Fasting but not postprandial (postmeal) glycemia predicts the risk of death in subjects with coronary artery disease

Anil Nigam MD MSc[1,3], Martial G Bourassa MD[1,3], Annik Fortier MSc[2,3], Marie-Claude Guertin PhD[2,3], Jean-Claude Tardif MD[1,3]

A Nigam, MG Bourassa, A Fortier, M-C Guertin, J-C Tardif. Fasting but not postprandial (postmeal) glycemia predicts the risk of death in subjects with coronary artery disease. Can J Cardiol 2007;23(11):873-878.

BACKGROUND: Chronic hyperglycemia plays a role in the pathogenesis of coronary artery disease (CAD); however, the cut-off level beyond which glycemia becomes detrimental is still controversial. Postprandial glycemia may be a stronger CAD risk factor than fasting glycemia in patients without documented heart disease.
OBJECTIVES: To identify the contributions of fasting and postprandial glycemia to cardiovascular risk in patients with documented coronary artery disease.
METHODS: The Coronary Artery Surgery Study (CASS) registry is a database of 24,958 patients with suspected or proven CAD who underwent cardiac catheterization between 1974 and 1979. Median long-term follow up was 14.7 years (interquartile range 9.8 to 16.2 years). Clinical outcomes were evaluated according to fasting glucose levels and 2 h postprandial (postmeal) plasma glucose (2hPG) levels. A total of 13,176 patients with baseline fasting glucose levels and 1691 patients with 2hPG levels were identified.
RESULTS: Impaired fasting glycemia was associated with a 1.2-fold increase in both all-cause and cardiovascular mortality (adjusted hazard ratio 1.23; 95% CI 1.08 to 1.40 for cardiovascular mortality), while undiagnosed diabetes was associated with a 1.5-fold increased risk for the same end points. Postprandial hyperglycemia (2hPG of 7.8 mmol/L to 11.0 mmol/L following an average meal) was not associated with a significant risk of death after adjustment for traditional risk factors or in the presence of fasting glucose of less than 6.1 mmol/L.
CONCLUSIONS: In CAD patients, impaired fasting glucose is associated with increased all-cause and cardiovascular mortality, whereas postprandial hyperglycemia following an average meal does not appear to be a risk factor.

Key Words: *Coronary artery disease; Glucose; Obesity; Risk factors; Survival*

La glycémie à jeun, mais pas la glycémie postprandiale, prédit le risque de décès chez des sujets atteints d'une coronaropathie

HISTORIQUE : L'hyperglycémie chronique participe à la pathogenèse de la coronaropathie, mais le seuil au-delà duquel la glycémie devient nuisible demeure controversé. La glycémie postprandiale (après le repas) pourrait constituer un plus grand facteur de risque de coronaropathie que la glycémie à jeun chez les patients atteints d'une coronaropathie documentée.
OBJECTIFS : Dépister l'apport de la glycémie à jeun et de la glycémie postprandiale sur le risque cardiovasculaire chez les patients atteints d'une coronaropathie documentée.
MÉTHODOLOGIE : Le registre de l'étude CASS sur les chirurgies des artères coronaires est une base de données de 24 958 patients atteints d'une coronaropathie présumée ou démontrée qui ont subi un cathétérisme cardiaque entre 1974 et 1979. Le suivi médian à long terme était de 14,7 ans (fourchette interquartile de 9,8 à 16,2 ans). Les issues cliniques ont été évaluées d'après la glycémie à jeun et le taux de glucose plasmatique deux heures après le repas (GP2h). Au total, on a repéré 13 176 patients dont on connaissait la glycémie de base à jeun et 1 691 patients dont on connaissait le GP2h.
RÉSULTATS : Une perturbation de la glycémie à jeun s'associait à une augmentation de 1,2 fois la mortalité toutes causes confondues et la mortalité cardiovasculaire (ratio de risque rajusté 1,23; 95 % IC 1,08 à 1,40 pour la mortalité cardiovasculaire), tandis que le diabète non diagnostiqué s'associait à une augmentation de 1,5 fois le risque d'atteindre les mêmes paramètres ultimes. L'hyperglycémie postprandiale (GP2h de 7,8 mmol/L à 11,0 mmol/L après un repas moyen) n'était pas reliée à un risque significatif de décès après rajustement compte tenu des facteurs de risque classiques ou en présence de glycémie à jeun (GP2h inférieure à 6,1 mmol/L).
CONCLUSIONS : Chez les patients souffrant de coronaropathie, une perturbation de la glycémie à jeun s'associait à une augmentation de la mortalité toutes causes confondues et de la mortalité cardiovasculaire, tandis que l'hyperglycémie postprandiale après un repas moyen ne semble pas représenter un facteur de risque.

