initially IGT. For DM subjects at 3 months, the apparent excess of IGT and of DM at 6 and 12 months is not significant. For NGT subjects at 3 months, comprehensive data were available only for 3- and 12-month time points. The observed prevalence of glucose tolerance at 12 months (91% NGT, 8% IGT, and 0.5% DM) was significantly different from the predicted values (98% NGT, 2% IGT, and 0% DM; $P < .025$).

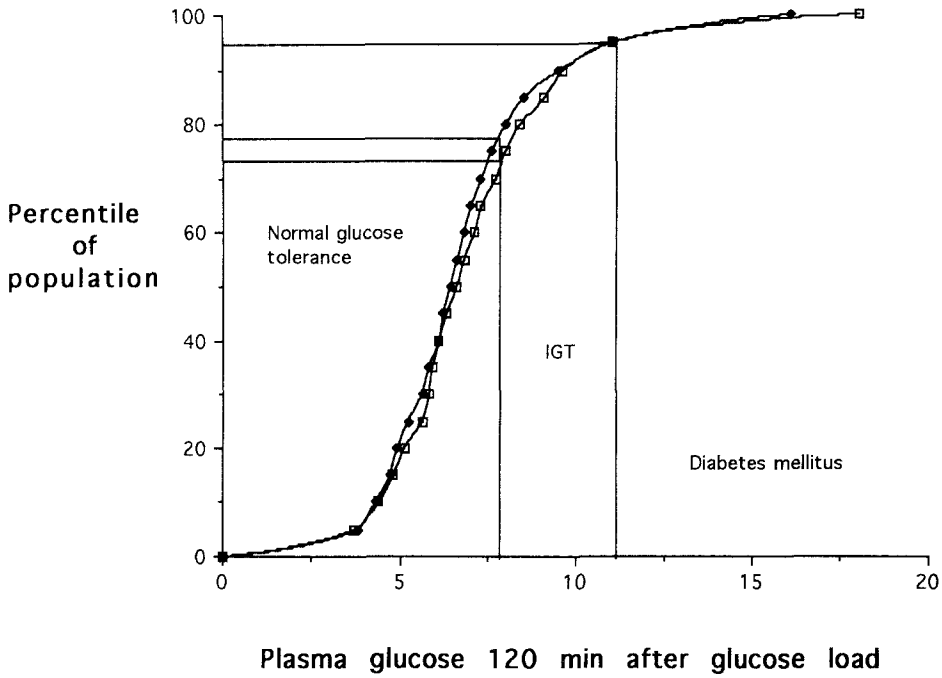

Fig 1. Cumulative frequency (vertical axis) of 120-minute plasma glucose measurements (horizontal axis) for 261 patients who had OGTTs at 3 (□) and 12 (◆) months after CABG surgery. Geometric mean for 120-minute plasma glucose: 3 months, 6.8 (4.8-9.5) mmol/L; 12 months, 6.6 (4.8-9.1). Median 120-minute plasma glucose: 3 months, 6.7 mmol/L; 12 months, 6.5.

Relationship Between Glycemia, Insulinemia, and Other Patient Characteristics

All classes of glucose tolerance at 3 and 12 months were similar with respect to gender, age, BMI, diastolic blood pressure, fasting insulin, total cholesterol, HDL cholesterol, and HOMA β-cell function (Table 4). There were significant differences between classes of glucose tolerance for fasting glucose, systolic blood pressure, triglycerides, NEFA, HbA_1, and HOMA insulin resistance. For glucose-stimulated data, incremental glucose area in the OGTT differed significantly ($P < .001$), but incremental insulin area over 120 minutes was no different. However, incremental insulin area over 30 and 60 minutes of the OGTT (12-month data) was smaller in DM than in IGT or NGT, and incremental area to 30 minutes was smaller in IGT than in NGT. Insulin levels at 120 minutes were higher in IGT and new DM than in NGT, but were no different for symptomatic DM subjects than for normals. The ratio of 120-minutes to 60-minute insulin is significantly different in IGT and DM than in normals at 3 and 12 months, as is the ratio of insulin to glucose incremental areas of the OGTT.

The relationship between incremental glucose area and incremental insulin area following a 75-g oral glucose load at 12 months after CABG is shown in Fig 4. The slope of the regression line was not significantly different for IGT subjects (n = 52) than for normals (n = 194). The slope for

