Natural History of Cardiovascular Disease in Patients With Diabetes

Role of hyperglycemia

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Atherosclerotic vascular disease is more common in diabetic than in nondiabetic individuals. Diabetic macrovascular disease also has a more severe course with greater prevalence of multiple-vessel coronary artery disease and more diffuse elongated atheromas in affected blood vessels. In this review, we discuss possible reasons for increased incidence of cardiovascular (CV) events in individuals with diabetes. Although an increased prevalence of standard CV risk factors has been clearly documented in association with diabetes, diabetes-related abnormalities, particularly hyperglycemia, also play an important role. Epidemiological studies suggest that the effect of hyperglycemia on CV risk is independent of other known risk factors, but no data from primary interventional trials are available yet. Analysis of datasets from populations that included individuals with impaired glucose tolerance and impaired fasting glucose suggest that the pathogenic role of hyperglycemia on the blood vessel wall already exists in the early stages of glucose intolerance. The effect of postprandial or postchallenge hyperglycemia seems to be greater than the effect of fasting blood glucose abnormalities. The relationship of postprandial glycemia, fasting blood glucose, and CV risk in individuals with diagnosed (or overt) diabetes is less clear, although most reports indicate a greater pathogenic potential of postprandial hyperglycemia rather than fasting hyperglycemia. Based on the results of epidemiological reports, the most appropriate targets in interventional trials are postprandial hyperglycemia or A1C.

Diabetes Care **31 (Suppl. 2):S155–S160, 2008**

We have known for many decades that diabetes increases the risk of cardiovascular (CV) disease (1–3). About 65% of deaths in individuals with type 2 diabetes are related to heart disease or stroke (3). An exceptionally high risk has been observed among patients with type 2 diabetes after they suffer their first CV event, for example, myocardial infarction (MI) (4–7).

Despite a clear association between diabetes and atherosclerotic vascular disease, the underlying mechanisms that link the two diseases are not understood. Recent medical literature has emphasized the importance of nonglycemic factors, such as abnormalities associated with the metabolic syndrome (arterial hypertension, dyslipidemia, and others) in causing progressive atherosclerosis (8,9). While the role of these other factors has been clearly documented, results from prospective epidemiological studies also suggest an independent effect of hyperglycemia on CV risk (10,11). This is true for both type 1 and type 2 diabetes. Despite substantial epidemiological evidence of the relationship between diabetes and atherosclerosis, data from available interventional trials that assess the effect of a glucose-lowering strategy on CV outcomes (as its primary end point) are limited. Another unresolved question is the most appropriate target to choose for intervention in patients with hyperglycemia and risk of CV disease: A1C or specific components of the daily blood glucose (BG) profile? To provide some insight into these issues, it is important to understand the natural course of CV disease in diabetic individuals and the role of hyperglycemia at different times in the progression of the disease.

EPIDEMIOLOGY OF CV DISEASE IN TYPE 1 AND TYPE 2 DIABETES

— Until recently, no definite epidemiological evidence with respect to the relationship between type 1 diabetes and diabetic macrovascular disease was available. In 2003, Laing et al. (12) reported results from a prospective study of 23,751 individuals from the U.K. type 1 diabetes cohort (patients were followed for up to 29 years). The primary objective was assessing the overall mortality from heart disease and coronary heart disease. While the CV event rate in this relatively young population remained significantly lower compared with the population of individuals with type 2 diabetes, their relative risk of coronary heart disease mortality was severalfold higher than in a matched nondiabetic population (12). Because the prevalence of other risk factors, including those associated with the metabolic syndrome, was significantly lower in type 1 diabetes compared with the prevalence in type 2 dia-

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This article is based on a presentation at the 1st World Congress of Controversies in Diabetes, Obesity and Hypertension (CODHy). The Congress and the publication of this article were made possible by unrestricted educational grants from MSD, Roche, sanofi-aventis, Novo Nordisk, Medtronic, LifeScan, World Wide, Eli Lilly, Keryx, Abbott, Novartis, Pfizer, Generx Biotechnology, Schering, and Johnson & Johnson.