Chronic hyperglycemia is believed to play a role in the pathogenesis of coronary artery disease (CAD); however, the cut-off level beyond which glycemia becomes detrimental remains controversial (1,2). Increasing average glycemia levels, as measured via glycated hemoglobin, are associated with an increased risk of myocardial infarction (3). Glycated hemoglobin levels reflect fasting and postchallenge glycemia (4), and both impaired fasting glycemia (IFG) and postchallenge hyperglycemia following an oral glucose tolerance test (OGTT) have been shown to confer a higher risk of cardiovascular (CV) death in nondiabetic individuals (5-7). In addition, postchallenge hyperglycemia in the diabetic range appears to be associated with CV disease risk independent of fasting glucose levels, according to one recent study (4). IFG and impaired glucose tolerance (IGT), measured after an OGTT, appear to result from different pathophysiological mechanisms, which explains why they may not be associated with the same CV risk (4). IGT appears to result from peripheral insulin resistance (4-8), whereas IFG may be a manifestation of defective insulin secretion (9,10).

IGT has been shown to be an independent risk factor for nonfatal and fatal CV events in patients without documented CAD

[1]Department of Medicine; [2]Biostatistics Department; [3]Research Centre, Montreal Heart Institute and Université de Montréal, Montreal, Quebec
Correspondence: Dr Jean-Claude Tardif, Montreal Heart Institute and Université de Montréal, 5000 Belanger Street, Montreal, Quebec H1T 1C8. Telephone 514-376-3330 ext 3564, fax 514-593-1355, e-mail jean-claude.tardif@icm-mhi.org
Received for publication March 15, 2006. Accepted August 6, 2006

(11-13). In contrast, the relationship between IFG and CV risk remains controversial. Earlier studies (13-15) have suggested a lack of association between IFG and CV events, while more recent studies have demonstrated an increased CV risk associated with this entity (16,17). However, little data exist on the prognostic importance of IFG and IGT in patients with documented CAD, as well as their relative contributions to CV risk. In addition, to our knowledge, postprandial (postmeal) glycemia, using a 2 h postmeal plasma glucose (2hPG) measurement, has never been used as a tool to evaluate the long-term risk of death. Thus, the aim of our study was to assess the impact and contributions of both IFG and postprandial (postmeal) hyperglycemia (PPH) on outcomes in patients with suspected or proven CAD from the Coronary Artery Surgery Study (CASS) registry (18).

METHODS

Study population

The CASS registry included 24,958 patients with suspected or proven CAD who were enrolled at 15 centres throughout North America between 1974 and 1979. Patients had an annual, scheduled follow-up until 1982, and afterward, vital status was obtained through a mail-in survey completed between 1989 and 1991. Vital status for nonresponders was obtained from the National Death Index for patients in the United States, and by next-of-kin, medical records and death certificates in Canada. Follow-up was complete for 96% of patients in the registry by the closing date of December 31, 1992. Patients without death records available were considered to be alive. CV mortality was defined according to the *International Classification of Diseases, eighth revision*, using codes 390 to 458. Intermediate-term end points were defined as those occurring by the end of scheduled follow-up in 1982, whereas long-term end points were defined as those occurring by December 31, 1992. Data on nonfatal events were available until 1982 from annual scheduled follow-up visits and were included in the intermediate-term end points. Nonfatal events studied included hospitalization for incident myocardial infarction, stroke and congestive heart failure.

Clinical variables

The clinical variables used were derived from the CASS registry and obtained at the time of enrolment in the study, and included age, sex, family history of premature CAD, medical history of diabetes, hypertension, hypercholesterolemia and smoking, as well as medication use. Additional variables studied included systolic and diastolic blood pressure, serum cholesterol, triglycerides, fasting plasma glucose (FPG), 2hPG and creatinine levels, left ventricular ejection fraction and extent of CAD. Postprandial blood glucose measurements were performed 2 h after asking patients to consume an 'average' breakfast meal. No other measures were used to ensure meal standardization. All blood marker measurements were performed at the time of blood collection from fresh samples. The number of diseased coronary arteries was based on whether the left anterior descending artery, the left circumflex artery or the right coronary artery had 70% diameter stenosis or more, or whether the left main artery had a 50% diameter stenosis or more. Left main artery disease was considered to be two-vessel disease in the presence of right-dominant coronary circulation and three-vessel disease in the presence of left-dominant coronary circulation. Coronary angiograms were interpreted using visual estimation in the CASS registry.

Definitions of IFG, PPH and diabetes

Two distinct analyses were performed to evaluate the importance of IFG, PPH and diabetes on outcomes in the cohort of the present study. In the first analysis using FPG levels only, normoglycemic patients were defined as having FPG of less than 6.1 mmol/L (110 mg/dL), IFG was defined as having FPG of 6.1 mmol/L to 6.9 mmol/L (110 mg/dL to 125 mg/dL) and undiagnosed diabetes mellitus was defined as FPG of 7.0 mmol/L (126 mg/dL) or higher in the absence of pharmacological therapy (19). In the second analysis using 2hPG levels, normoglycemic patients were identified as having 2hPG of lower than 7.8 mmol/L (140 mg/dL), PPH as 2hPG of 7.8 to 11.0 mmol/L (140 mg/dL to 199 mg/dL), and undiagnosed diabetes was identified as 2hPG 11.1 mmol/L (200 mg/dL) or higher (20). Patients with known or treated diabetes (diet or pharmacological treatment) were excluded from our analyses.

