Blood Glucose and Coronary Artery Disease in Nondiabetic Patients

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OBJECTIVE — Nondiabetic patients were studied to determine whether modest elevations in blood glucose may be associated with a greater incidence of coronary artery disease (CAD).

RESEARCH DESIGN AND METHODS — Baseline morning blood glucose determinations were evaluated with respect to subsequent coronary disease using records from 24,160 nondiabetic patients. CAD was identified from myocardial infarction, new diagnoses of angina, or new prescriptions for nitroglycerin that occurred more than a year after baseline glucose determinations.

RESULTS — Of 24,160 patients studied, 3,282 patients developed CAD over a total analysis time at risk of 77,048 years. Higher baseline morning glucose (100–126 vs. <100 mg/dl) was associated with a 53.9% greater myocardial infarction incidence rate, an 18.6% greater acute coronary syndrome incidence rate, and a 26.4% greater number of new prescriptions for nitrates (all $P < 0.05$). A Cox proportional hazards model with adjustment for age, BMI, sex, creatinine, lipids, smoking, and medications showed that elevated fasting glucose was associated with an increased hazard for new CAD (hazard ratio 1.13 [95% CI 1.05–1.21], glucose >100 vs. <100 mg/dl). Kaplan-Meier analysis showed that elevated baseline glucose was associated with a progressive increase risk of CAD with time.

CONCLUSIONS — Patients with higher baseline blood glucose levels in the absence of diabetes and after adjustment for covariants have a significantly greater risk for development of CAD.

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Nondiabetic patients were studied to determine whether elevations in blood glucose may be associated with increased risk for coronary artery disease (CAD). Although diabetes is a known risk factor for CAD (1–3), the risk of higher blood glucose in the absence of diabetes is unclear (4,5). Pathologic consequences from modest elevations of glucose are plausible since impaired glucose tolerance and impaired fasting glucose have been associated with macrovascular disease (6) and greater mortality (7). Patients presenting with acute coronary syndrome frequently have glucose intolerance (8), and it has been reported that glucose intolerance but not impaired fasting glucose may be associated with CAD (5,9). In contrast, meta-analysis indicates that glucose above a threshold of 100 mg/dl may also be a significant risk (10). Since impaired fasting glucose is increasingly common, affecting >35 million adults in the U.S. (11), and CAD affects a majority of older adults, associations between these common, morbid, and potentially fatal conditions are of clinical importance.

Adverse consequences from hyperglycemia may reflect effects of glucose as well as hyperinsulinemia. Glycemic effects include elevations in reactive oxygen species and formation of advanced glycation products (12). Hyperinsulinemia has been associated with mitogenic effects on vascular smooth muscle cells (13,14). Because elevated blood glucose is a common and potentially treatable condition, characterization of whether higher blood glucose may contribute to CAD is of particular clinical consequence.

The objectives of the current study were to determine whether elevated glucose in the absence of diabetes is a risk factor for CAD after correction for covariates. Because hyperglycemia is associated with additional risk factors for CAD including age, obesity, hypertension, and hyperlipidemia, the relevance of glucose was evaluated with multivariate regression models.

RESEARCH DESIGN AND METHODS

— Subjects received medical care from one or more of eight northwest Veterans Affairs medical centers in Seattle, Portland, Boise, Spokane, Walla Walla, Roseburg, White City, and Anchorage. Data were extracted from the electronic medical record systems of each facility and aggregated into a standard query language database without names, addresses, or other personal identifiers. The study was part of a larger project to develop automated methods for identification of associations between medication use, laboratory results, and medical outcomes. The project was reviewed and approved by the University of Washington-Seattle Investigational Review Board.

Computer-based records that included laboratory testing were used to identify nondiabetic subjects who had at least 2 years of medical care and blood glucose determinations at least 1 year before an initial indication of CAD as identified from ICD-9 coding and medication use. The record database included ICD-9 diagnostic information, medication use, laboratory data, and vital signs over the period from 1994 through December 2003. Records were excluded if there was any indication of possible diabetes including ICD-9 diagnosis of diabetes or a complication of diabetes, use of oral hy-

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Abbreviations: CAD, coronary artery disease.