Abbreviations: BG, blood glucose; CV, cardiovascular; DCCT, Diabetes Control and Complications Trial; EDIC, Epidemiology of Diabetes Interventions and Complications; FBG, fasting blood glucose; IGT, impaired glucose tolerance; MI, myocardial infarction.

DOI: 10.2337/dc08-s240

betes, Laing's report strongly suggested a causal relationship between hyperglycemia and CV disease.

The importance of hyperglycemia in the development and progression of diabetic macrovascular disease in type 2 diabetes has been described in numerous reports (5,10–15). The DECODE (Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe) study group analyzed databases from numerous European populations that included individuals with overt type 2 diabetes and individuals with borderline glucose intolerance (13–15). Their report suggested that people with type 2 diabetes have almost twice the risk of CV disease (including coronary heart disease and stroke) as nondiabetic individuals, after adjustment for other CV risk factors (15). In another published meta-analysis that included studies in both types of diabetes, Selvin et al. (16) reported that the presence of hyperglycemia increased the risk of new CV events. Based on the evidence presented in the literature, it is now accepted that chronic hyperglycemia has a role in the pathogenesis of diabetic macrovascular disease (10,11).

Borderline dysglycemia and its effect on CV risk

For many years, borderline categories of glucose intolerance (impaired glucose tolerance [IGT] and impaired fasting glucose) were only considered as risk factors for the development of diabetes, with minimal or no relevant effect on micro- and/or macrovascular complications. Systematic assessment of available databases, as reported by the DECODE group, have shown that the relationship between glycemia and CV risk starts within the normal BG range, with a linear relationship, and shows no indication of a threshold effect (13–15). Both fasting and postchallenge (a surrogate of postprandial) hyperglycemia correlate with CV risk (15). Since fasting and postprandial BG themselves correlate strongly, it is important to separately analyze their effect on the risk of new CV events, adjusting for other possible confounding factors. A number of authors have performed these adjustments and reported that postprandial BG correlates more strongly with CV risk than fasting blood glucose (FBG) (13,17,18).

Another way to study the relationship between mild (borderline) dysglycemia and vascular complications is to prospectively follow patients with isolated fasting hyperglycemia and isolated postprandial hyperglycemia and compare how these variables affect CV risk over time. This approach enables researchers to study the effect of different forms of hyperglycemia (postchallenge and fasting) on new CV outcomes in separate subpopulations of individuals. The Funagata study group (19) showed higher CV mortality in people with IGT compared with individuals with impaired fasting glucose. Other reports have also shown that postchallenge hyperglycemia was associated with the risk of CV events more strongly than fasting hyperglycemia (13,17,18). This association is independent of A1C or FBG (13,17). It is important to emphasize that postchallenge BG correlates with glycemia in the postprandial period and may be considered a surrogate for postprandial BG (20).

These observations can be interpreted in several ways. One possibility is that postprandial hyperglycemia contributes more to the overall glycemic exposure in the early stages of diabetes than FBG (21). This, however, cannot explain why the effect of postprandial glycemia is independent of A1C. Another explanation is that IGT correlates better with risk of CV events because of a higher prevalence of the metabolic syndrome in this population, which by itself greatly increases the risk of CV events (22). This hypothesis contradicts reports showing that the effect of postprandial glycemia is independent of other CV risk factors (17,18). Finally, it is possible that postprandial BG is associated with the highest diurnal levels of glycemia and that these may have a more damaging effect on vasculature and heart function (oxidative stress, abnormal vasomotion, blood flow, etc.) than the glycemic state during the fasting period. Differences between peak levels of glycemia during the postprandial and fasting periods may translate into differing risks for CV disease in these individuals (23,24).

Overt hyperglycemia and risk of CV disease

Epidemiological reports from the Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) studies (10) and the U.K. Prospective Diabetes Study (11) have provided evidence to support the notion that the relationship between the degree of hyperglycemia and CV risk is independent of other risk factors in individuals with type 1 or type 2 diabetes, respectively. As already discussed, a recent report from the DECODE study indicates this relationship is continuous across the range of glycemic levels (15). Relative risk of CV mortality plotted against glycemia for both FBG and postprandial BG indicates this positive continuous relationship in the diabetic range of glycemia.

