Impaired Glucose Tolerance Increases Stroke Risk in Nondiabetic Patients With Transient Ischemic Attack or Minor Ischemic Stroke

Sarah E. Vermeer, MD, PhD; Willemijn Sandee, MSc; Ale Algra, MD, FAHA; Peter J. Koudstaal, MD, PhD; L. Jaap Kappelle, MD, PhD; Diederik W.J. Dippel, MD, PhD; on behalf of the Dutch TIA Trial Study Group

Background and Purpose—Impaired glucose tolerance, an intermediate metabolic state between normal glucose and diabetes characterized by nonfasting glucose levels between 7.8 to 11.0 mmol/L, is associated with an increased stroke risk in patients with coronary heart disease. Whether impaired glucose tolerance increases the risk of stroke in patients with transient ischemic attack (TIA) or minor ischemic stroke is unknown.

Methods—In total, 3127 patients with a TIA or minor ischemic stroke participated in the Dutch TIA Trial, testing 2 different doses of aspirin and atenolol versus placebo. We estimated the risk of stroke and the risk of myocardial infarction or cardiac death in relation to baseline nonfasting glucose levels (mean 6.0, SD 2.2 mmol/L) with Cox proportional hazards regression analysis, adjusted for cardiovascular risk factors.

Results—During 2.6 years follow-up, 272 patients (9%) experienced a stroke and 200 (6%) a myocardial infarction or cardiac death. We found a J-shaped relationship between baseline nonfasting glucose levels and stroke risk. Stroke risk was nearly doubled in patients with impaired glucose tolerance (glucose 7.8 to 11.0 mmol/L) compared with those with normal glucose levels (hazard ratio [HR] 1.8, 95% CI, 1.1 to 3.0) and nearly tripled in diabetic patients (glucose ≥11.1 mmol/L; HR 2.8, 95% CI, 1.9 to 4.1). Patients with low glucose levels (<4.6 mmol/L) had a 50% increased stroke risk (HR 1.5, 95% CI, 1.0 to 2.2) compared with those with normal glucose levels. There was no association between glucose levels and risk of myocardial infarction or cardiac death.

Conclusion—Impaired glucose tolerance is an independent risk factor for future stroke in nondiabetic patients with TIA or minor ischemic stroke. (Stroke. 2006;37:1413-1417.)

Key Words: glucose ■ glucose intolerance ■ risk ■ transient ischemic attack

Cardiovascular disease is the leading cause of death and morbidity in diabetic patients.1 The presence of diabetes increases the risk of stroke 2- to 5-fold.2,3 Recently, impaired glucose tolerance, an intermediate metabolic state between normal glucose tolerance and diabetes mellitus, is also found to be associated with an increased stroke risk in patients with coronary heart disease.4 It is unknown whether the risk of stroke is increased in patients with impaired glucose tolerance who had a transient ischemic attack (TIA) or minor ischemic stroke. Approximately one quarter of patients with a history of TIA or minor ischemic stroke have an impaired glucose tolerance.5 If there is an association between impaired glucose tolerance and (recurrent) stroke in patients with TIA or minor ischemic stroke, this might offer new options for secondary prevention. We therefore investigated the relationship between nonfasting glucose levels, the risk of (recurrent) stroke and the risk of myocardial infarction or cardiac death in patients with a history of TIA or minor ischemic stroke.

Methods

Patients

The study population comprised all participants of the Dutch TIA Trial, a secondary prevention trial that took place in 1986 to 1990. The original cohort consisted of 3150 patients, who had had a TIA or minor disabling ischemic stroke in the past 3 months (modified Rankin Scale of ≤3).6 Patients with cerebral ischemia resulting from other causes than arterial thrombosis or arterial embolism were excluded from the study. Twenty-three patients were incorrectly diagnosed at the time of randomization, and they were excluded from the analyses, leaving 3127 patients in the study. They were randomized by means of a 2×2 factorial design to 2 different doses of aspirin (30 or 283 mg) and 50 mg atenolol or placebo.7 The trial showed no differences in effects of aspirin and no efficacy of atenolol.8,9 All patients received information about the study (written and oral) and gave their consent to participate in the trial. The medical ethics committees of the participating centers approved the study protocol.
Glucose Measurement and Other Baseline Variables

