Blood Glucose and Cerebrovascular Disease in Nondiabetic Patients

Christopher Nielson, MD,* and Richard M. Fleming, MD†

The objective of this study was to determine if elevations in blood glucose, in a range classified as impaired fasting glucose, are associated with a greater incidence of cerebrovascular disease in nondiabetic patients. Morning blood glucose determinations were evaluated with respect to subsequent stroke using records from 28 477 nondiabetic patients. Strokes and transient ischemic attacks (TIA) were identified from ICD-9 coding for a new event more than a year after baseline glucose determinations. Of the patients studied, 593 suffered stroke or TIA over a total risk analysis time of 100 982 years. Higher baseline morning glucose (100 to 126 mg/dL vs under 100 mg/dL) was associated with 31% more diagnoses (2.4% vs 1.8%, $P <$ .001). Incidence rate was 5.3 per 1000 patient-years for those patients with glucose over 100 mg/dL and 3.9 per 1000 patient-years for those with glucose under 100 mg/dL ($P <$.001). Kaplan-Meier analysis showed that elevated baseline glucose was associated with a progressive, increased risk with time. A Cox proportional hazards model with adjustment for age, body mass index, sex, creatinine, lipids, smoking, and medications showed that elevated fasting glucose was associated with an increased hazard for a new event (hazard ratio 1.24, 95% CI 1.05-1.46, glucose over 100 mg/dL vs under 100 mg/dL). Thus, 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 cerebrovascular disease.

Keywords: cerebrovascular disease; glucose intolerance; diabetes

Nondiabetic patients were studied to determine whether modest elevations in blood glucose may be associated with increased risk for cerebrovascular disease (CVD). Diabetes is a known risk factor for atherosclerosis and stroke.[1] Although some studies have suggested that elevated blood glucose in the absence of diabetes may be associated with CVD,[2,3] the association is complicated by additional risk factors including obesity and hypertension. Pathologic consequences may occur with modest elevations of glucose since both glucose intolerance and impaired fasting glucose (fasting plasma glucose 100 to 125 mg/dL)[4] have been associated with macrovascular disease[5] and mortality.[6] The relevance of elevated blood glucose to cerebrovascular disease has been recognized since more than half of nondiabetic patients with recent transient ischemic attacks (TIA) or stroke have elevated fasting glucose or impaired glucose tolerance,[7] and hyperglycemia has been associated with worse stroke outcome.[8] Studies

Angiology 58:625–629, October/November 2007

From the *University of Nevada Reno School of Medicine, NV; *Critical Care and Pulmonary Medicine, Veteran Affairs Medical Center, Reno, Nevada; *MSTI/MSMRI Research Institute of St. Luke's Regional Medical Center, Boise, Idaho; and *,†Critical Care and Cardiology, Department of Internal Medicine, Sierra Nevada Veterans Affairs Health Care System, Reno, Nevada.

Correspondence: Christopher Nielson, MD, 1000 Locust St. (111), Reno, NV 89502-2597; phone (775) 786-7200; e-mail: cnielson@med.unr.edu.

This work was supported by funding through grants from the American Heart Association and the MSTI/MSMRI Research Institute and was performed using facilities of the Department of Veterans Affairs.

DOI: 10.1177/0003319707303695

of carotid atherosclerosis with impaired fasting glucose have reached inconsistent conclusions.[9,10] Unfortunately, impaired fasting glucose is increasingly common, affecting over 35 million adults in the United States[11], and cerebrovascular disease is associated with severe morbidity as well as mortality.

Adverse consequences of hyperglycemia may be related to vascular disease as well as brain injury. Elevations in glucose associated with greater release of reactive oxygen species as well as generation of advanced glycation products can accelerate vascular injury.[12] Hyperglycemia has been associated with increased lactate levels in ischemic brain leading to intracellular acidosis, altered calcium regulation, and greater neuronal injury.[8] Increases in HbA1c have been associated with greater risk for carotid atherosclerosis,[13] and intensive treatment of diabetes to reduce hyperglycemia has been associated with reduced carotid artery disease.[14] Because elevated blood glucose is a common and potentially treatable condition, characterization of whether higher blood glucose may contribute to CVD is of particular clinical consequence.

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

Research Design and Methods

Subjects

The study included subjects who were cared for at 1 or more of 8 northwest Veterans Affairs medical centers in Seattle, Portland, Boise, Spokane, Walla Walla, Roseburg, White City, and Anchorage. Unidentified data were extracted from the electronic medical record systems of each facility and aggregated in an SQL database. No names, addresses, or other personal identifiers were included. The study was pursued as part of a 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. The University of Nevada Investigational Review Board exempted the project because data included no personal identifiers.

