

Glucose Metabolism and Coronary Heart Disease in Patients With Normal Glucose Tolerance

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DIABETES MELLITUS IS ONE OF the classic risk factors for coronary heart disease (CHD). It is well known, in fact, that the risk of CHD is 2- to 6-fold higher in patients with type 2 diabetes than in patients without diabetes¹⁻³ and that men with diabetes have a worse survival from CHD than do those without diabetes.⁴ Patients with diabetes but without prior myocardial infarction have for some years been considered to have the same risk of CHD events as patients without diabetes but with a prior myocardial infarction,⁵ as recently acknowledged by the recommended treatment goals for lipoprotein therapy.⁶

A body of information now available suggests the need for a careful consideration not only of diabetes, but also of other disturbances of glucose metabolism, such as impaired glucose tolerance (IGT), that have emerged as independent risk factors for cardiovascular disease mortality.^{7,8} Moreover, several prospective studies have shown a significant correlation between glycemic variables and morbid-

Context Several investigations as well as prospective studies have shown a significant correlation between glucose metabolism and atherosclerosis in patients without diabetes, but differences in parameters of glucose metabolism among the various degrees of coronary disease in such patients have not been specifically evaluated.

Objective To investigate glucose metabolism in patients with normal glucose tolerance (NGT) and coronary heart disease (CHD).

Design, Setting, and Participants Cross-sectional study of 234 men (mean [SD] age, 56.2 [6.1] years) with NGT and suspected CHD who were admitted from January 1 through June 30, 2001, to an academic medical center in Italy for coronary angiography.

Main Outcome Measures Correlation of glucose metabolic factors and extent of atherosclerosis determined by coronary angiography. Factors included levels of fasting and postload glucose and insulin, glycosylated hemoglobin (HbA_{1c}), and lipids, as well as insulin resistance measured by homeostasis model assessment (HOMA-IR).

Results Patients were divided into 4 groups based on coronary angiography: no significant stenosis (n=42), 1-vessel disease (n=72), 2-vessel disease (n=64), and 3-vessel disease (n=56). Simple correlation analysis showed that the factors correlated with the extent of atherosclerosis were levels of postload glucose ($r=0.667$), HbA_{1c} ($r=0.561$), postload insulin ($r=0.221$), and fasting insulin ($r=0.297$), as well as HOMA-IR ($r=0.278$) ($P<.001$ for all). Multiple stepwise regression analysis suggested that the factors independently associated with the number of stenosed coronary arteries were levels of postload plasma glucose ($r=0.572$), HbA_{1c} ($r=0.413$), postload insulin ($r=0.267$), and fasting insulin ($r=0.174$), as well as HOMA-IR ($r=0.250$) ($P<.001$ for all). Similar results were obtained after grouping patients by Duke Myocardial Jeopardy Score.

Conclusions For patients with NGT and different extents of atherosclerotic disease, postload glycemia and HbA_{1c} level are not equally distributed but are significantly higher in those with more severe disease. This suggests that the glycemic milieu correlates with the cardiovascular risk according to a linear model.

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ity from CHD in patients without diabetes.^{4,9-13} Generally, the prevalence of impairments of glucose metabolism, such as diabetes or IGT, in patients with CHD confirmed by coronary arteriography is established by the medical history or by the presence of fasting glycemia. Such diagnostic criteria, however, are not able to correctly classify the true glycemic status of patients with CHD. Some observa-

tions,^{14,15} in fact, have estimated the prevalence of impaired glucose metabolism to be between 30% and 67%

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Table 1. Clinical Characteristics of the Studied Groups