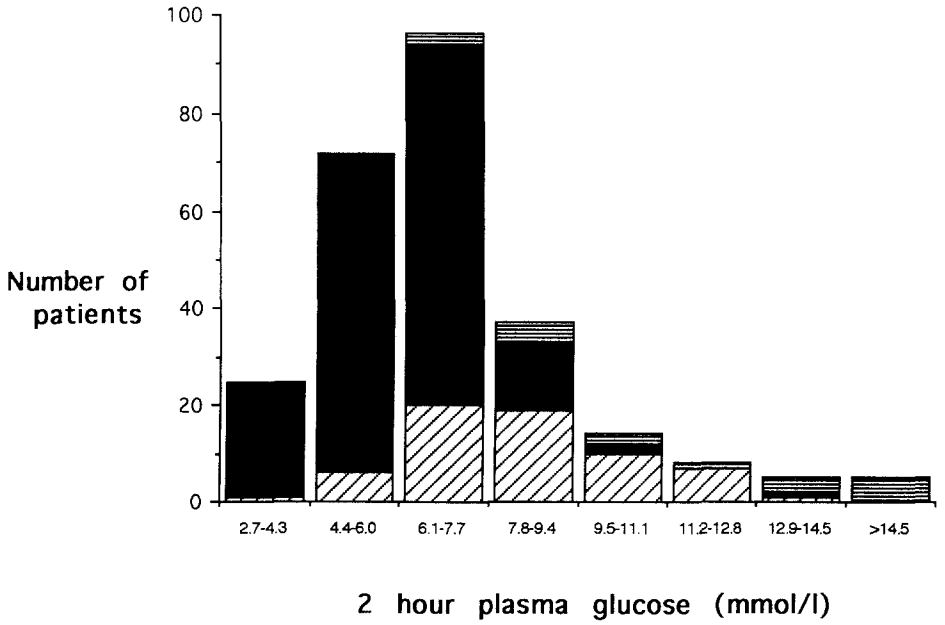

Fig 2. Distribution of 120-minute plasma glucose at the 12-month OGTT according to class of glucose tolerance at the 3-month OGTT. (▤) DM; (■) NGT; (▨) IGT.

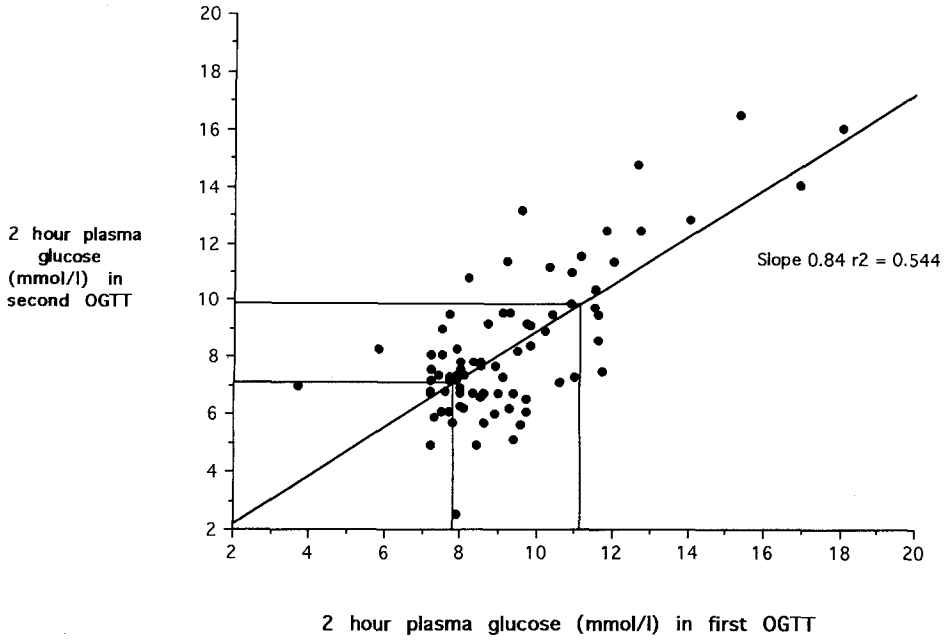

Fig 3. Relationship between 120-minute plasma glucose at the 3-month 75-g OGTT (test 1) and the OGTT repeated within 10 days (test 2).

DM subjects (n = 13) was negative, ie, for increasing glucose intolerance, the insulin response was smaller than for those with NGT (slope for DM −4.12 [SE 4.20] *v* normal 18.56 [SE 3.00], $P < .001$). In NGT subjects, there was no difference in the relationship according to whether BMI was greater or less than 25 kg/m^2 (data not presented).

Predictors of Abnormal Glucose Tolerance

Those subjects known to have DM preoperatively were excluded from these analyses. The relationship between changes in incremental insulin and glucose responses, HOMA insulin resistance, and β-cell function with deterioration or improvement in glucose tolerance were explored. In this study population, IGT subjects with values in upper or lower quintiles of the distributions of each of these factors were no more likely to show improvement or deterioration in glucose tolerance than other subjects with IGT (with 95% confidence intervals embracing the relative risk of 1 in all cases).