Statistical analysis

Results are expressed as the mean ± SD or median (minimum, maximum) for continuous variables and as frequency for categorical variables. Univariate analyses (*t* test or Wilcoxon test for continuous variables and Pearson χ^2 test for categorical variables) were used to compare the different glucose level groups. Univariate Cox proportional hazard regression models were used to evaluate the influence of glucose levels on outcomes. Multivariate Cox regression models were also created, adjusting for potential confounders (baseline characteristics and clinical variables). Survival analyses using the Kaplan-Meier method and log-rank test were used to study freedom from outcomes according to glucose level group definitions. $P<0.05$ was considered statistically significant. Statistical analyses were performed with SAS version 8.02 (SAS Institute, USA).

RESULTS

Baseline characteristics

The investigators identified 10,346, 1521 and 1309 patients in the normal, IFG and undiagnosed diabetes groups, respectively, who were included in the first analysis (Table 1). With increasing FPG levels, increases in mean age, body weight, systolic blood pressure, serum triglycerides, history of hypertension and extent of CAD were noted.

2hPG measurements were available for 1691 patients. In the second analysis using 2hPG levels only, 1101, 422 and 168 persons were identified in the normal, PPH and undiagnosed diabetes groups, respectively (Table 2). PPH patients had a risk factor profile that was intermediate between normoglycemic and diabetic patients.

Outcomes

Analysis 1 – normal, IFG and diabetic patients: After a median long-term follow up of 14.7 years (interquartile range 9.8 to 16.2 years), 3843 (37.1%), 684 (45.0%) and 702 (53.6%) patients had died in the normal, IFG and undiagnosed diabetes groups, respectively ($P<0.0001$) (Figure 1). CV disease accounted for 27.2%, 33.9% and 39.9% of all deaths in the same groups, respectively ($P<0.0001$). After adjusting for age, sex, weight, hypertension, serum triglyceride and total cholesterol levels, and smoking status, IFG patients continued to demonstrate a risk of clinical events that was intermediate between those with diabetes and those with normal FPG (Table 3). The long-term risk of all-cause or CV death was approximately 1.5-fold higher in undiagnosed diabetic patients than normal patients, with IFG patients showing a 1.2-fold higher risk than normoglycemic patients for these same end points. Intermediate-term (five-year follow-up) combined end points showed similar results (Table 3).

Analysis 2 – normal, PPH and undiagnosed diabetic patients: In the second analysis using postprandial glucose levels, 441 (40.1%),

TABLE 1
Baseline characteristics for analysis 1: Patients with normal glucose levels, impaired fasting glycemia and diabetes mellitus

Characteristic	Normoglycemic patients (FPG <6.1 mmol/L), mean ± SD or median (minimum, maximum) (n=10,346)	Impaired fasting glycemia (FPG 6.1 mmol/L–6.9 mmol/L), mean ± SD or median (minimum, maximum) (n=1521)	Undiagnosed diabetes mellitus (FPG ≥7.0 mmol/L), mean ± SD or median (minimum, maximum) (n=1309)	P
Age (years)	51.8±9.2	54.3±8.8	56.0±8.8	<0.0001
Body weight (kg)	74.4± 3.1	77.4±13.8	77.1±13.8	<0.0001
Body mass index (kg/m^2)	25.6±3.7	26.4±3.8	26.4±4.0	<0.0001
Left ventricular ejection fraction (%)	58.2±14.3	58.9±16.0	58.8±16.0	0.23
Systolic blood pressure (mmHg)	130.6±20.3	131.9.6±21.2	132.2±20.8	0.0035
Diastolic blood pressure (mmHg)	80.9±11.9	81.1±12.0	80.5±12.3	0.37
Serum total cholesterol (mmol/L)	6.02±1.30	6.09±1.26	6.07±1.30	0.13
Serum triglycerides (mmol/L)	1.94 (0.17, 38.1)	2.12 (0.38, 16.9)	2.18 (0.43, 43.1)	<0.0001
FPG (mmol/L)	5.10 (2.44, 6.05)	6.38 (6.10, 6.94)	8.05 (6.99, 30.5)	<0.0001
Characteristic	**n (%)**	**n (%)**	**n (%)**	
Male sex	7870 (76.1)	1188 (78.1)	990 (75.6)	0.18
Active smoking	3502 (33.9)	436 (28.7)	304 (23.3)	<0.0001
Medical history of hypertension	3028 (29.3)	531 (34.9)	489 (37.4)	<0.0001
Abnormal coronary angiogram	8399 (81.2)	1303 (85.7)	1153 (88.1)	<0.0001
Extent of coronary artery disease				<0.0001
0-vessel disease	2975 (29.0)	344 (22.8)	233 (18.0)	
1-vessel disease	2152 (20.9)	279 (18.5)	260 (20.0)	
2-vessel disease	2310 (22.5)	370 (24.6)	307 (23.7)	
3-vessel disease	2839 (27.6)	514 (34.1)	498 (38.4)	