Characteristic	No. of Stenosed Vessels				P Value*
	0	1	2	3	
No. of patients	42	72	64	56	
Age, mean (SD), y	55.3 (4.8)	55.2 (6.4)	54.6 (6.5)	57.7 (3.6)	.005
Body mass index, mean (SD)†	24.1 (2.8)	23.7 (2.6)	23.7 (2.9)	24.1 (1.7)	.25
Blood pressure, mean (SD), mm Hg					
Systolic	126.5 (13.2)	125.5 (19.8)	128.5 (14.8)	126.0 (19.2)	.70
Diastolic	74.0 (8.1)	74.5 (7.5)	73.8 (8.9)	75.0 (7.5)	<.001‡
LVEF, mean (SD), %	52.5 (6.8)	52.2 (6.4)	52.4 (5.8)	52.3 (5.0)	.74
Smokers, No. (%)	4 (9.5)	7 (9.7)	6 (9.4)	6 (10.7)	.32§
The metabolic syndrome, No. (%)	8 (19)	6 (8.3)	12 (18.7)	17 (30.4)	<.001§

Abbreviation: LVEF, left ventricular ejection fraction.

*By analysis of variance.

†Calculated as weight in kilograms divided by the square of height in meters.

‡For group 0 vs group 3.

§From χ^2 test.

in patients with CHD, often in patients without a previous diagnosis of metabolic disease.

This evidence raises 2 questions. First, of the glycemic variables, which are the best indicators of cardiovascular risk in patients with normal glucose tolerance (NGT)? And second, do their values correlate with the severity of CHD? The results of the Rancho-Bernardo Study¹⁰ show that level of glycosylated hemoglobin (HbA_{1c}) is a better predictor of CHD and ischemic heart disease mortality than is fasting or postload glycemia, while the results of the Hoorn Study¹¹ indicate that postload glycemia and to a lesser extent HbA_{1c} level are associated with increased cardiovascular mortality. Moreover, some data are consistent with a linear association¹⁶ and others with a threshold effect.⁴

Finally, the results of a recent study¹⁷ of men with CHD but without a history of diabetes confirmed the high prevalence of glycemic imbalance (approximately 50%) in these patients and showed that more-pronounced metabolic disturbances were present in patients with greater changes in the coronary arteries. However, this was established by diagnosis of diabetes, IGT, or NGT, irrespective of oral glucose tolerance test (OGTT) results. Therefore, differences in metabolic parameters among the various degrees of coronary disease in patients with NGT

were not evaluated alone. The aim of this study was to specifically investigate glucose metabolism in patients with NGT and CHD.

METHODS

Patients

From January 1 through June 30, 2001, 602 consecutive men with suspected CHD were admitted to the hospital of the Second University of Naples, Naples, Italy, to undergo coronary angiography. A total of 358 patients (59.5%) were initially excluded because they met 1 or more of the following exclusion criteria: diabetes and/or family history of diabetes (160 patients [26.6%]), acute coronary event in the last 3 months (227 patients [37.7%]), left ventricular ejection fraction less than 40% and/or valve disease and/or cardiomyopathy (83 patients [13.8%]). After providing written informed consent, the remaining 244 (40.5%) underwent a standard 75-g OGTT, which revealed impaired glucose metabolism (ie, IGT or diabetes mellitus) in 10 patients, leaving 234 (38.8%) eligible for the study. All patients had previous clinical symptoms of CHD and/or positive result of exercise testing and/or history of myocardial infarction. The clinical characteristics of the patients appear in TABLE 1.

The patients were treated with nitrates (n=217 [92.3%]), platelet aggregation inhibitors (n=201 [85.5%]), an-

giotensin-converting enzyme inhibitors or angiotensin II type 1 receptor antagonists (n=133 [56.5%]), selective α -blockers (n=126 [53.6%]), calcium channel blockers (n=116 [49.4%]), and inhibitors of hydroxymethyl glutaryl coenzyme A (n=96 [40.8%]).

The study protocol was in accordance with the Helsinki Declaration and was approved by the ethical committee of the Second University of Naples.