The relationship was explored between preoperative patient characteristics and classification of glucose tolerance at the 12-month postoperative time point (Table 5). This includes characteristics routinely available to all clinicians (fasting plasma glucose, blood pressure, BMI, triglycerides, and HbA_1) and factors for which an application in routine management of the pre-CABG patient has yet to be defined (fasting serum insulin, fasting NEFA, computer model–estimated HOMA β-cell function, and insulin resistance). The relative risk for DM was 0.6 for the lower

Table 3. Changes in OGTT Results During First Postoperative Year

	Repeat 3-Month OGTT				OGTT at 6 Months				OGTT at 12 Months			
	Observed		Expected		Observed		Expected		Observed		Expected	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
IGT at 3 months												
NGT	30	61	18	37	32	51	14	22	27	44	14	22
IGT	16	33	29	59	27	44	43	70	29	47	43	70
DM	3	6	2	4	3	5	5	8	6	9	5	8
Missing	19		19		6		6		6		6	
Total	68		68		68		68		68		68	
	$P < .05$				$P < .005$				$P < .05$			
DM at 3 months												
NGT	1	7	0	0	2	15	0	0	1	8	0	0
IGT	4	29	3	24	4	31	2	13	5	46	1	9
DM	9	64	11	75	7	54	11	87	5	46	10	91
Missing	0		0		1		1		3		3	
Total	14		14		14		14		14		14	
	P = NS				P = NS				P = NS			

NOTE. Subjects with either IGT or DM at the first 3-month OGTT were repeatedly restudied over the first year after surgery. The expected partitioning of subjects across diagnostic cutoff points of 2-hour glucose tolerance was based on the CV of the 2-hour glucose and the mean 2-hour glucose for the group observed at the first 3-month OGTT. Differences between observed and expected are compared using χ^2 analysis.

Table 4. Relationship Between Patient Characteristics and Glucose Tolerance at 3 and 12 Months After CAB Surgery

Characteristic	3 Months				12 Months				ANOVA	
	NGT (n = 193)	IGT (n = 68)	New DM (n = 13)	Known DM (n = 10)	NGT (n = 200)	IGT (n = 50)	New DM (n = 13)	Known DM (n = 6)	3 Months	12 Months
Gender (M:F)	169:24	56:14	9:4	8:2	171:29	44:6	11:2	5:1	NS	NS
Age, (yr)	56.0 ± 7.7	58.2 ± 6.4	61.0 ± 5.3	58.6 ± 6.5	57.7 ± 7.6	59.0 ± 7.0	58.9 ± 7.4	59.5 ± 6.7	NS	NS
BMI (kg/m^2)	24.9 ± 2.9	25.2 ± 2.8	26.7 ± 2.3	24.9 ± 2.6	25.6 ± 3.2	26.3 ± 3.1	26.9 ± 4.0	24.7 ± 6.6	NS	NS
Waist-to-hip ratio	0.93 ± 0.05	0.93 ± 0.05	0.94 ± 0.05	0.95 ± 0.03‡	0.92 ± 0.05	0.93 ± 0.05	0.93 ± 0.93	0.95 ± 0.03	$P < .05$	NS
Systolic BP (mm Hg)	124 ± 17	132 ± 17‡	134 ± 23‡	127 ± 18	133 ± 19	140 ± 18‡	141 ± 12‡	139 ± 19	$P < .01$	$P < .05$