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

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Table 1—*Subgroup characteristics with respect to baseline glucose determinations*

Glucose subgroup	<100 mg/dl	100–125 mg/dl
n	13,224	10,936
Sex (% female)	9.3	4.9*
Years of care	6.66 ± 2.42	6.61 ± 2.43
Glucose (mg/dl)	91.1 ± 6.6	108.2 ± 6.6*
Age	54.4 ± 13.3	57.2 ± 12.2*
BMI	28.4 ± 5.0	29.6 ± 5.3*
Creatinine	1.01 ± 0.27	1.02 ± 0.31*
Systolic blood pressure	136 ± 13	139 ± 14*
Diastolic blood pressure	78 ± 8	79 ± 9*
LDL cholesterol	129 ± 33	129 ± 33
HDL cholesterol	48 ± 14	47 ± 14
Triglycerides	167 ± 101	186 ± 111*
Smoker	42%	41%
Mortality	3.9%	4.3%*

Data are means ± SD, unless otherwise indicated. Subgroups based upon baseline morning glucose determinations. Years of care indicate the period of follow-up after initial laboratory studies. *$P < 0.05$.

poglycemic medication, use of insulin, or a blood glucose >126 mg/dl (7.0 mmol) at any time during the patient's care. Since glucocorticoids (oral or parenteral) could affect glucose determinations, patients who used these medications before a diagnosis of CAD were also excluded. With the objective of including predominantly fasting glucose determinations, only morning glucose determinations before 10 A.M. were included. The mean of measures during the 1st year of care were used to establish a baseline. Results were similar if only the single first measures were evaluated. Blood glucose determinations were performed at each hospital most often as part of an initial screening chemistry panel. Ninety-three percent of patients followed at least 2 years with any laboratory testing had measures of blood glucose performed. After exclusions, 24,160 records were available for nondiabetic subjects with information concerning at least 2 years of care, ICD-9 diagnostic coding, and baseline information including age, sex, BMI, blood pressure, smoking status, glucose, creatinine, lipid determinations, and medications. Medications were identified from pharmacy data (prescription issue dates corresponding to period of follow-up).

The onset of CAD was identified from a new ICD-9 diagnosis (ICD-9 codes, including 410, 411, 413, and 414 subgroups) in clinic or at admission. New prescriptions for nitroglycerin or isosorbide were identified from pharmacy data.

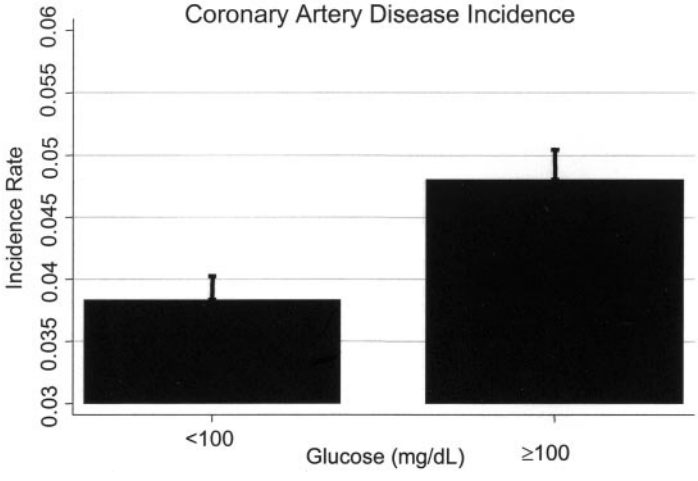

Figure 1—*Incidence rate of CAD (person-years; multiply by 1,000 for cases per 1,000 person-years) was significantly increased for patients with higher glucose (≥100 mg/dl,* n = *1,623; 33,784 years,* n = *985,* P < *0.05) as compared with those who had baseline glucose of <100 mg/dl (*n = *1,659; 43,264 years).*

Statistical analysis

Subjects with baseline blood glucose <100 mg/dl were compared with those who had glucose of 100–125 mg/dl with respect to risk for subsequent CAD using Cox proportional hazards regression models and Kaplan-Meier survival analysis. Statistical significance was defined by a two-tailed *P* value of <0.05. Data were aggregated using Microsoft SQL Server 2000 and analyzed using Stata SE version 8.0 (Stata, College Station, TX).