Biochemical Analysis

The OGTT was performed in the morning after an overnight fast at least 3 months after an acute coronary event. This was to avoid any influence on glucose tolerance or levels of HbA_{1c}. Blood samples for determination of glucose and insulin levels were collected before and 120 minutes after loading. The American Diabetes Association criteria¹⁸ were used to classify results of the patients with NGT and to exclude patients with IGT or diabetes. The insulin resistance index was measured by homeostasis model assessment (HOMA-IR) (HOMA-IR=fasting insulin level [mU/L] \times fasting plasma glucose level [mmol/L]/22.5).¹⁹ We used HOMA-IR instead of the better euglycemic-hyperinsulinemic glucose clamp technique²⁰ because of the number of patients studied; however, HOMA-IR is a valid indicator of insulin resistance in patients with NGT.²¹

Blood samples were collected before the OGTT for determination of levels of HbA_{1c}, total cholesterol, high-density lipoprotein cholesterol (HDL-C), and triglycerides. The concentration of low-density lipoprotein cholesterol (LDL-C) was determined using the Friedewald formula (LDL-C level=total cholesterol level – HDL-C level – triglycerides level/5).

Plasma glucose level was assessed by a glucose oxidase method (Beckman Glucose Analyzer II, Fullerton, Calif). Level of HbA_{1c} was determined by column chromatography using a commercial kit (Bio-Rad Laboratories, Richmond, Calif); reference levels were 4% to 6%, and the interassay coefficient of variation was 3%. Insulin concentra-

tion was assessed using enzyme-linked immunosorbent assay (AIA-PACK IRI, Euro Genetics, Saran, France). Levels of total cholesterol, HDL-C, and triglycerides were assessed by enzymatic methods using a commercial kit (Spinreact, Sant Esteve De Bas, Girona, Spain).

Coronary Angiography

Coronary angiography was performed after positive results of exercise testing in patients with clinical evidence of angina pectoris. All patients requiring urgent percutaneous transluminal coronary angioplasty, as judged by coronary angiography, were excluded from the study. Analyses of coronary angiograms were performed by independent experienced cardiologists. Internal luminal narrowing greater than 50% in 1 major coronary artery or its major branches was considered significant evidence of CHD. To classify the extent of CHD, coronary arteries were grouped as left anterior descending artery or diagonal and septal branch; as left circumflex artery or obtuse marginal branch; and as right coronary artery or posterior descending and posterolateral branch.²²

Based on coronary angiography, patients were divided into 4 groups: no significant stenosis, 1-vessel disease, 2-vessel disease, and 3-vessel disease (Table 1).

Statistical Analysis

Quantitative variables were expressed as mean (SD). Differences between the 4 groups of patients were compared by 1-way analysis of variance with the Bonferroni correction for multiple comparisons. A test for linearity was used to evaluate the trend with increased number of stenosed vessels. Categorical variables were presented as No. (%) and the significance of difference between percentages in the 4 groups was evaluated with the χ^2 test. Statistical analysis was performed with 80% power to detect a between-group difference in means of at least 10%, with an α level of less than .05.

Correlations between the metabolic parameters and the number of stenosed

vessels were examined by determination of the Pearson correlation coefficient. Metabolic factors independently related to the number of involved vessels were established through multiple stepwise regression analysis (with stepping method criteria: probability of F to enter $\leq .05$ and to remove $\geq .10$). All statistical analyses were performed using SPSS version 7.5 (SPSS Inc, Chicago, Ill), and all tests were conducted at the 5% level of significance.

RESULTS

A total of 234 patients were studied, grouped according to those with no-vessel disease (group 0, n=42), 1-vessel disease (group 1, n=72), 2-vessel disease (group 2, n=64), and 3-vessel disease (group 3, n=56) (Table 1).

Treatment regimens, including drugs that potentially interfere with glucose metabolism, as well as family history of CHD and other cardiovascular diseases, were not statistically different among the 4 groups.