Data

Electronic records were used to identify nondiabetic subjects who had at least 2 years of medical care and blood glucose determinations at least 1 year prior to an initial indication of CVD as identified from ICD-9 coding. 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 hypoglycemic medication, use of insulin, or a blood glucose greater than 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 prior to a diagnosis of CVD were also excluded. With the objective of including predominantly fasting glucose determinations, only morning glucose determinations before 10 AM were included. Blood glucose determinations were performed at each hospital and were most often as part of an initial screening chemistry panel. Over 90% of patients followed for at least 2 years with any laboratory testing had measures of blood glucose performed. After exclusions, 28 477 records were available for nondiabetic subjects with information concerning at least 2 years of care, ICD9 diagnostic coding, and baseline information including age, sex, body mass index (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).

New cerebrovascular disease diagnoses of stroke or TIA were identified from ICD-9 coding (436, 435.8, 435.9, and 437.1 subgroups).

Statistical Analysis

Subjects were grouped with respect to baseline blood glucose of less than 100 mg/dL as compared with those who had glucose of 100 to 125 mg/dL. Stroke or TIA occurring more than 1 year after the initial glucose determination was evaluated using Cox proportional hazards regression

Table 1. Subgroups Based on Baseline Morning Glucose Determinations

Glucose Subgroup	<100 mg/dL	100-125 mg/dL
n	15 300	13 177
Sex (% female)	7.9	4.1
Years of care	6.7 ± 2.4	6.7 ± 2.4
Glucose (mg/dL)	91.2 ± 6.6	108.2 ± 6.5
Age	55.9 ± 13.3	58.4 ± 12.1
Body mass index	28.3 ± 4.8	29.4 ± 5.1
Creatinine	1.0 ± 0.3	1.0 ± 0.3
Systolic BP	135 ± 13	138 ± 13
Diastolic BP	77 ± 7.8	78 ± 7.8
LDL	128 ± 33	127 ± 33
HDL	47 ± 14	46 ± 13
Triglyceride	168 ± 99	187 ± 110
Smoker	43%	42%

Abbreviations: HDL, high density lipoprotein; LDL, low density lipoprotein

Years of care indicates the period of follow up after initial laboratory studies.

Data show means ± standard deviation.

Subgroup characteristics are with respect to baseline glucose determinations.

models and Kaplan-Meier survival analysis. Statistical significance was defined by a two-tailed *P* value of less than .05. Data was aggregated using Microsoft SQL Server 2000 and analyzed using Stata SE version 9.0 (Stata Corporation, College Station, Texas).

Results

Subject groups defined by baseline glucose determinations were compared between glucose levels less than 100 mg/dL and glucose of 100 to 125 mg/dL. As shown in Table 1, characteristics of the groups were similar although the higher glucose groups had slightly greater age, body mass index, and blood pressure. Over the average 6- to 7-year period of care following an initial glucose determination, higher glucose

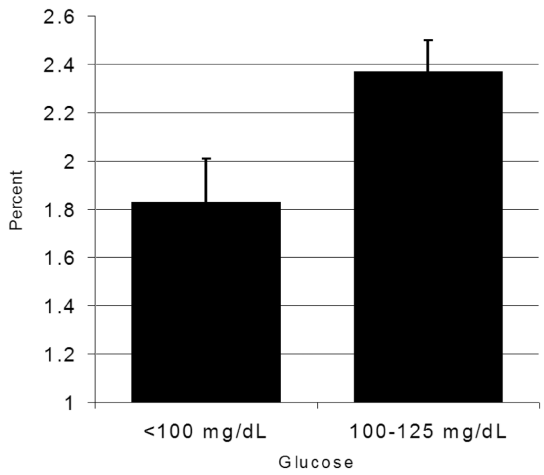

Figure 1. Frequency of transient ischemic attack or stroke was significantly increased for patients with higher glucose (100 to 125 mg/dL, n = 13 177, $P < .001$) as compared with those who had a baseline glucose of less than 100 (n = 15 300).

was associated with greater occurrence of TIA or stroke. Of patients with glucose under 100 mg/dL, 1.8% suffered an event, in contrast to 2.4% of patients with glucose 100 to 126 mg/dL, revealing a 31% greater frequency ($P < .001$). The incidence rate increased from 3.9 cases per 1000 patient-years (baseline glucose < 100 mg/dL) to 5.3 cases/1000 patient-years (glucose 100 to 125 mg/dL, $P < .001$). Thus, a new diagnosis of cerebrovascular disease including TIA and stroke was significantly more frequent when the baseline morning glucose was 100 to 125 mg/dL (5.5 to 7 mM) in contrast to under 100 mg/dL (Figure 1).