RESULTS — Subject groups were defined by baseline glucose determinations with comparisons between subjects who had glucose <100 mg/dl and those with glucose of 100–125 mg/dl. As shown in Table 1, characteristics of the groups were similar, although the higher glucose groups had slightly greater age, BMI, and blood pressure. Over the average 6- to 7-year period of care following an initial glucose determination, higher glucose was associated with more frequent myocardial infarction, more new diagnoses of CAD (including diagnoses of angina and acute coronary syndrome), and greater numbers of new prescriptions for nitroglycerin. The incidence rate of myocardial infarction increased from 2.1 cases/1,000 person-years (baseline glucose <100 mg/dl) to 3.2 cases/1,000 person-years (glucose 100–125 mg/dl, $P < 0.05$). The incidence rate for CAD increased from 11.9 cases/1,000 to 14.1 cases/1,000 person-years ($P < 0.05$), while new nitrate prescriptions increased from 22.6/1,000 to 28.6/1,000 person-years ($P < 0.05$) for patients with higher baseline glucose determinations. Thus, a new diagnosis of CAD that included myocardial infarction, a new diagnosis of CAD, or a new prescription for nitroglycerin was significantly more frequent when the baseline morning glucose was 100–125 mg/dl (5.5–7 mmol/l) in contrast to <100 mg/dl (Fig. 1).

Kaplan-Meier survival/morbidity analysis showed that patients with higher baseline glucose had a progressive increase in incidence of CAD that may approach 30% after 8 years (Fig. 2).

Multivariate regression analysis was performed to evaluate the risk of elevated glucose in the context of additional factors associated with coronary disease. Without correction for covariates, a Cox

Figure 2—*Kaplan-Meier failure analysis for CAD (myocardial infarction, diagnosis of angina/acute coronary syndrome, and new prescription of nitroglycerin) from patients with baseline glucose <100 mg/dl or 110–125 mg/dl as indicated.*

proportional hazards regression model showed that baseline glucose >100 mg/dl was associated with a significant risk for CAD (hazard ratio 1.24 [95% CI 1.16–1.33]). A model was then constructed with correction for age, sex, BMI, creatinine, diagnosis of hypertension (using ICD-9 coding), smoking, LDL cholesterol, HDL cholesterol, triglycerides, and medication use (β-blockers, statins, thiazide diuretics, ACE inhibitors, and angiotensin receptor blockers). Age, BMI, creatinine, LDL and HDL cholesterol, and triglycerides were analyzed as continuous variables. Cox regression analysis of 24,160 records comprising 77,048 years at risk and 3,282 instances of new coronary disease demonstrated increased risk for CAD (hazard ratio 1.13 [95% CI 1.05–1.21], $P < 0.001$) after corrections.

To evaluate whether progressively greater glucose may be associated with more frequent CAD, subjects were evaluated in four groups. A total of 12.1% of patients with glucose <90 mg/dl (n = 4,404) manifested coronary disease compared with 12.8 (glucose 90–100 mg/dl, n = 8,820, NS), 13.9 (glucose 100–110 mg/dl, n = 7,103, $P < 0.05$), and 16.6% (glucose 110–125 mg/dl, n = 3,833, $P < 0.05$) of patients with higher glucose (ANOVA $P < 0.001$). Subgroup evaluation showed patients with glucose 100–110 mg/dl or glucose 110–125 mg/dl had significantly more CAD than groups with glucose <100 mg/dl (Bonferroni, $P < 0.05$).