Diastolic BP (mm Hg)	75 ± 9	77 ± 10	79 ± 10	73 ± 10	80 ± 12	83 ± 10	84 ± 14	78 ± 11	NS	NS
Fasting plasma glucose (mmol/L)										
Geometric mean	5.2	5.5	6.0	8.1	5.2	5.5	5.9	7.6	$P < .001$	$P < .001$
Geometric SD	4.8-5.8	4.9-6.2‡	5.1-7.1*§	5.9-11.2*§	4.7-5.6	4.9-6.2*	4.9-7.1*§	5.4-10.7*§		
Fasting serum insulin (μU/mL)										
Geometric mean	7	7	11	11	7	8	12	11	NS	NS
Geometric SD	4-14	3-16	5-24	5-27	2-14	4-14	7-22	5-26		
HbA_1 (%)	6.2 ± 0.8	6.4 ± 0.8	6.9 ± 1.0	7.3 ± 1.1†	6.5 ± 0.8	6.5 ± 0.7	7.0 ± 1.1‡	8.0 ± 1.8†	$P < .001$	$P < .001$
Total cholesterol (mmol/L)	5.7 ± 1.1	5.7 ± 1.0	5.6 ± 0.8	5.8 ± 1.2	5.9 ± 1.1	6.2 ± 1.1	6.1 ± 0.9	6.1 ± 1.1	NS	NS
HDL cholesterol (mmol/L)	1.13 ± 0.25	1.11 ± 0.25	1.06 ± 0.23	1.07 ± 0.27	1.20 ± 0.27	1.14 ± 0.29	1.06 ± 0.32	1.13 ± 0.26	NS	NS
Triglyceride (mmol/L)										
Geometric mean	1.51	1.55	2.14	1.78	1.51	1.78	2.24	1.66	$P < .01$	$P < .05$
Geometric SD	0.98-2.34	1.07-2.24	1.38-3.31†‖	0.95-3.31*¶	0.95-2.40	1.12-2.82‡	1.20-4.17†	0.95-2.88		
NEFA (mmol/L)										
Geometric mean	0.54	0.65	0.71	0.59	0.48	0.55	0.69	0.55	$P < .005$	$P < .005$
Geometric SD	0.36-0.79	0.42-1.00‡	0.48-1.05†	0.37-0.93	0.32-0.72	0.40-0.78‡	0.41-1.17†	0.33-1.10		
HOMA β-cell function	29.9 ± 21.6	29.8 ± 23.8	43.5 ± 44.2	36.0 ± 34.0	32.2 ± 28.2	37.5 ± 30.5	38.2 ± 24.9	36.0 ± 30.6	NS	NS
HOMA insulin resistance	2.03 ± 1.35	2.44 ± 2.07	4.46 ± 5.17†‖	13.0 ± 19.80†‖	2.2 ± 1.9	2.8 ± 2.2	4.5 ± 5.0*¶	3.2 ± 2.1*	$P < .001$	$P < .001$
120-minute serum insulin (μU/mL)†										
Geometric mean	43	82	101	45	44	87	95	47	$P < .001$	$P < .005$
Geometric SD	20-91	42-159*	57-77†	21-93	22-90	48-160*	50-179†	24-93		
Area under glucose curve to 120 minutes#	15.0 ± 2.7	19.3 ± 2.8*	23.9 ± 3.0*	31.0 ± 7.6*	15.5 ± 2.7	20.2 ± 2.8*§	25.3 ± 4.1*§	29.9 ± 6.4*§	$P < .001$	$P < .001$
Area under insulin curve to 30 minutes#	—	—	—	—	24 ± 13	21 ± 11	16 ± 7‡¶	11 ± 11†‖	—	$P < .001$
Area under insulin curve to 60 minutes#	—	—	—	—	70 ± 38	65 ± 36	54 ± 28	25 ± 21†‖	—	$P < .001$
Area under insulin curve to 120 minutes#	154 ± 111	155 ± 93	152 ± 88	94 ± 64	171 ± 123	189 ± 110	166 ± 91	106 ± 72	NS	NS
Ratio of incremental insulin to glucose area in 120-minutes OGTT	10.4 ± 7.6	8.1 ± 4.4†	6.4 ± 3.9*‖	2.9 ± 2.1*§	10.8 ± 6.7	9.3 ± 5.4†	6.6 ± 3.6*‖	2.3 ± 1.5*§	$P < .001$	$P < .001$
Insulin 120 min/60 min	0.64 ± 0.35	1.21 ± 0.47*	1.45 ± 0.36*	1.32 ± 0.62*	0.59 ± 0.38	0.96 ± 0.31*	1.20 ± 0.27*	1.13 ± 0.77*	$P < .001$	$P < .001$