Kaplan-Meier survival/morbidity analysis showed that patients with higher baseline glucose had a progressive increase in incidence of cerebrovascular disease over a period of 8 years (Figure 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 proportional hazards regression model showed that baseline glucose over 100 mg/dL was associated with a significant risk for CVD (hazard ratio 1.35, 95% CI 1.15-1.59, $P < .001$). A model was then constructed with corrections for age, sex, body mass index, creatinine, diagnosis of hypertension, smoking, low density lipoprotein (LDL), high density lipoprotein (HDL), triglycerides, and medication use (beta-blockers, statins, thiazide diuretics, angiotensin converting enzyme

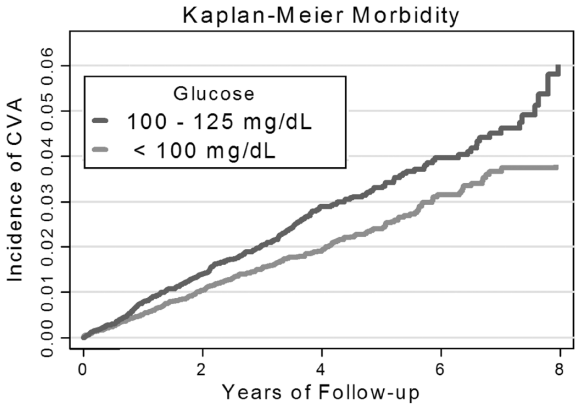

Figure 2. Kaplan-Meier failure analysis for cerebrovascular disease (acute transient ischemic attack or stroke) from patients with baseline glucose less than 100 mg/dL or 110 to 125 mg/dL as indicated.

inhibitors, and angiotensin receptor blockers). Age, body mass index, creatinine, LDL, HDL, and triglycerides were analyzed as continuous variables. Cox regression analysis of 28 477 records comprising 100 982 years at risk and 593 instances of new TIA or stroke demonstrated increased risk for CVD (hazard ratio 1.24, 95% CI 1.05-1.46, $P = .01$) after corrections.

Discussion

The results of this study demonstrate that elevated glucose in the absence of diabetes is associated with greater incidence of cerebrovascular disease independent of other recognized risk factors including age, weight, hyperlipidemia, renal failure, and hypertension. Both the relative risk for cerebrovascular disease and the progressive increase in incidence indicate that modest increases in blood glucose are associated with an increased incidence of TIA and stroke. These results extend previous descriptions of the association between elevated glucose and CVD and confirm that commonly used morning glucose determinations can provide a significant indication of CVD risk.

Studies of elevated glucose are commonly confounded by additional risk factors for CVD including age, gender, BMI, renal failure, hyperlipidemia, and hypertension. One study that included diabetics showed an association of fasting glucose with risk for CVD after correction for covariants.[3] Our results show that nondiabetic patients who have elevations in glucose above 100 mg/dL are at increased risk for CVD even after adjustment for multiple covariants. Furthermore, because glucose determinations were performed at least 1 year before a first diagnosis of CVD, the results are consistent with the possibility that elevated glucose contributes to the pathogenesis of CVD. Since elevated fasting glucose is an increasingly common problem, it may be clinically useful to include consideration of glucose in addition to other better recognized risk factors including hyperlipidemia, hypertension, and obesity. The identification of elevated glucose as a risk factor is of interest both with respect to identification of patients at risk and possibly as a basis for treatment.

Although elevated fasting glucose and glucose intolerance have been associated with CVD,[3,13] common covariates have not always been studied,[2] and it remains unclear whether elevations in glucose contribute to disease pathogenesis. It is known that elevation of blood glucose can contribute to the pathogenesis of cerebrovascular disease. Elevated glucose induces nonenzymatic protein glycosylation, protein kinase C activation, and oxidative stress.[15] Vascular disease may be related to endothelial dysfunction,[16] proinflammatory changes,[17] and a prothrombotic state.[18] Since effects of glucose may not have a lower threshold, modest changes in blood glucose could be of clinical significance.