There was a significant difference between groups for mean (SD) age (group 0, 55.3 [4.8] years; group 1, 55.2 [6.4] years; group 2, 54.6 [6.5] years; and group 3, 57.7 [3.6] years; $P < .005$), but linearity with the number of increased stenosed vessels was not demonstrated ($P = .13$) (Table 1). Mean (SD) body mass index was different among the groups, even if multiple comparison showed a statistically significant difference only for group 1 vs group 3 (23.7 [2.6] vs 24.1 [1.7], respectively; $P = .001$). Mean (SD) systolic blood pressure was statistically higher in group 2 (128.5 [14.8] mm Hg) when compared with the other groups ($P < .001$). Diastolic blood pressure tended to be higher in the groups of patients with CHD (groups 1, 2, and 3), even if statistically significant only in group 0 vs group 3 (74.0 [8.1] vs 75.0 [7.5] mm Hg; $P < .001$), but with a significant linearity ($P < .001$). Mean (SD) left ventricular ejection fraction was similar in the 4 groups (Table 1).

The metabolic syndrome, as defined by the Adult Treatment Panel III,²³ was diagnosed in 19.7% (46/234) of the

patients, and was statistically more prevalent in group 3 (30.4% [n=17]) than in group 0, group 1, and group 2 (19% [n=8]; 8.3% [n=6]; and 18.7% [n=12], respectively; $P < .001$).

The 4 groups of patients had similar levels of fasting plasma glucose (TABLE 2). All the groups showed statistically different concentrations of postload glucose, total cholesterol, and LDL-C ($P < .001$ for all). Significantly different HDL-C concentrations were observed between the groups ($P < .001$ for all), except for group 1 vs group 2 ($P = .97$). Serum levels of fasting insulin, postload insulin, and triglycerides, as well as HOMA-IR, were statistically different between the groups ($P < .001$), except when patients with 1-vessel disease were compared with those with no-vessel disease ($P = .58$ for fasting insulin; $P > .99$ for postload insulin; $P > .99$ for triglycerides; and $P = .75$ for HOMA-IR). Mean (SD) levels of HbA_{1c} were statistically different in all the comparisons between groups ($P < .001$), except when group 0 was compared with group 2 (4.7% [0.4%] vs 4.9% [0.6%], $P = .09$).

The increase in the number of stenosed vessels was accompanied by an increasing linear trend for levels of postload glucose, fasting and postload insulin, HbA_{1c}, total cholesterol, LDL-C, and triglycerides, as well as for HOMA-IR ($P < .001$ for trend), while a decreasing linear trend was observed for levels of HDL-C ($P < .001$ for trend) (Table 2).

As shown in TABLE 3, the number of stenosed vessels was correlated with levels of postload plasma glucose, HbA_{1c}, postload insulin, fasting insulin, triglycerides, total cholesterol, HDL-C, and LDL-C, and as well as with HOMA-IR, diastolic blood pressure, and smoking. The multiple stepwise regression analysis suggested that the factors independently associated with the number of involved vessels were levels of postload plasma glucose, HbA_{1c}, postload insulin, fasting insulin, triglycerides, total cholesterol, HDL-C, and LDL-C, as well as HOMA-IR and diastolic blood pressure ($P < .001$ for all).

For greater prognostic value, we successively reanalyzed patients after grouping them by the Duke Myocardial Jeopardy Score²⁴ (TABLE 4). Based on the distribution of the coronary tree, the patients were divided into 7 groups: score 0 (n=44), score 2 (n=56), score 4 (n=33), score 6 (n=28), score 8 (n=26), score 10 (n=23) and score 12

(n=24). An examination of baseline characteristics showed no difference in BMI ($P=.05$), age ($P=.27$), and left ventricular ejection fraction ($P=.65$), and a statistically significant difference ($P<.001$) in systolic and diastolic blood pressure. The percentage of smokers was higher in the patients with the lower score, while the percentage of

those with the metabolic syndrome was statistically higher in the group with the highest score ($P<.001$). Analysis of variance showed that the statistically different metabolic parameters ($P<.001$) with a linear trend ($P<.001$) among the 7 groups of patients were levels of postload glucose, HbA_{1c}, postload and fasting insulin, triglycerides,