FPG Fasting plasma glucose

TABLE 2
Baseline characteristics for analysis 2: Postprandial glucose levels

Characteristic	Normoglycemic patients (2hPG <7.8 mmol/L), mean ± SD or median (minimum, maximum) (n=1101)	Postprandial hyperglycemia (2hPG 7.8 mmol/L–11.0 mmol/L), mean ± SD or median (minimum, maximum) (n=422)	Undiagnosed diabetes mellitus (2hPG ≥11.1 mmol/L), mean ± SD or median (minimum, maximum) (n=168)	P
Age (years)	53.0±9.6	55.2±9.3	55.4±7.8	<0.0001
Body weight (kg)	75.7±13.8	76.9±14.4	78.8±12.6	0.014
Body mass index (kg/m^2)	25.4±3.7	25.9±4.1	26.7±3.9	<0.0001
Left ventricular ejection fraction (%)	58.7±14.7	57.3±16.1	54.7±15.4	0.0088
Systolic blood pressure (mmHg)	131.9±20.2	134.7±20.3	136.8±22.2	0.0068
Diastolic blood pressure (mmHg)	82.2±12.6	83.5±12.1	84.8±11.3	0.020
Serum total cholesterol (mmol/L)	5.86±1.18	5.89±1.24	5.95±1.37	0.68
Serum triglycerides (mmol/L)	1.77 (0.31, 25.1)	1.94 (0.23, 19.4)	2.17 (0.60, 23.3)	<0.0001
Fasting plasma glucose (mmol/L)	5.22 (3.39, 12.21)	5.27 (3.72, 13.60)	5.91 (3.66, 18.21)	<0.0001
2hPG (mmol/L)	5.77±0.98	9.13±0.90	13.42±2.09	<0.0001
Characteristic	**n (%)**	**n (%)**	**n (%)**	
Male sex	820 (74.5)	300 (71.2)	129 (76.8)	0.27
Active smoking	354 (32.2)	125 (29.6)	37 (22.0)	0.061
Medical history of hypertension	346 (31.4)	165 (39.1)	74 (44.1)	0.0004
Abnormal coronary angiogram	837 (76.0)	336 (79.6)	146 (86.9)	0.0043
Extent of coronary artery disease				0.090
0-vessel disease	361 (32.9)	128 (30.3)	42 (25.0)	
1-vessel disease	199 (18.1)	76 (18.0)	25 (14.9)	
2-vessel disease	227 (20.7)	76 (18.0)	40 (23.8)	
3-vessel disease	312 (28.4)	142 (33.7)	61 (36.3)	

2hPG 2 h postprandial glucose

184 (43.6%) and 86 (51.2%) patients had died in the normal, PPH and diabetic groups, respectively (P<0.019 for trend), after the same median follow-up of 14.7 years. Similar trends were observed for long-term CV mortality and the intermediate-term combined end points; however, neither PPH (2hPG 7.8 mmol/L to 11.0 mmol/L) nor diabetes (2hPG 11.1 mmol/L or higher) were associated with significant risk after adjustment for traditional risk factors (Table 4). Similarly, neither PPH nor diabetes were associated with a significant risk of long-term death in the presence of FPG of lower than 6.1 mmol/L (data not shown).