CONCLUSIONS — The results of this study demonstrate that elevated glucose in the absence of diabetes is associated with greater incidence of CAD independent of other recognized risk factors including age, weight, hyperlipidemia, renal failure, and hypertension. Both the relative risk for coronary disease and the progressive increase in incidence that appeared to approach 30% after 8 years indicate that modest increases in blood glucose are associated with an increased incidence of CAD. These results extend previous descriptions of the association between elevated glucose and CAD (4,8,15,16) and confirm that commonly used morning glucose determinations can provide a significant indication of CAD risk.

Our results indicate that elevations in glucose are significant even after adjustment for other variables that contribute to CAD. Furthermore, because glucose determinations were performed at least a year before a first diagnosis of coronary disease, the results are consistent with the possibility that elevated glucose contributes to the pathogenesis of coronary disease. Although risk factors including hyperlipidemia, hypertension, obesity, and sedentary lifestyle are well recognized, a substantial percentage of apparently lower-risk individuals manifest coronary disease. Elevations of glucose in the absence of diabetes appear to be an important additional risk factor that may improve identification of patients requiring further evaluation or treatment.

Glucose intolerance has been associated with coronary disease (4), while studies of fasting glucose have been less consistent (17,18). Since fasting glucose is the standard approach to initial evaluation of glycemic control, it is clinically important that our results confirm that morning glucose can identify patients at risk for coronary disease. Elevated fasting glucose is often associated with impaired glucose intolerance and assessment with an oral glucose tolerance test may more sensitively detect patients at risk. It is not clear whether impaired glucose tolerance is a necessary factor in CAD risk. The fact that an association of elevated glucose with CAD was significant in contrast to some past studies is likely due to the large size of the current study.

Pathologic consequences associated with elevated blood glucose may be related to both glucose concentration and insulin. Vascular disease may be related to endothelial dysfunction (19), proinflammatory changes (20), and a prothrombotic state (21). Elevated glucose induces nonenzymatic protein glycosylation, protein kinase C activation, and oxidative stress (22). Hyperinsulinemia has been associated with collagen deposition and myocardial fibrosis (23). Many effects of glucose may not have a lower threshold. To the extent that hyperinsulinemia precedes recognized hyperglycemia, it is plausible that the disease process initiates with very modest changes in blood glucose.

Because elevations of glucose were independently associated with risk for future onset of symptomatic coronary disease and mechanisms of glucose-induced adverse effects are recognized, it is plausible that treatment or lifestyle changes to control glucose even in nondiabetic patients could reduce coronary events. Intensive insulin therapy has been shown to improve outcomes for patients suffering acute myocardial infarction (24) or undergoing coronary bypass grafting (25). However, there is little clinical evidence that improved glycemic control can improve cardiac function and prevent CAD. Unfortunately, clinical evaluation is difficult. Multiple comorbidities contribute in the pathogenesis of CAD and complicate evaluation of glycemic control. Modest improvements in glycemic control are associated with less marked clinical improvement with the consequence that studies evaluating interventions in better controlled patients may not demonstrate statistical significance (26) unless many patients are included. Finally, since our current data suggest that even modest degrees of hyperglycemia may be of pathologic significance, a relatively stringent degree of glycemic control may be required to achieve some clinical end points.

The results of this study are from retrospective analysis, and clearly conclusions concerning interventions with respect to effects of controlling glucose to low levels are not warranted. Since the study population was older and includes few females, results may not be applicable to all patients. While it is plausible that elevated glucose has pathologic effects, it is not possible from retrospective study to exclude the possibility that glucose is only a covariant.

In summary, our data demonstrate the association of elevated glucose with subsequent risk for CAD in a population of predominantly male, nondiabetic veterans. Although it remains unclear whether there is a lower glucose threshold for adverse effects, our results demonstrate a significant risk >100 mg/dl. Elevated fasting glucose appears to be an additional indication for careful clinical evaluation with respect to risks for subsequent CAD.

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