Table 2. Metabolic Parameters of the Studied Groups

Parameter	No. of Stenosed Vessels*				P Value		
	0	1	2	3	ANOVA	Multiple Pairwise Comparison†	Linear Trend
Glucose, mg/dL							
Fasting	90.1 (11.1)	90.0 (9.2)	89.7 (7.8)	90.6 (7.9)	.05		
Postload	110.2 (11.5)	114.1 (10.2)	128.1 (5.6)	130.0 (5.6)	<.001	<.001	<.001
Insulin, µU/L							
Fasting	7.9 (2.2)	8.2 (3.1)	10.1 (4.1)	10.9 (4.8)	<.001	.58‡	<.001
Postload	61.2 (36.9)	65.5 (28.0)	80.3 (38.6)	82.6 (45.3)	<.001	>.99‡	<.001
HOMA-IR	1.8 (0.7)	1.9 (0.9)	2.3 (1.1)	2.7 (1.8)	<.001	.75‡	<.001
HbA _{1c} , %	4.7 (0.4)	4.9 (0.5)	4.9 (0.6)	5.6 (0.3)	<.001	.09§	<.001
Lipids, mg/dL							
Total cholesterol	186.6 (24.4)	201.1 (35.9)	226.5 (29.3)	230.2 (30.8)	<.001	<.001	<.001
LDL-C	120.5 (21.4)	130.6 (20.8)	153.2 (30.2)	157.6 (22.5)	<.001	<.001	<.001
HDL-C	35.3 (9.3)	40.0 (13.2)	41.5 (12.8)	31.7 (9.4)	<.001	.97	<.001
Triglycerides	150.4 (28.9)	152.7 (24.1)	158.4 (24.8)	204.5 (35.7)	<.001	>.99‡	<.001

Abbreviations: ANOVA, analysis of variance; HbA_{1c}, glycosylated hemoglobin; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, insulin resistance by homeostasis model assessment; LDL-C, low-density lipoprotein cholesterol.
 SI conversion factors: To convert mg/dL to mmol/L for glucose, multiply values by 0.0555; to convert mg/dL to mmol/L for LDL-C, HDL-C, and total cholesterol, multiply values by 0.0259; to convert mg/dL to mmol/L for triglycerides, multiply values by 0.0113.
 *Data are mean (SD).
 †P value <.001 for all pairwise comparisons unless otherwise indicated.
 ‡For group 0 vs group 1.
 §For group 0 vs group 2.
 ||For group 1 vs group 2.

Table 3. Correlation With the Number of Stenosed Vessels as Dependent Variable

Factor	Simple Correlation		Multiple Stepwise Correlation			
	r	P Value	R ² *	SE	Coefficient (β)	P Value
Postload glucose	0.667	<.001	0.445	0.7954	0.572	<.001
HbA _{1c}	0.561	<.001	0.630	0.6490	0.413	<.001
HOMA-IR	0.278	<.001	0.670	0.6132	0.250	<.001
Postload insulin	0.221	<.001	0.690	0.5940	0.267	<.001
Fasting insulin	0.297	<.001	0.711	0.5734	0.174	<.001
Triglycerides	0.531	<.001	0.723	0.5612	0.195	<.001
Total cholesterol	0.432	<.001	0.735	0.5494	0.203	<.001
HDL-C	-0.156	.009	0.738	0.5458	-0.099	<.001
Fasting glucose†	-0.003	.83	NA	NA	NA	NA
LDL-C	0.501	<.001	0.743	0.5406	0.101	<.001
Diastolic BP	0.067	<.001	0.746	0.5374	0.033	.02
Systolic BP†	0.004	.76	NA	NA	NA	NA
Age†	0.020	.14	NA	NA	NA	NA
Smoking	0.087	<.001	0.742	0.0280	0.009	.52

Abbreviations: BP, blood pressure; HbA_{1c}, glycosylated hemoglobin; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, insulin resistance by homeostasis model assessment; LDL-C, low-density lipoprotein cholesterol; NA, not available.
 *Calculated for the model after each variable is added.
 †Data for multiple stepwise correlation not available because the stepwise analysis model excluded parameters that did not have a statistically significant correlation with the number of stenosed vessels.