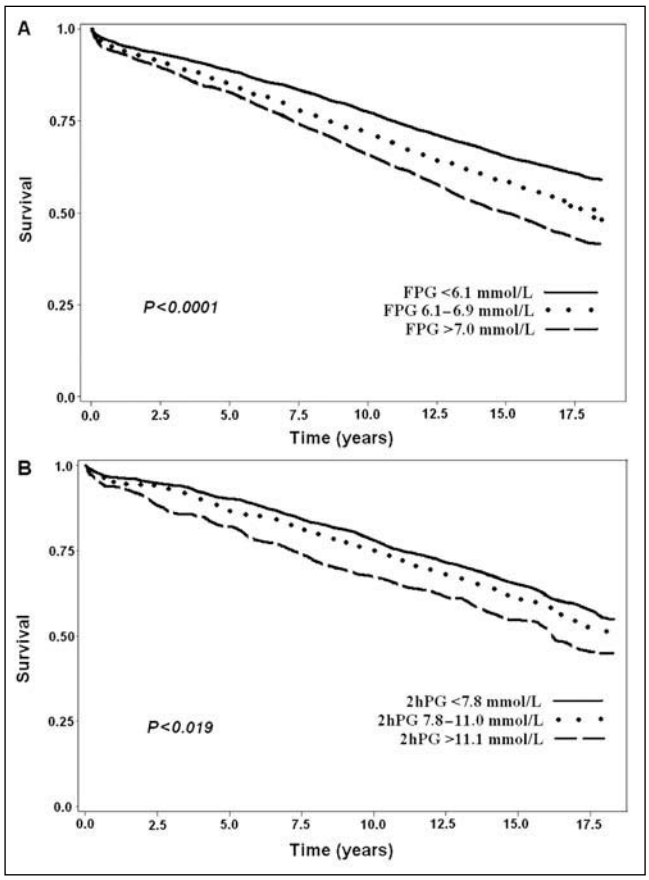

Figure 1) *Cumulative survival according to glycemic status*. **A** *Fasting plasma glucose (FPG) and freedom from long-term all-cause death*. **B** *2 h postprandial glucose (2hPG) and freedom from long-term all-cause death*

Multivariate Cox regression models were also created for intermediate- and long-term outcomes, in which both fasting and 2hPG levels were entered into the models as continuous variables using the data of the 991 subjects in whom both parameters were measured. For long-term all-cause and CV mortality, neither fasting nor postprandial glucose were predictive of long-term fatal events. However, in models addressing the intermediate-term end points, increasing FPG was associated with a significantly higher likelihood of a nonfatal or fatal event (adjusted hazard ratio 1.39 per 1 mmol/L increase in FPG, 95% CI 1.09 to 1.78 for intermediate-term all-cause death, myocardial infarction, congestive heart failure or stroke; adjusted hazard ratio 1.48 per 1 mmol/L increase in FPG, 95% CI 1.16 to 1.88 for intermediate-term CV death, myocardial infarction, congestive heart failure or stroke), whereas PPH was not predictive of increased morbidity or mortality.

DISCUSSION

In this CAD cohort, elevated fasting rather than postprandial (postmeal) glucose levels were predictive of future all-cause and CV mortality. Impaired FPG was associated with a risk of death and major CV events intermediate between normoglycemic and diabetic subjects. As expected, diabetic patients, based on FPG levels, possessed highest risk of fatal or nonfatal outcomes in this cohort. To our knowledge, the present study was the first to examine the potential prognostic significance of 2hPG levels measured following an average meal. 2hPG measurements after a standardized meal have been shown to correlate with 2 h postchallenge glucose levels measured after an OGTT (21-23). In addition, IGT, as diagnosed during an OGTT, is a known risk factor for long-term mortality, as noted previously (11-13). Despite this fact, no study has yet evaluated whether elevated postprandial blood glucose levels measured after an average meal are also predictive of future fatal events. From our analyses, PPH was not associated with a significant risk of fatal or nonfatal outcomes in patients with FPG levels of lower than 6.1 mmol/L. Similarly, diabetic patients, based on 2hPG levels, did not possess a higher risk of death in multivariate models. In contrast, increasing levels of FPG were predictive of an increased risk of nonfatal and fatal events after controlling for 2hPG levels.

The prevalence of CAD disease risk factors has been shown to be higher in individuals with IFG than in persons with normal FPG levels (20). In the Diabetes Epidemiology: Collaborative analysis Of Diagnostic criteria in Europe (DECODE) study (16), comprising 25,364 persons in 13 prospective European cohorts followed on average for 7.3 years, IFG was associated with a 1.2-fold higher risk of all-cause death in individuals without known CAD in univariate analyses, although the risk of death was not significantly higher in multivariate models. IFG has been shown to be associated with a significantly increased risk of mortality in patients with documented CAD (17).

In the DECODE study, the presence of IGT following a 75 g glucose challenge was associated with a higher risk of death than IFG (16). In addition, IGT was shown to be an independent predictor of CV mortality in patients with normal FPG levels, whereas IFG was not associated with any significant CV risk after controlling for 2hPG levels (15). Recent data (24) have also indicated that treatment of IGT with acarbose to reduce PPH significantly reduces CV events and the development of hypertension. Similarly, reduction of peak PPH with the insulin secretagogue ripaglinide has been shown to reduce carotid atherosclerosis in type 2 diabetes (25). These data suggest that postprandial glucose may be a stronger risk factor than FPG in certain populations.