It is not very clear how various components of the daily BG profile correlate with the risk of CV disease and CV mortality in people with overt diabetes. In 1996, Hanefeld et al. (25) described a progressive positive correlation between the degree of postprandial glycemia and the risk of MI and CV mortality in people with diabetes. They did not find a similar relationship with respect to fasting glycemia and CV outcomes. The main weakness of this study is the lack of data on daily BG profiles (the investigators assessed BG based on regular breakfast at baseline) (25). However, evidence has accumulated indicating that postchallenge glycemia strongly correlates with postprandial BG (20). This is further supported by the results of the San Luigi Gonzaga Diabetes Study (26) that assessed the effect of fasting and postprandial glycemia on the risk of new CV events in a population of 529 consecutive prospectively followed patients with type 2 diabetes who were observed for up to 5 years (26). This study shows that only postprandial BG, not FBG, independently predicts the risk of new CV events in this population. This relationship seems to be stronger in female than in male individuals (26).

MORPHOLOGICAL CHARACTERISTICS OF BLOOD VESSELS IN DIABETIC MACROVASCULAR DISEASE

— Both pathologic studies and angiographic reports in individuals with coronary heart disease have shown that patients with diabetes have a greater number of coronary blood vessels involved with a more diffuse distribution of atherosclerotic lesions (27,28). Similar differences have been described in the peripheral vasculature (29). Individuals with diabetes also have an increased risk of plaque ulceration and thrombosis compared with nondiabetic individuals (30). Other morphological differences have been observed (27–29). It is reasonable to conclude that different morphological and clinical characteristics of diabetic versus nondiabetic macrovascular disease may be related to the effect of hyperglycemia and other diabetes-specific disorders,

Table 1—*Differences among five geographically defined subpopulations in the HEART2D trial with respect to various demographic and clinical parameters*

	Total	India	CEE	West Asia	South Africa	WE/Canada	*P*
n	1,110	70	718	149	89	84	—
Age (years)	61.0 ± 9.8	54.5 ± 8.7	62.7 ± 9.2	59.0 ± 10.2	55.0 ± 9.0	61.7 ± 10.0	<0.0001*
Sex (M)	702 (63)	56 (80)	415 (58)	106 (71)	64 (72)	61 (73)	<0.0001*
BMI (kg/m^2)	29.1 ± 4.8	25.0 ± 3.6	29.6 ± 4.6	28.3 ± 4.8	28.5 ± 4.8	30.6 ± 5.9	<0.0001*
Duration of diabetes (years)	9.1 ± 7.2	8.6 ± 6.3	9.3 ± 7.3	8.7 ± 7.2	9.3 ± 7.7	8.5 ± 7.3	0.71*
A1C (%)	8.3 ± 1.5	8.7 ± 1.5	8.3 ± 1.4	8.4 ± 1.5	8.5 ± 1.7	8.2 ± 1.4	0.09*
Fasting blood glucose (mmol/l)	8.3 ± 2.5	8.8 ± 2.6	8.1 ± 2.3	8.8 ± 2.8	8.1 ± 3.0	8.4 ± 3.2	0.01*
2-h postprandial BG (mmol/l) (mean of all meals)	11.0 ± 2.9	13.1 ± 3.5	10.6 ± 2.7	11.5 ± 2.9	11.2 ± 3.4	11.3 ± 3.5	<0.0001*
Albumin-to-creatinine ratio (mg/g)	139 ± 528	184 ± 454	119 ± 500	180 ± 547	248 ± 781	93.9 ± 486	0.24*
Triglycerides (mmol/l)	1.8 ± 1.1	1.6 ± 0.8	1.9 ± 1.1	1.8 ± 1.2	1.8 ± 0.9	1.6 ± 0.7	0.02†
Total cholesterol (mmol/l)	4.5 ± 1.3	3.7 ± 0.8	4.7 ± 1.3	4.2 ± 1.0	4.2 ± 1.1	3.8 ± 0.9	<0.0001†
HDL cholesterol (mmol/l)	1.0 ± 0.2	0.9 ± 0.2	1.0 ± 0.2	0.9 ± 0.3	1.0 ± 0.2	1.0 ± 0.2	0.09†
LDL cholesterol (mmol/l)	2.7 ± 1.0	2.2 ± 0.7	2.9 ± 1.1	2.5 ± 0.8	2.5 ± 0.9	2.1 ± 0.7	<0.0001†
Tobacco use	173 (15.6)	6 (8.6)	125 (17.4)	22 (14.9)	11 (12.4)	9 (10.7)	0.0002†
Systolic blood pressure (mmHg)	127 ± 17.2	126 ± 15.6	129 ± 15.6	120 ± 18.7	126 ± 21.5	127 ± 20.8	0.10†
Diastolic blood pressure (mmHg)	76.7 ± 9.3	79.5 ± 10.1	77.7 ± 8.2	71.9 ± 10.7	77.4 ± 9.9	74.2 ± 11.2	0.25†
QTC interval (ms)	435 ± 33.3	429 ± 37.6	439 ± 31.4	427 ± 34.7	434 ± 34.1	420 ± 35.3	<0.0001†