*$P < .001$, †$P < .01$, ‡$P < .05$: *v* NGT group.

§$P < .001$, ‖$P < .01$, ¶$P < .05$: *v* IGT group.

#For area under curve, units are: glucose, mmol · 120 min/L; insulin, μU · time/mL.

quartile of β-cell function and 0.8 for the upper quartile of NEFA, and the data for these is therefore not presented. In addition, we attempted to identify as many of the cases of DM at 12 months after surgery using the minimum number of freely available preoperative characteristics. This is summarized in Table 6. Those subjects with preoperative fasting blood glucose values above the 75th percentile (fasting glucose ≥5.4 mmol/L) contained 69% of all cases of DM at 1 year. However, all of the DM subjects were identified in the two subgroups who had a fasting glucose ≥5.4 mmol/L and either had a systolic blood pressure of greater than 140 mm Hg or were overweight (BMI > 25 kg/m^2). These two subgroups represented 13% of the preoperative cohort and 15% of those who were tested at 12

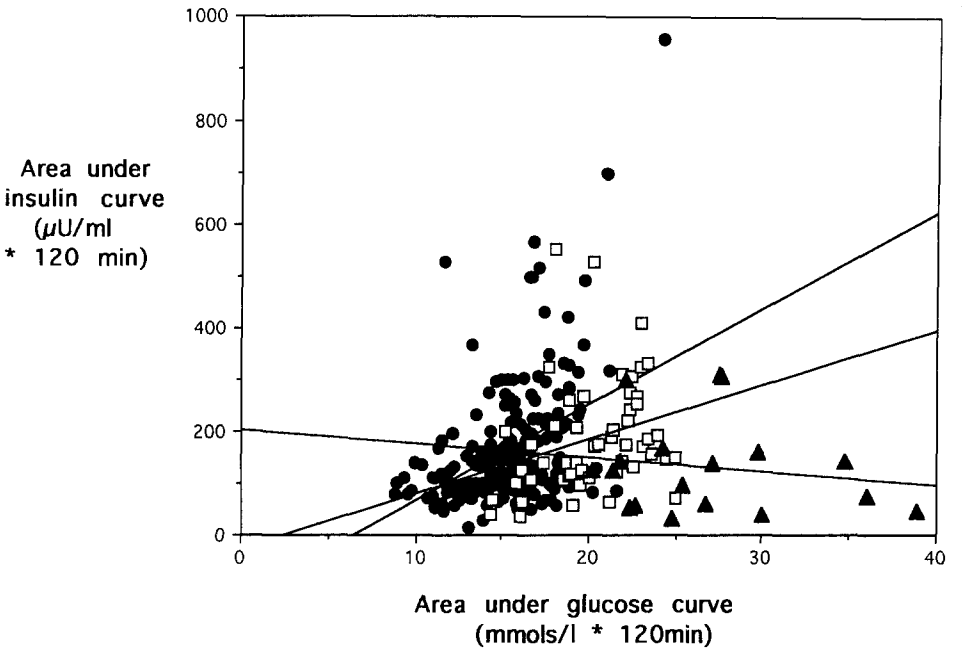

Fig 4. Insulin and glucose responses at the 120-minute OGTT measured as incremental insulin area (Inc I_{120}) and incremental glucose area (Inc G_{120}). Patients responses are shown in relation to class of glucose tolerance at 12-month OGTT. For (●) NGT (n = 194), Inc I_{120} = 18.6 · Inc G_{120} − 117, r^2 = .166. For (□) IGT (n = 50), Inc I_{120} = 10.5 · Inc G_{120} − 23, r^2 = .073 (P = NS *v* NGT). For (▲) DM (n = 13), Inc I_{120} = −4.1 · Inc G_{120} + 218, R^2 = .025 (P < .001 *v* NGT and IGT).

months. There remained 31% of those with DM unidentified, and a similar approach in those subjects with fasting blood glucose less than 5.4 mmol/L allowed identification of all four DM subjects at 12 months based on 27% of the preoperative subjects and 50% of those who were studied at 12 months. From 72% of subjects with glocuse ≥ 5.4 mmol/L (subgroups of patient group A in Table 6), 18 of 21 (86%) of IGT and nine of nine (100%) DM at 12 months were identified. From 54% of subjects with glucose less than 5.4 mmol/L (subgroups of patient group B in Table 6),

Table 5. Relative Risk of DM and IGT 1 Year Postoperatively in Relation to Preoperative Characteristics

Preoperative Characteristic	Preoperative Subjects		Relative Risk of DM at 12 Months After CABG		% of Those Studied Who Have DM	Relative Risk of IGT at 12 Months After CABG		% of Those Studied Who Have IGT
	No.	%	RR	95% CI		RR	95% CI	
Fasting plasma glucose ≥5.4 mmol/L	88	25	5.0	1.4-18.1	14	1.5	0.3-8.0	24
Systolic BP ≥ 140 mm Hg	88	25	4.0	3.3-13.2	11	1.6	0.5-5.4	27
HOMA insulin resistance ≥2.90	88	25	5.5	1.8-17.2	14	1.7	1.0-3.0	29
Fasting serum insulin ≥ 12 mU/L	88	25	5.0	1.2-20.3	12	1.4	0.9-2.2	26
BMI >25 kg/m²	194	55	3.5	1.3-10.0	11	1.4	0.8-2.4	21
Fasting triglyceride ≥2.49 mmol/L	88	25	2.7	0.4-19.1	9	1.3	1.0-1.8	23
HbA_1 ≥7.2%	88	25	1.8	0.1-25.1	10	1.4	0.6-3.1	24
Female sex	56	16	1.6	0.3-9.1	8	1.0	1.0-1.0	18
Fasting plasma glucose ≥5.4 mmol/L and BMI >25 kg/m²	52	15	3.6	1.1-11.4	12	1.7	0.9-3.9	28
Fasting plasma glucose ≥5.4 mmol/L and systolic BP ≥140 mm Hg	16	4.5	2.8	2.0-4.0	38	1.3	0.2-7.2	25
Fasting plasma glucose ≥5.4 mmol/L, BMI >25 kg/m², and systolic BP ≥140 mm Hg	12	3.4	9.3	3.0-28.4	33	1.3	0.1-16.5	29
Fasting plasma glucose ≥5.4 mmol/L and serum insulin ≥12 μU/mL	28	7.9	5.3	1.7-16.5	18	1.6	0.7-3.7	29
Fasting plasma glucose ≥5.4 mmol/L, serum insulin ≥12 μU/ml, and systolic BP ≥140 mm Hg	10	2.8	11.2	4.0-31.7	40	1.1	0.8-1.6	20
Fasting plasma glucose ≥5.4 mmol/L and triglycerides >2.49 mmol/L	22	6.2	6.9	2.3-20.4	23	1.2	0.2-8.8	23
Fasting plasma glucose ≥5.4 mmol/L, triglycerides >2.49 mmol/L, and systolic BP ≥140 mm Hg	8	2.3	14.2	5.2-38.9	50	1.3	0.7-2.3	25
Fasting plasma glucose ≥5.4 mmol/L and HOMA insulin resistance ≥2.90	33	9.3	5.9	2.1-16.8	18	1.8	0.8-3.8	30
Fasting plasma glucose ≥5.4 mmol/L, HOMA insulin resistance ≥2.90, and systolic BP ≥140 mm Hg	11	3.1	14.5	5.7-37	46	0.9	0.5-1.7	18