In the Dutch TIA trial, we used a checklist in plain language to obtain information about symptoms, medical history, smoking and drug use. All patients underwent a computed tomography (CT) scan, except those with transient monocular blindness. Nonfasting venous plasma glucose levels were measured at baseline, with a mean interval of 3 weeks to the preceding event. Glucose measurements were not available for 17 participants because of failure to obtain a sample or some other error in the blood collection process. We defined diabetes mellitus as a previous diagnosis of diabetes, the use of oral antidiabetic drugs or insulin, or a nonfasting plasma glucose level of $\geq 11.1 \text{ mmol/L}$. We considered patients to have an impaired glucose tolerance if they had nonfasting plasma glucose levels between 7.8 and 11.0 mmol/L.10 Blood pressure was measured at study entry as a part of the physical examination. Hypertension was defined as the self-reported history of hypertension with or without use of antihypertensive drugs, a systolic blood pressure of 160 mm Hg or over, or a diastolic blood pressure of 95 mm Hg or over at baseline.

Follow-Up

Patients were seen every 4 months by a neurologist or, if that was not possible, by their general practitioner. We collected information about outcome events, TIAs, surgical procedures, blood pressure and degree of disability using the modified Rankin Scale by means of a standardized questionnaire. An ECG was made every 2 years (for most patients it came to 1 or 2 ECGs). All surviving patients had their last follow-up visit in 1990. The mean follow-up was 2.6 years. No patient was lost to follow-up.

Outcome Events

We examined vascular events in general, with special attention to stroke and myocardial infarction or cardiac death. We defined stroke, both fatal or nonfatal, as a new infarct or bleeding visible on CT, together with matching symptoms lasting for $>24$ hours. If CT scan was normal, an increase in disability of at least 1 grade on the modified Rankin Scale was sufficient for the diagnosis of stroke. Myocardial infarction was defined as the presence of at least 2 of the following criteria: a history of chest pain, changes in cardiac enzymes more than twice the upper range of normal, or relevant changes visible on ECG. Cardiac death included death from myocardial infarction, heart failure, and sudden death.

Statistical Analysis

We categorized patients based on quintiles of glucose levels, with the upper quintile further divided based on standardized criteria of impaired glucose tolerance and diabetes mellitus,10 into the following groups: $< 4.6, 4.6$ to $5.0, 5.1$ to $5.7, 5.8$ to $7.7, 7.8$ to $11.0$, and $\geq 11.1 \text{ mmol/L}$. The highest category also comprised patients with known diabetes mellitus with lower glucose measurements. We used the Kaplan-Meier method to estimate the vascular event rate for each glucose category. The follow-up time was calculated from the date of study entry until the date of a (recurrent) stroke, myocardial infarction, death, or end of follow-up, whichever came first. We estimated the relative risk of vascular events in relation to nonfasting glucose levels with Cox proportional hazards regression analysis with 95% CI, adjusted for cardiovascular risk factors (age, sex, smoking, hypertension, and minor ischemic stroke in history). The reference group consisted of patients with a nonfasting glucose level of 5.8 to $7.7 \text{ mmol/L}$.

Results

The Table shows the baseline characteristics of the study population. The nonfasting plasma glucose levels ranged from 2.6 to $25.1 \text{ mmol/L}$. In total, 165 (5%) had impaired glucose tolerance and 284 (9%) patients had diabetes mellitus. Of this latter group, 112 had acceptable or well-controlled glucose levels ($< 11.1 \text{ mmol/L}),$ 48 low glucose levels ($< 4.6 \text{ mmol/L}),$ and 124 diabetic glucose levels ($\geq 11.1 \text{ mmol/L}).$ Despite antidiabetic therapy. Patients with impaired glucose tolerance were significantly older (mean age 67.8 years) than those with normal glucose tolerance (mean age 65.6 years). Patients with low nonfasting glucose levels ($< 4.6 \text{ mmol/L})$ were significantly younger (mean age 63.7 years), more often male (31% women) and less frequently had hypertension (64%) compared with patients with normal glucose tolerance. Compared with all other glucose categories (mean weight normal glucose 75.4 kg, impaired glucose tolerance 75.4 kg, diabetes mellitus 75.3 kg), patients with low nonfasting glucose levels weighed less (mean weight 73.5 kg). The qualifying event of the diabetic patients more often was of lacunar subtype (65%, $P=0.08$), although this was not statistically different from the other glucose categories (mean 57%). During 2.6 years follow-up, 272 patients (9%) experienced a fatal or nonfatal stroke and 200 patients (6%) had a myocardial infarction or cardiac death. Nineteen (12%) of the patients with impaired glucose tolerance had a stroke during follow-up and another 9 patients (6%) a myocardial infarction or cardiac death. Fifty (18%) of the diabetic patients experienced a stroke and 31 (11%) a cardiac event. After 2.6 years, 82% of the diabetic patients were stroke-free, compared with 94% of those with normal glucose tolerance and 88% of the patients with impaired glucose tolerance (Figure 1).