Data are means ± SD or *n* (%). *Categorical data were analyzed using χ^2 tests. Mean data were analyzed using type III sum of squares ANOVA using region in the model. †Additional covariate analyses were done for coefficient of variation risk factors assessing regional differences adjusted for sex and age using ANCOVA and a logistic regression model for continuous and categorical variables, respectively. Covariate analysis included age, sex, and region by age-sex interaction in the model, with region as an independent variable. CEE, central and eastern Europe; WE, western Europe; QTC, QT_c interval.

although this hypothesis requires additional prospective studies to confirm.

INTERVENTIONAL STUDIES —

No data from a prospective glucose-lowering interventional trial with a primary end point of CV outcomes are currently available. In several large-scale interventional trials of individuals with diabetes, CV outcomes were collected as a part of the primary composite end point or as a secondary end point only.

In patients with IGT, treatment with acarbose (a drug predominantly affecting postprandial glycemia) (STOP-NIDDM trial) reduced the risk of CV events, especially MI (31). The CV benefits of targeting postprandial glucose are also evident from a meta-analysis of seven randomized placebo-controlled trials with acarbose in patients with type 2 diabetes. Treatment of postprandial hyperglycemia was associated with a reduction in developing any CV disease of 35% (32).

In the U.K. Prospective Diabetes Study, intensive treatment with metformin in a subgroup of patients with type 2 diabetes resulted in decreased risk for MI and stroke compared with the conventional treatment group (33). In the same study, intensive treatment with sulfonylurea or insulin improved long-term outcomes of diabetes (micro- and macrovascular combined), but the improvement in CV risk did not reach statistical significance. In the STENO-2 trial, a multifaceted approach with multiple-drug intervention and behavioral modification, including intensified glycemic management, improved CV outcomes (34). In another recent study, insulin-glucose infusion after acute MI with subsequent intensive insulin treatment improved survival rates (35), but some of the observations were not confirmed in a follow-up study (36). In a randomized study of women with gestational diabetes (37), insulin dosage was adjusted to either premeal glucose values or postmeal values. Only women with postmeal glucose control achieved A1C target levels. Even more importantly, women and their babies in the postmeal glucose control group had fewer complications.

In a study of patients with type 2 diabetes and preexisting macrovascular disease, it was reported that patients treated with pioglitazone (in combination with other glucose-lowering treatments) had better outcomes, namely, all-cause mortality, nonfatal MI, and nonfatal stroke (main secondary composite endpoint), compared with those receiving other glucose-lowering treatments and placebo (38). DCCT/EDIC (10) was designed as an epidemiological study. Because of its close connection with the DCCT trial population, this report provided more evidence that long-term reduction of glycemic exposure in individuals with type 1 diabetes results in improved CV outcomes.