Abbreviations: CI, confidence interval; BP, blood pressure; RR, relative risk.

Table 6. Relationship Between Preoperative Characteristics and Glucose Tolerance at 12 Months After CABG

Preoperative Characteristic		1 Year Postoperative IGT No.	IGT %	DM No.	DM %
Patient group A with fasting plasma glucose ≥5.4 mmol/L	(n = 82)	21	26	9	11
Select subgroups with Systolic BP ≥ 140 mm Hg *or* Systolic BP < 140 mm Hg and BMI > 25 kg/m²	(n = 10)	4	40	6	60
	(n = 37)	9	24	3	8
Subtotal	(n = 47)	13	28	9	19
Add a further subgroup					
Fasting plasma glucose ≥5.4 mmol/L, Systolic BP < 140 mm Hg, BMI < 25 kg/m², with HOMA IR ≥ 2.9, HbA_1 ≥ 7.2%, triglyceride ≥ 2.49 mmol/L	(n = 13)	5	38	0	0
Total	(n = 60)	18	31	9	15
Patient group B with fasting plasma glucose <5.4 mmol/L	(n = 201)	29	14	4	2
Select subgroups with					
Systolic BP ≥ 140 mm Hg *or* Systolic BP < 140 mm Hg and BMI > 25 kg/m²	(n = 43)	12	28	1	2
	(n = 53)	7	13	3	6
Subtotal	(n = 96)	19	20	4	4
Add a further subgroup					
Fasting plasma glucose <5.4 mmol/L, systolic BP < 140 mm Hg, BMI < 25 kg/m², with HOMA IR ≥ 2.9, HbA_1 ≥ 7.2%, triglyceride ≥ 2.49 mmol/L	(n = 13)	6	46	0	0
Total	(n = 109)	25	23	4	4

Abbreviations: BP, blood pressure; IR, insulin resistance.

25 of 29 (86%) of IGT and four of four (100%) DM at 12 months were identified. To identify all subjects who would test positive for DM at 12 months, all subjects either with a systolic blood pressure of 140 mm Hg or who were overweight could be chosen. This represents 51% of the cohort. Of those characteristics listed in Table 5, no other simple combination of routinely available factors was as efficient. The only other factors that added to the proportion of IGT identified were the upper quartile of HOMA insulin resistance, HbA_1, and triglyceride. Eighty-six percent of all IGT subjects could be identified from 60% of the cohort. An alternative view of the data is that any subject who was not overweight, did not have a systolic blood pressure ≥ 140 mm Hg, and had a HOMA insulin resistance estimate less than 2.9, a HbA_1 less than 7.5, and a triglyceride concentration less than 2.49 mmol/L comprised 40% of the cohort, contained only 12% of those destined to test positive for IGT and none who were found to have DM.

Combinations of risk factors that identify smaller groups with higher relative risks are also listed in Table 5. Those subjects with a combination of three factors comprised small groups with between 60% and 75% prevalence of abnormal glucose tolerance (33% to 50% prevalence of DM). This approach is less useful for identification of IGT with relative risks close to 1 and 95% confidence intervals embracing 1 for all combinations of factors. Using logistic regression, a maximum of 87% of the between-group variance (between groups of post-CABG glucose tolerance: NGT = 0, IGT = 1, and DM = 2) was explained using the following model derived by minimizing the between-group residual variance: glucose tolerance group = −16.0 + 18.1(log preoperative fasting glucose) + 0.9(log preoperative triglyceride) + 0.7(gender: 1 = men and 2 = women) + 0.02(preoperative systolic blood pressure). Additional variables did not add significantly to the predictive accuracy of the model, which at best correctly allocated 58% of cases to their postoperative class of glucose tolerance (62% of NGT, 43% of IGT, and 53% of DM were correctly allocated).