total cholesterol, and LDL-C, as well as HOMA-IR. Simple regression analysis showed that the Duke score was correlated with levels of postload plasma glucose ($r=0.603$, $P<.001$), HbA_{1c} ($r=0.514$, $P<.001$), postload insulin ($r=0.216$, $P<.001$), fasting insulin ($r=0.275$, $P<.001$), triglycerides ($r=0.513$, $P<.001$), total cholesterol ($r=0.401$, $P<.001$), HDL-C ($r=-0.182$, $P<.001$), and LDL-C ($r=0.420$, $P<.001$), as well as with HOMA-IR ($r=0.379$, $P<.001$), diastolic blood pressure ($r=0.052$, $P<.001$), and systolic blood pressure ($r=0.067$, $P<.001$). Multiple stepwise regression analysis suggested that all these factors were independently associated with the Duke stratification groups ($P<.001$ for all, except for diastolic blood pressure, $P=.02$).

COMMENT

The role of diabetes and IGT in cardiovascular risk, as well as the high prevalence of impairments of glucose metabolism among people with CHD, has been well investigated.¹⁻⁸ All these studies showed a consistent gradient across categories of worsening glucose intolerance. Moreover, some reports indicate a correlation between glucose metabolism and CHD even in patients without diabetes or IGT.^{4,5,10-13} Instead, there is no consensus regarding the better metabolic predictors of CHD in patients with NGT, whether their effect is linear or threshold, and if their values are correlated with the severity of CHD.

The present study showed that, among patients with NGT and CHD: (1) postload glycemia was statistically higher in all groups of patients with CHD, while fasting insulinemia, postload insulinemia, and HOMA-IR were significantly higher in patients with 2- or 3-vessel disease and HbA_{1c} level was significantly higher in those with 1- or 3-vessel disease; (2) these parameters were independently correlated to the number of involved vessels, as assessed by coronary angiography; (3) postload glycemia and HbA_{1c} level were the glycemic variables having the higher correlation with CHD.

Table 4. Multiple Stepwise Regression With the Duke Myocardial Jeopardy Score as Dependent Variable

	R ² *	SE	Coefficient (β)	P Value
Postload glucose	0.364	1.56	0.391	<.001
HbA _{1c}	0.521	1.35	0.337	<.001
HOMA-IR	0.620	1.20	0.274	<.001
Postload insulin	0.641	1.17	0.144	<.001
Fasting insulin	0.661	1.14	0.167	<.001
Triglycerides	0.672	1.12	0.108	<.001
Total cholesterol	0.679	1.11	0.095	<.001
HDL-C	0.685	1.10	-0.103	<.001
Systolic BP	0.687	1.09	0.053	<.001
LDL-C	0.688	1.09	-0.040	<.001
Diastolic BP	0.688	1.09	-0.020	.02

Abbreviations: BP, blood pressure; HbA_{1c}, glycosylated hemoglobin; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, insulin resistance by homeostasis model assessment; LDL-C, low-density lipoprotein cholesterol.

*Calculated for the model after each variable is added.

These data support some previous prospective studies of the associations of glycemic variables with cardiovascular mortality in patients without diabetes. The Hoorn Study¹¹ reported that postload glycemia and HbA_{1c} level were associated with an increased risk of cardiovascular mortality in patients without diabetes after adjustment for age, sex, and known cardiovascular risk factors. The combined analysis of the 20-year mortality from CHD of men without diabetes in 3 European studies⁴ showed that, even if their distributions of postload glycemia were not fully comparable because of the different protocols used, those in the upper 2.5% of the postload glycemia distribution were at higher risk. The Rancho Bernardo Study¹⁰ concluded that HbA_{1c} level is predictive for future cardiovascular disease and CHD mortality in women without diabetes.

In our study fasting glycemia was not statistically different between patients with and without CHD, while some previous data⁴ reported an increased risk for death from CHD in the upper percentiles of this variable. Otherwise, other investigations¹⁰ found no relationship between fasting glycemia and risk of CHD in patients with NGT.