Our data from the CASS registry indicate that IFG was a stronger risk factor for all-cause and CV disease mortality than PPH in patients with CAD. While PPH was a predictor of death in univariate analyses, its impact on outcomes was negligible in the presence of normal FPG levels of less than 6.1 mmol/L. Similarly, when analyzed as a continuous variable, 2hPG was not predictive of increased morbidity and mortality after adjusting for FPG. In contrast, FPG was predictive of future nonfatal and fatal clinical events, even after adjusting for postprandial plasma glucose. Several potential hypotheses may explain why our results differed from those of epidemiological studies in patients without CAD. First, the measurement of 2hPG levels was not standardized in the CASS registry and might have varied considerably due to the type and quantity of food consumed, as well as geographical factors, given that this study was undertaken across North America. Second, 2hPG levels may not reflect glucose metabolism occurring after a standard 75 g OGTT and may therefore not be associated with the same CV risk. Third, patients with IFG had a slightly higher body mass index, as well as higher levels of total cholesterol and triglycerides than patients with PPH, and were similar to diabetic subjects. Although we did adjust for available confounders in our multivariate models, other confounding factors might have continued to affect CV and non-CV risk in our cohort. Fourth, IFG is perhaps a stronger CV risk factor relative to IGT in individuals without other components of the metabolic syndrome. Patients with PPH had a mean body mass index of 25.9 kg/m^2 and a median triglyceride level of 1.94 mmol/L, only slightly higher than the cut-off of 1.7 mmol/L used for the

TABLE 3
Intermediate- and long-term risk of cardiovascular (CV) and all-cause death and complications according to fasting glycemia status

	Long-term all-cause death	Long-term CV death	Intermediate-term risk of all-cause death, MI, CHF or stroke, hazard ratio (95% CI)	Intermediate-term risk of CV death, MI, CHF or stroke
Impaired fasting glycemia (unadjusted models)	1.29 (1.19–1.40)	1.33 (1.21–1.46)	1.27 (1.15–1.41)	1.3 (1.17–1.45)
Impaired fasting glycemia (adjusted models)	1.20* (1.08–1.34)	1.23* (1.08–1.40)	1.22† (1.06–1.40)	1.25† (1.09–1.45)
Undiagnosed diabetes (unadjusted models)	1.65 (1.52–1.79)	1.66 (1.51–1.83)	1.47 (1.32–1.63)	1.46 (1.30–1.63)
Undiagnosed diabetes (adjusted models)	1.48* (1.31–1.66)	1.51* (1.32–1.73)	1.36† (1.17–1.59)	1.41† (1.20–1.65)

**Adjusted for age, sex, smoking status, hypertension, weight and serum total cholesterol levels; †Adjusted for age, sex, smoking status, hypertension, weight, and serum triglyceride and total cholesterol levels. CHF Congestive heart failure; MI Myocardial infarction*

TABLE 4
Intermediate- and long-term risk of cardiovascular (CV) and all-cause death and complications according to postprandial glycemia status

	Long-term all-cause death	Long-term CV death	Intermediate-term risk of all-cause death, MI, CHF or stroke, hazard ratio (95% CI)	Intermediate-term risk of CV death, MI, CHF or stroke
PPH (2hPG 7.8 mmol/L–11.0 mmol/L) (unadjusted models)	1.14 (0.96–1.35)	1.26 (1.03–1.54)	1.1 (0.88–1.40)	1.19 (0.93–1.52)
PPH (2hPG 7.8 mmol/L–11.0 mmol/L) (adjusted models)	0.99* (0.78–1.26)	1.03* (0.78–1.37)	1.11† (0.81–1.54)	1.18† (0.83–1.67)
Undiagnosed diabetes (2hPG ≥11.1 mmol/L) (unadjusted models)	1.45 (1.15–1.83)	1.38 (1.04–1.84)	1.54 (1.15–2.06)	1.63 (1.19–2.23)
Undiagnosed diabetes (2hPG ≥11.1 mmol/L) (adjusted models)	1.10* (0.79–1.53)	0.89* (0.59–1.36)	1.03† (0.66–1.30)	1.01† (0.62–1.65)

**Adjusted for age, sex, smoking status, weight and serum triglyceride levels; †Adjusted for age, weight, serum triglyceride levels and fasting glycemia. 2hPG 2 h postprandial glucose; CHF Congestive heart failure; MI Myocardial infarction; PPH Postprandial hyperglycemia*

diagnosis of the metabolic syndrome. Therefore, patients with PPH in the CASS registry were less likely to have possessed insulin resistance and its pathophysiological consequences, which are often associated with CV risk. Postprandial hyperinsulinemia appears to be a more significant determinant of CAD than postprandial glycemia in patients with the metabolic syndrome, according to one recent study (26). In addition, the small sample size may also explain why neither PPH nor diabetes, based on a postprandial glucose level of 11.1 mmol/L or higher, were associated with a significant risk of clinical events in our multivariate models, because we did note a significant trend of increasing mortality with increasing levels of postprandial glucose in unadjusted models. Finally, given that this study involved a coronary population with a relatively high risk of recurrent events, the ability to differentiate risk based on glycemic status might have been lower than in a noncoronary population.