DISCUSSION

After CABG surgery, 35% of patients have abnormal glucose tolerance at 3 months and 29% continue to have abnormal glucose tolerance at 12 months; 10% have DM, of whom 40% were not identified as such before surgery. This is much higher than the prevalence of abnormal glucose tolerance in the United Kingdom population from which these patients are drawn, in which the prevalence of DM is approximately 2% and of IGT approximately 4%.[13,14] These findings are dependent on the quality of the test applied to establish disease prevalence, particularly for IGT, in which the range of values of 120-minute blood glucose to allocate a subject to the class is comparatively small.[14] In several populations, glucose has a bimodal distribution,[15-18] and it has been suggested that any population with a prevalence of diabetes of ≥ 10% may show a bimodal distribution. The population studied in this report contains 10% DM subjects, but the glucose distribution appears continuous and positively skewed, as it does in a mixed US population with lower prevalence of diabetes.[19] The lack of bimodality may reflect unique characteristics of the CABG surgery population, the incomplete study of subjects known to have DM (14 of 20 known to have DM before surgery were not studied at 12 months), or the effect of treatment on the DM subgroup. When subjects were classified DM by OGTT in this study, it was deemed unethical not to advise achievement of ideal body weight and changes to diet that would potentially alter the classification of glucose tolerance at subsequent testing.

Reproducibility of the OGTT

Reproducibility of the test applied is important. The proportion of subjects in the tail of the distribution or the second mode will also affect the number of subjects

allocated by chance to the wrong diagnostic group at a single test. Although this is more tolerable in cross-sectional studies in which overall population prevalences are unlikely to be affected, in the prospective study it may result in fluxes across diagnostic cutoff points over time, which obscures the pattern of real deterioration or improvement in glucose tolerance occurring in important subgroups. The measurement of the 120-minute glucose value is altered by a number of factors, which include the choice of blood sample (venous, capillary, whole blood, and plasma), reliability of the glucose solution ingested, speed at which it is ingested, and pretest carbohydrate loading of the subject.[14,20-24] In this study, diet sheets were supplied to standardize the carbohydrate content of the previous 3-day diet, and tests were performed under standard conditions with timed ingestion of the glucose load and enforced physical inactivity during the test. In our study, the CV of 120-minute glucose is 14% to 18% for the three classes of glucose tolerance, which is small as compared with previous studies (estimated 20% to 35%[14,25-30]). As well as the tightly standardized conditions of the OGTT in this study, the population studied is familiar with medical investigation and unlikely to demonstrate a defense response to investigation.[14] The interval for retest does not appear important, with the CV of 120-minute glucose being no different between an interval of retest of 10 days or 9 months. The high CV will inevitably affect the partitioning of retest values across the diagnostic cutoff points for each class of glucose tolerance, but with the most impact in the IGT group (interval, 3.3 mmol/L; SD of 2-hour glucose, 1.53; mean 120-minute plasma glucose, 8.3 mmol/L). In the situation of OGTT retest (Table 3), the observed frequency of the various classes of glucose tolerance differs significantly from the expected for NGT and IGT, but not for the smaller group of newly identified DM. The redistribution in the IGT group can be partly explained by regression to the mean, because the mean and median blood glucose of the population has not changed between 3 and 12 months after surgery (Fig 3) while the slope of the regression between 120-minute glucose in the second OGTT against the first test is 0.84. The excess of IGT at retest in those previously NGT and a similar excess of DM in those previously IGT suggests that there may also be deterioration of glucose tolerance in some subjects.

Metabolic Change After CABG

An immediate decrease in total cholesterol, LDL cholesterol, and HDL cholesterol may be expected in patients undergoing CABG surgery at commencement of extracorporeal circulation,[31] and it persists in the postoperative period[32] in a pattern similar to that seen after myocardial infarction.[33] The effects of surgery are thought to resolve during the first 3 postoperative months.[32] The present data suggest that some metabolic effects are still present at 3 months, with a significant increase in fasting plasma glucose and NEFA from the preoperative values (Table 1). Estimation of β-cell function shows a significant decrease that resolves by 12 months after surgery with a return to preoperative levels of glycemia. This may be causally associated with a simultaneous deterioration in glycemic control. Basing such conclusions on homeostatic computer modeling of fasting values of glucose and insulin (HOMA) has its limitations compared with a stimulated measure of insulin action or secretion. It is perhaps not surprising that the β-cell function estimate by HOMA is not perfectly correlated with that derived from stimulated studies (hyperglycemic clamp [$r = .61$, $P < .04$] and intravenous glucose tolerance test [$r = .64$, $P < 0.05$]).[12] The proof of the mechanism will require confirmatory stimulated studies. The time course of β-cell dysfunction may reflect endocrine pancreatic injury related to extracorporeal circulation analogous to its known effect on exocrine pancreatic function.[34] It would be surprising for the metabolic effects of surgery to persist for 12 months, and in this study all measures of fasting glycemia had returned to preoperative levels by 12 months.