In a meta-analysis that included most of the trials discussed in this article, a similar positive effect of BG lowering on the risk of CV events has been suggested (16). This effect seems to be greater in individuals with type 2 diabetes than in type 1 diabetic individuals (16). The importance of postprandial glycemia is confirmed by two studies with measurement of intima-media thickness. In a substudy of the STOP-NIDDM trial, treatment of IGT with acarbose reduced mean increase in intima-media thickness by ~50% (the acarbose group and the placebo group were treated with state-of-the-art therapy for hypertension and dyslipidemia) (39). The Campanian postprandial hyperglycemia study compared the effect of repaglinide (a prandial insulin secretagogue) with glyburide (a long-acting sulfonyl-

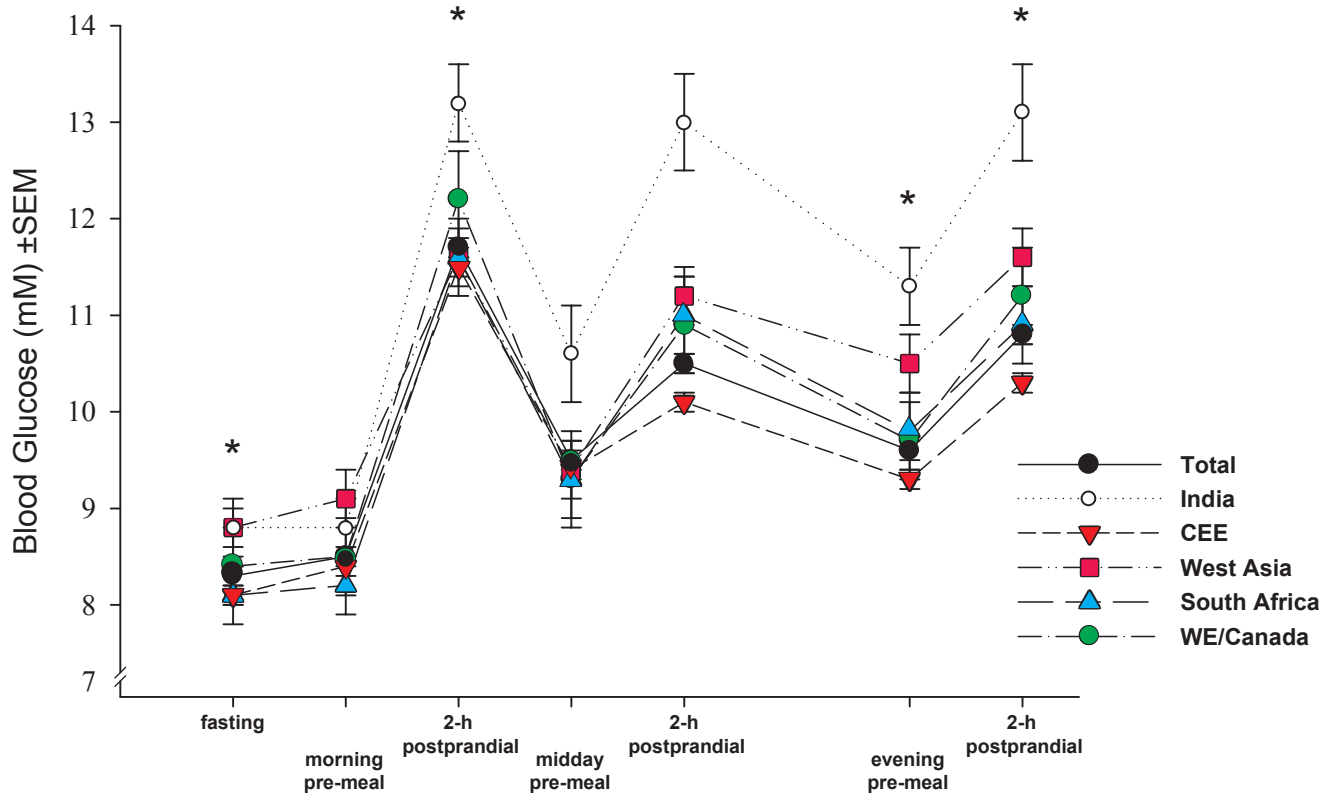

Figure 1—*Daily seven-point BG profiles in patient subpopulations from five different geographic regions and total group of patients from HEART2D. Figure shows means (± SE), with "*" representing significant* P *value (ANOVA) among the regions. Although significant differences were observed between the groups, all subpopulations displayed signs of poor postmeal glucose tolerance, as reflected in high postprandial BG excursions. Data were collected after patients entered the trial, but before randomization. During that period, they were treated with conventional insulin therapy (premixed human insulin twice daily). CEE, central and eastern Europe; WE, western Europe.*