Most of the previous prospective studies did not apply current American Diabetes Association criteria for the definition of impaired glucose metabolism; thus, many of the patients in the

upper percentiles of the glycemic values would now be classified as having diabetes or impaired fasting glucose. However, the effect of HbA_{1c} level was evident both at the upper end^{10,11} and at the lower end¹² of the population distribution. Interestingly, the results of the European Prospective Investigation of Cancer and Nutrition (EPIC)-Norfolk Study¹² showed that an increase of 1% in HbA_{1c} level was associated with a significant increase in risk of cardiovascular death in men without diabetes (relative risk, 1.46) and with no apparent threshold effect. The mean difference in levels of HbA_{1c} (approximately 1%) we found between patients without coronary stenosis and those with 3-vessel disease seems to indirectly confirm the findings of the EPIC-Norfolk Study.¹²

The correlation between glucose metabolism and the severity of CHD has recently been investigated by a Polish study,¹⁷ the aims of which were to use the OGTT to detect the actual prevalence of glycemic impairments among patients with CHD but without a previous history of diabetes, and to correlate this prevalence with the number of stenosed vessels. Kowalska et al¹⁷ observed that approximately 50% of patients had impairments of glucose metabolism (16% had type 2 diabetes mellitus, 36% had IGT) and that those with advanced damage in the coronary arteries experienced a higher preva-

lence of glycemic disturbances. Moreover, from the analysis of glucose variables in the different groups of CHD disease, these authors also observed that postload glycemia and levels of fasting plasma insulin, postload plasma insulin, and HbA_{1c} significantly, but not independently, correlated with the number of involved vessels.

Instead, our data are consistent with an independent correlation between postload glycemia, fasting and postload insulinemia, HbA_{1c} levels, and HOMA-IR and the number of substantially stenosed vessels. This different result could be explained because we investigated the differences in metabolic parameters among the various degrees of coronary damage specifically in OGTT-screened patients with NGT, while the study by Kowalska et al¹⁷ considered patients with diabetes, IGT, and NGT together.

This was designed as a prevalence study and hence does not attempt to offer a pathogenic explanation for the relationship between glucose metabolism and CHD in patients with NGT. In this regard, some authors suggest that advanced glycation end products (AGEs) could play a pathogenic role by impairing cytokine production,²⁵ monocyte activation,²⁶ or endothelial function.²⁷ Deposits of AGEs have been detected in the atherosclerotic plaques of patients with diabetes²⁸ but also in normoglycemic patients.²⁹ Similarly, serum concentrations of AGEs were statistically higher not only in patients with CHD and type 2 diabetes,³⁰ but also in patients with CHD and with IGT and NGT³¹ when compared with those without CHD. The finding that AGE concentrations correlated with the severity of CHD in patients without diabetes³¹ seems to indirectly confirm the hypothesis of a gradient in tissue damage by glucose variables. Even oxidative stress is thought to be involved in macroangiopathic complications,³² but similar data in patients with NTG are lacking. Otherwise, AGE concentrations and oxidative stress are strictly intertwined.³³

We found that glucose parameters, especially postload glycemia and HbA_{1c}

levels, in patients with NGT and with different atherosclerotic damage are not equally distributed but are significantly higher in those with more severe disease. There appears to be a linear relationship between glucose metabolism and the severity of CHD, even when glucose values are within the "normal" range. Like other metabolic variables such as serum cholesterol,³ the glycemic milieu may also correlate with the cardiovascular risk according to a linear model.

Classifying patients according to the number of stenosed vessels could lack great prognostic value. Otherwise, many studies exploring the relation between 1 or more factors and the extent and severity of CHD classify coronary angiography data anatomically (ie, as single-, double-, or triple-vessel disease). On the other hand, a number of classifications of coronary lesions were developed mainly to predict morbidity and mortality in patients with CHD.^{24,34} In order to provide more prognostic value, we successively reanalyzed patients after grouping them according to Duke Myocardial Jeopardy Score and found that parameters of glucose metabolism also correlated with this classification. However, our results suggest an association that can only be validated by specifically designed prospective studies.

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To know truly is to know by causes.
—Francis Bacon (1561-1626)