Postoperative abnormal glucose tolerance, lipids, and insulinemia. Differences in lipid characteristics between patients with different classes of glucose tolerance at 3 and 12 months (Table 4) are broadly in keeping with previously published data.[35-40] There was a significant decrease of incremental insulin concentration during both the first 30 and the first 60 minutes of the OGTT in IGT and DM subjects, but incremental insulin area over the whole 120 minutes was no different between groups. This suggests that a deficiency in acute insulin release may not be restricted to those with DM, but may include those with IGT. There was a decrease in the ratio of incremental insulin to glucose areas over 120 minutes in IGT and DM as compared with NGT. This demonstrates a relative insulin deficiency consistent with decreased pancreatic β-cell function, insulin resistance, or both. Insulin resistance (again using the HOMA model) was significantly higher in IGT and new DM than in NGT subjects. Although fasting insulin concentrations were not significantly different between groups (NGT group demonstrated relative hyperinsulinemia), 120-minute insulin concentrations were higher in IGT and DM, compatible with the accepted relationship between hyperinsulinemia and insulin resistance already observed in epidemiologic studies.[41-43] For subjects with DM, the relationship was significantly different, with a decrease in insulin area with increasing glucose area (Fig 4). This is a characteristic pattern observed in Pima Indians and other populations[43-47] in which DM is characterized by a significant reduction in β-cell function coexisting with insulin resistance and a declining insulin response with increasing glucose levels. The relationship between incremental insulin and glucose in IGT subjects was not significantly different from that in NGT subjects. This is consistent with data from Pima Indians, in which the same relationship was observed and the metabolic defect was characterized by insulin resistance rather than β-cell dysfunction.[43] However, the Pima Indian population was obese (mean BMI in NGT, 32 ± 8 kg/m^2; IGT, 37 ± 8) compared with our population (BMI in NGT, 26 ± 3; IGT, 26 ± 3). It may be that the underlying mechanism in a leaner population is different, with less insulin

resistance and the same degree of glucose intolerance requiring a greater degree of β-cell dysfunction. However, the relationship between insulin and glucose responses is no different in IGT subjects with normal BMI as compared with IGT subjects with elevated BMI (BMI < 25 kg/m^2 [n = 13], incremental insulin area to 2 hours = 9.8 · incremental glucose area to 2 hours − 29, r^2 = .159; BMI > 25 kg/m^2 [n = 27], incremental insulin area to 2 hours = 27.4 · incremental glucose area to 2 hours − 356, R^2 = .478, P = NS), which argues against a different mechanism in our population.

Assessing deterioration in glucose tolerance and predicting abnormal postoperative glucose tolerance. If we assume a bimodal distribution of blood glucose to apply, patients with IGT belong to the tails of the distribution of the NGT and DM groups, with relatively few in the nadir between the two.[48] IGT may therefore be regarded as a combination of IGT normals, IGT in transition, and false-negative DM. There are two important implications of this hypothesis. The first is that IGT is not a stable category, and some individuals will be in transition to DM. The criteria used for describing change in glucose tolerance then assume great importance. Using stringent criteria, we find a rate of progression of 4% from IGT to DM in 9 months (using less strict criteria, this increases to 9%). This is among the highest rates of deterioration in glucose tolerance yet recorded.[14] Follow-up evaluation of this cohort will establish if the trend continues beyond the first postoperative year. The second implication is that there are metabolic differences between the different subgroups of IGT that may predict their future glucose tolerance. Obesity is a predictor of DM,[49-55] but insulin resistance is also predictive of deterioration to DM in several populations[50,51,53,55,56] as a risk factor that may be independent of obesity.[57] Consistent with this, the upper-quartile preoperative fasting insulin and HOMA insulin resistance along with upper-quartile fasting plasma glucose in the present study give the highest relative risk for DM at 12 months after surgery (Tables 5 and 6). However, logistic regression is unhelpful in predicting postoperative abnormal glucose tolerance.

Identification of persons at high risk for DM is important because of the established risk of microvascular complications[58] with the onset of diabetes and the undoubted risk of macrovascular complications.[1,2,4,5] In patients undergoing CABG, it predicts a poor outcome.[6,7] IGT has been associated with ischemic heart disease and a risk of deterioration to DM of 1% to 4% per year in most populations (for review, see Yudkin et al[14]) and a higher rate in this population. This may reflect an altered natural history after CABG surgery perhaps secondary to pancreatic injury. It suggests that surveillance of this patient group is essential.

Conclusion

This report demonstrates that after CABG surgery, patients are at a high risk of IGT and DM. Groups with a particularly high risk of DM postoperatively may be identified even using routinely measured biologic variables (Tables 5 and 6), and this may be improved by estimation of fasting insulin and calculation of HOMA insulin resistance. However, none of these subgroups identify all patients with IGT. With a 29% prevalence of abnormal glucose tolerance at 12 months after CABG surgery, a case could be made for submitting all patients to an OGTT. Previous studies of DM in CABG surgery have been restricted to those patients with overt DM identified preoperatively. This cohort will allow us to examine in future reports whether the risk of progression to DM remains high beyond the first postoperative year and whether IGT and DM are risk factors for graft patency and clinical outcome after surgery.

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