urea). After 12 months, A1C was reduced by a similar extent. Significantly lower levels of fasting plasma glucose were achieved with glyburide, whereas repaglinide reduced postprandial hyperglycemia to an even greater extent. Intima-media thickness regression was only significant with repaglinide (40).

In addition to a more general question about the relationship between BG and atherosclerotic vascular disease, it is necessary to determine the best intervention target in individuals with diabetes who are at risk of developing CV end points, such as stroke, MI, or CV death. In almost all completed and ongoing clinical trials that aim to assess the effect of glucose-lowering strategies on the risk of new CV events as their primary or secondary objective, A1C is the primary target of intervention (16). As already discussed, the available epidemiological data seem to indicate that in addition to A1C, the best predictor of CV outcomes is postprandial hyperglycemia and should be seriously considered as a new target for intervention in CV trials (15,17–20).

We are addressing the effect of postprandial hyperglycemia on CV outcomes in the *H*yperglycemia and its *E*ffect After *A*cute Myocardial Infarction on *C*ardiovascular Outcomes in Patients with *T*ype *2 D*iabetes Mellitus (HEART2D) trial (41). This multinational interventional trial aims to assess the impact of two insulin regimens on CV outcomes in patients with type 2 diabetes and acute myocardial infarction (41). One group targets postprandial BG to achieve A1C <7%; the other group targets fasting and premeal BG levels to achieve a similar A1C level. The primary objective of HEART2D is to demonstrate a difference between the two insulin regimens on time until the first recurrent CV event (CV death, nonfatal MI, nonfatal stroke, coronary revascularization, or hospitalized acute coronary syndrome).

ADDITIONAL CHALLENGES IN DESIGNING INTERVENTIONAL TRIALS TO ASSESS THE EFFECT OF BG LOWERING ON CV RISK

The choice of the study population (its demographic and clinical characteristics) can influence the outcome of the trial and the interpretation of its results. As discussed, risk for new CV events in people with diabetes is associated with major traditional CV risk factors and diabetes-related abnormalities. In addition, factors associated with geographic origin of the population may also affect CV risk. This effect can, at least in part, be explained by environmental factors, such as lifestyle and socioeconomic characteristics, as well as genetic factors. Clinical research centers from new geographic areas are included more often than in the past (40,42,43). Thus, it is important to understand how CV risk factors and predictors vary in different populations around the world. Limited information is available in this regard, and it suggests that a broad range of CV risk profiles can be found worldwide (38,44,45). We assessed the magnitude of these differences using the HEART2D trial database. As shown in Table 1, significant differences among regions were observed in all groups of parameters assessed.

We were specifically interested in how the main treatment targets (fasting

and postprandial BG) in the groups differ among the geographic subpopulations. To be able to achieve the main study objective in HEART2D, that is, to separate the two groups with respect to postprandial glycemia (at least 2–2.5 mmol/l difference is expected), it is important to determine the feasibility of separating the two treatment groups in each subpopulation based on their prestudy postprandial BG levels. Significant differences were found in FBG and postprandial BG in each of the five subpopulations (Fig. 1).

CONCLUSIONS — Available evidence indicates that hyperglycemia increases CV risk in both type 1 and type 2 diabetes. Epidemiological reports show that the effect of postprandial or postchallenge hyperglycemia on this risk is greater than the effect of fasting hyperglycemia. This seems to be the case in individuals with borderline abnormalities (IGT versus impaired fasting glucose), as well as in those with diagnosed diabetes. According to the available epidemiological reports in the literature, including DCCT/EDIC, DECODE, and the San Luigi Gonzaga study, the most appropriate targets for future interventional trials that deal with the effect of hyperglycemia on CV risk are postprandial hyperglycemia or A1C.

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