Because elevations of glucose were independently associated with risk for future cerebrovascular events and mechanisms of glucose associated pathology are recognized, it is plausible that interventions to control glucose even in nondiabetic patients could reduce TIA and stroke. Control of postprandial hyperglycemia has been shown to improve carotid atherosclerosis[19]; however, there is little clinical evidence that improved glycemic control can reduce or prevent cerebrovascular events. Since consequences of stroke are severe, small reductions in frequency that may be difficult to statistically detect are of clinical importance.

In summary, our data demonstrate the association of elevated glucose above 100 mg/dL with subsequent risk for TIA and stroke in the absence of diabetes. Although it remains unclear whether interventions to lower glucose can reduce risk, elevated fasting glucose appears to be an additional indication for careful clinical evaluation with respect to cerebrovascular disease.

REFERENCES

1. Tuttolomondo A, Pinto A, Di RD, Fernandez P, Licata G: Stroke patterns, etiology, and prognosis in patients with diabetes mellitus. Neurology 8:581, 2005.
2. Vermeer SE, Sandee W, Algra A, Koudstaal PJ, Kappelle LJ, Dippel DW: Impaired glucose tolerance increases stroke risk in nondiabetic patients with transient ischemic attack or minor ischemic stroke. Stroke 37:1413-1417, 2006.
3. Tanne D, Koren-Morag N, Goldbourt U: Fasting plasma glucose and risk of incident ischemic stroke or transient ischemic attacks: a prospective cohort study. Stroke 35:2351-2355, 2004.
4. American Diabetes Association: Diagnosis and classification of diabetes mellitus. Diabetes Care 27:S5-S10, 2004.
5. Baron AD: Impaired glucose tolerance as a disease. Am J Cardiol 20:16H-9H, 2001.
6. Saydah SH, Loria CM, Eberhardt MS, Brancati FL: Subclinical states of glucose intolerance and risk of death in the U.S. Diabetes Care 24:447-53, 2001.
7. Kernan WN, Viscoli CM, Inzucchi SE, Brass LM, Bravata DM, Shulman GI, McVeety JC: Prevalence of abnormal glucose tolerance following a transient ischemic attack or ischemic stroke. Arch Intern Med 165:227-233, 2005.
8. Parsons MW, Barber PA, Desmond PM, Baird TA, Darby DG, Byrnes G, Tress BM, Davis SM: Acute hyperglycemia adversely affects stroke outcome: a magnetic resonance imaging and spectroscopy study. Ann Neurol 52:20-28, 2002.
9. 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 16:212-218, 1999.
10. Hanefeld M: Treatment of impaired glucose tolerance with acarbose and its effect on intima-media thickness: a substudy of the STOP-NIDDM trial (study to prevent non-insulin-dependent diabetes mellitus). Endocr Pract 12:56-59, 2006.
11. Schriger DL, Lorber B: Lowering the cut point for impaired fasting glucose: where is the evidence? Where is the logic? Diabetes Care 27:592-601, 2004.
12. Singleton JR, Smith AG, Russell JW, Feldman EL: Microvascular complications of impaired glucose tolerance. Diabetes 52:2867-2873, 2003.
13. Jorgensen L, Jenssen T, Joakimsen O, Heuch I, Ingebretsen OC, Jacobsen BK: Glycated hemoglobin level is strongly related to the prevalence of carotid artery plaques with high echogenicity in nondiabetic individuals: the Tromso study. Circulation 110:466-470, 2004.
14. Nathan DM, Lachin J, Cleary P, et al: Intensive diabetes therapy and carotid intima-media thickness in type 1 diabetes mellitus. N Engl J Med 348:2294-303, 2003.
15. Aronson D, Rayfield EJ: How hyperglycemia promotes atherosclerosis: molecular mechanisms. Cardiovasc Diabetol 1:1, 2002.
16. Vehkavaara S, Seppala-Lindroos A, Westerbacka J, Groop PH, Yki-Jarvinen H: In vivo endothelial dysfunction characterizes patients with impaired fasting glucose. Diabetes Care 22:2055-2060, 1999.
17. Festa A, Hanley AJ, Tracy RP, D'Agostino R, Jr., Haffner SM: Inflammation in the prediabetic state is related to increased insulin resistance rather than decreased insulin secretion. Circulation 108:1822-1830, 2003.
18. Carr ME: Diabetes mellitus: a hypercoagulable state. J Diabetes Complications 15:44-54, 2001.
19. Esposito K, Giugliano D, Nappo F, Marfella R: Regression of carotid atherosclerosis by control of postprandial hyperglycemia in type 2 diabetes mellitus. Circulation 110:214-219, 2004.