Our data are consistent with two other studies performed in CAD patients (17,27). Among 11,853 patients with a previous myocardial infarction who were followed on average for 7.7 years, IFG was associated with a 1.4-fold increased risk of all-cause death and a 1.3-fold increased risk of CAD death (17). In 1612 patients with CAD who were undergoing percutaneous coronary intervention, IFG was associated with a threefold higher risk of death compared with patients with normal fasting glycemia after a mean follow-up of 2.8 years (27). In contrast, Arcavi et al (28) failed to demonstrate a significant association between IFG and mortality in 293 survivors of myocardial infarction with IFG, presumably due to the small sample size. We extend current knowledge by demonstrating that IFG confers a higher long-term risk (median follow-up 14.7 years) of death in CAD patients. In addition, IFG remained an independent predictor of clinical events in multivariate models, even after adjusting for 2hPG. Thus, IFG alone is capable of exerting a significant negative effect on outcomes in a CAD population, presumably through multiple mechanisms, including impaired endothelial function (29), oxidative stress (30) and inflammation (31).

CASS was performed during the 1970s and 1980s, and the outcomes we measured necessarily reflect the treatment practices at the time the original study was undertaken. Approximately one-quarter of patients in CASS were women. While one may question whether our results are applicable to women, the CASS cohort contained a higher percentage of women than a previous study (17) that obtained similar results. Third, a single blood specimen performed at study entry was used to define each patient's glycemic status. Finally, we did not use the new American Diabetes Association (32) definition for IFG of 5.6 mmol/L to 6.9 mmol/L; however, when analyzed as continuous variables, both fasting and postprandial glucose level behaved in ways similar to those reported here.

CONCLUSIONS

Our study showed that IFG is an independent risk factor for CV and all-cause mortality in patients with documented CAD. The data in the present study suggest that in a CAD population with

a low prevalence of the metabolic syndrome, PPH does not appear to be an independent risk factor for death in the presence of normal FPG levels. The presence or absence of IFG is easy to measure in routine clinical practice. Management of this prediabetic state must be re-evaluated in light of these data, and aggressive lifestyle changes should be considered to improve glycemic control and to potentially improve outcomes in CAD patients. The pharmacological treatment of IFG must also be evaluated in the context of clinical trials before clear recommendations can be made.

ACKNOWLEDGEMENTS: The authors thank Mrs Diane Campeau for her help with manuscript preparation.

REFERENCES

1. Coutinho M, Gerstein HC, Wang Y, Yusuf S. The relationship between glucose and incident cardiovascular events. A metaregression analysis of published data from 20 studies of 95,783 individuals followed for 12.4 years. Diabetes Care 1999;22:233-40.
2. Meigs JB, Nathan DM, Wilson PW, Cupples LA, Singer DE. Metabolic risk factors worsen continuously across the spectrum of nondiabetic glucose tolerance. The Framingham Offspring Study. Ann Intern Med 1998;128:524-33.
3. Stratton IM, Adler AI, Neil HA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): Prospective observational study. BMJ 2000;321:405-12.
4. Meigs JB, Nathan DM, D'Agostino RB Sr, Wilson PWF; Framingham Offspring Study. Fasting and postchallenge glycemia and cardiovascular disease risk: The Framingham Offspring Study. Diabetes Care 2002;25:1845-50.
5. Balkau B, Shipley M, Jarrett RJ, et al. High blood glucose concentration is a risk factor for mortality in middle-aged nondiabetic men. 20-year follow-up in the Whitehall Study, the Paris Prospective Study, and the Helsinki Policemen Study. Diabetes Care 1998;21:360-7.
6. Barrett-Connor E, Ferrara A. Isolated postchallenge hyperglycemia and the risk of fatal cardiovascular disease in older women and men. The Rancho Bernardo Study. Diabetes Care 1998;21:1236-9.
7. Bjornholt JV, Erikssen G, Aaser E, et al. Fasting blood glucose: An underestimated risk factor for cardiovascular death. Results from a 22-year follow-up of healthy nondiabetic men. Diabetes Care 1999;22:45-9.
8. Piche ME, Lemieux S, Perusse L, Weisnagel SJ. High normal 2-hour plasma glucose is associated with insulin sensitivity and secretion that may predispose to type 2 diabetes. Diabetologia 2005;48:732-40.
9. Carnevale Schianca GP, Rossi A, Sainaghi PP, Maduli E, Bartoli E. The significance of impaired fasting glucose versus impaired glucose tolerance: Importance of insulin secretion and resistance. Diabetes Care 2003;26:1333-7.
10. Festa A, D'Agostino R Jr, Hanley AJ, Karter AJ, Saad MF, Haffner SM. Differences in insulin resistance in nondiabetic subjects with isolated impaired glucose tolerance or isolated impaired fasting glucose. Diabetes 2004;53:1549-55.
11. Shaw JE, Hodge AM, de Courten M, Chitson P, Zimmet PZ. Isolated post-challenge hyperglycaemia confirmed as a risk factor for mortality. Diabetologia 1999;42:1050-4. (Erratum in 1999;42:1444).
12. Feskens EJ, Kromhout D. Glucose tolerance and the risk of cardiovascular disease: The Zutphen Study. J Clin Epidemiol 1992;45:1327-34.
13. Tominaga M, Eguchi H, Manaka H, Igarashi K, Kato T, Sekikawa A. Impaired glucose tolerance is a risk factor for cardiovascular disease, but not impaired fasting glucose. The Funagata Diabetes Study. Diabetes Care 1999;22:920-4.
14. Hanefeld M, Temelkova-Kurktschiev T, Schaper F, Henkel E, Siegert G, Koehler C. Impaired fasting glucose is not a risk factor for atherosclerosis. Diabet Med 1999;16:212-8.
15. DECODE Study Group, the European Diabetes Epidemiology Group. Glucose tolerance and cardiovascular mortality: Comparison of fasting and 2-hour diagnostic criteria. Arch Intern Med 2001;161:397-405.
16. DECODE Study Group, European Diabetes Epidemiology Group. Is the current definition for diabetes relevant to mortality risk from all causes and cardiovascular and noncardiovascular diseases? Diabetes Care 2003;26:688-96.
17. Fisman EZ, Motro M, Tenenbaum A, Boyko V, Mandelzweig L, Behar S. Impaired fasting glucose concentrations in nondiabetic patients with ischemic heart disease: A marker for a worse prognosis. Am Heart J 2001;141:485-90.
18. National Heart, Lung, and Blood Institute Coronary Artery Surgery Study. A multicenter comparison of the effects of randomized medical and surgical treatment of mildly symptomatic patients with coronary artery disease, and a registry of consecutive patients undergoing coronary angiography. Circulation 1981;63:I1-81.
19. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 1997;20:1183-97.
20. Alexander CM, Landsman PB, Teutsch SM. Diabetes mellitus, impaired fasting glucose, atherosclerotic risk factors, and prevalence of coronary heart disease. Am J Cardiol 2000;86:897-902.
21. Owens DR, Wragg KG, Briggs PI, Luzio S, Kimber G, Davies C. Comparison of the metabolic response to a glucose tolerance test and a standardized test meal and the response to serial test meals in normal healthy subjects. Diabetes Care 1979;2:409-13.
22. Wolever TM, Chiasson JL, Csima A, et al. Variation of postprandial plasma glucose, palatability, and symptoms associated with a standardized mixed test meal versus 75 g oral glucose. Diabetes Care 1998;21:336-40.
23. Ezenwaka CE, Kalloo R. Determination of the differences in 2-h plasma glucose values after ingestion of carbohydrate foods and oral glucose in Caribbean non-diabetic subjects. Int J Food Sci Nutr 2005;56:483-90.
24. Chiasson JL, Josse RG, Gomis R, et al; STOP-NIDDM Trial Research Group. Acarbose treatment and the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance: The STOP-NIDDM trial. JAMA 2003;290:486-94.
25. Esposito K, Giugliano D, Nappo F, Marfella R; Campanian Postprandial Hyperglycemia Study Group. Regression of carotid atherosclerosis by control of postprandial hyperglycemia in type 2 diabetes mellitus. Circulation 2004;110:214-9.
26. Baltali M, Korkmaz ME, Kiziltan HT, Muderris IH, Ozin B, Anarat R. Association between postprandial hyperinsulinemia and coronary artery disease among non-diabetic women: A case control study. Int J Cardiol 2003;88:215-21.
27. Muhlestein JB, Anderson JL, Horne BD, et al; Intermountain Heart Collaborative Study Group. Effect of fasting glucose levels on mortality rate in patients with and without diabetes mellitus and coronary artery disease undergoing percutaneous coronary intervention. Am Heart J 2003;146:351-8.
28. Arcavi L, Behar S, Caspi A, Reshef N, Boyko V, Knobler H. High fasting glucose levels as a predictor of worse clinical outcome in patients with coronary artery disease: Results from the Bezafibrate Infarction Prevention (BIP) study. Am Heart J 2004;147:239-45.
29. Thomas GN, Chook P, Qiao M, et al. Deleterious impact of "high normal" glucose levels and other metabolic syndrome components on arterial endothelial function and intima-media thickness in apparently healthy Chinese subjects: The CATHAY study. Arterioscler Thromb Vasc Biol 2004;24:739-43.
30. Menon V, Ram M, Dorn J, et al. Oxidative stress and glucose levels in a population-based sample. Diabet Med 2004;21:1346-52.
31. Nakanishi N, Shiraishi T, Wada M. Association between fasting glucose and C-reactive protein in a Japanese population: The Minoh study. Diabetes Res Clin Pract 2005;69:88-98.
32. American Diabetes Association. Standards of medical care in diabetes. Diabetes Care 2004;27:S15-35.