The relationship between nonfasting glucose levels and stroke risk was J-shaped (Figure 2A). Patients with low nonfasting glucose levels had a 50% increased risk of stroke compared with those with normal glucose tolerance (hazard ratio [HR] 1.5, 95% CI, 1.0 to 2.2), after adjustment for cardiovascular risk factors. The adjusted risk of stroke was nearly doubled in patients with impaired glucose tolerance (HR 1.8, 95% CI, 1.1 to 3.0) and nearly tripled in diabetic patients (HR 2.8, 95% CI, 1.9 to 4.1). Further adjustment for history of myocardial infarction did not alter these associations. There was no association between impaired glucose tolerance and myocardial infarction or cardiac death (Figure 2B). The relative risk of myocardial infarction or cardiac death was doubled in diabetic patients (HR 2.0, 95% CI, 1.3 to 3.2). Diabetic patients had a 2.5-fold increased risk of
having a vascular event (95% CI, 1.9 to 3.4) and patients with impaired glucose tolerance a borderline significant risk of 1.4 (95% CI, 0.9 to 2.2; Figure 2C). Patients with glucose levels <4.6 mmol/L had a relative risk of 1.4 (95% CI, 1.0 to 1.9) compared with those with normal glucose tolerance.

Discussion
We found a J-shaped relationship between glucose levels and (recurrent) stroke risk in patients with a recent TIA or minor ischemic stroke. The risk of stroke not only was increased in patients with diabetes mellitus and impaired glucose tolerance, but also in those with low nonfasting glucose levels (<4.6 mmol/L). There was no association between impaired glucose tolerance and the risk of myocardial infarction or cardiac death.

The strengths of this study are the large number of patients, the prospective design of the Dutch TIA Trial, the meticulous follow-up, and adjudication of outcome events that was blinded to the treatment assignment but also to the glucose level at baseline. Because the original study was a large and randomized clinical trial, we do not expect any confounding by treatment regimen. However, there are some methodological limitations. We measured nonfasting venous plasma glucose levels. Randomly taken glucose samples do not meet the definition of impaired glucose tolerance. Some patients might have been in a fasting state at the time of glucose measurement, resulting in lower glucose levels than if it was a postprandial measurement. The glucose levels were measured without knowledge of other risk factors and outcome events that were diagnosed blinded to all other data as well. Therefore, any misclassification will be random and result in an underestimation of the strength of the risk associations. Furthermore, the interval between baseline glucose measurement and preceding event differed among patients, with a range of <1 week to 3 months. Glucose levels can be increased in the first hours of acute stroke.11 However, the vast majority had their glucose levels measured >1 week after the acute event, when glucose levels are normalized. If anything, misclassification will again result in an attenuation of the associations. Finally, the use of a single glucose measurement to classify patients may have underestimated the strength of any associations attributable to regression dilution. Another limitation is that we did not have insulin measurements, which would have given more information and could strengthen this study.

Generalizability of the results might be limited by patient selection. With exclusion of patients with cardiac sources of emboli from the trial, the mean age and presence of cardiovascular risk factors, such as hypertension, will differ from that of a general TIA population. Old age and hypertension are known risk factors for stroke. However, because the relationship of glucose levels and stroke risk was consistent over all age strata and we adjusted for cardiovascular risk factors, we do not think that this would have materially altered the conclusions of the present study. Another limitation might be that this trial was conducted more than a decade ago. During that period, treatment with blood pressure- and cholesterol-lowering drugs was less common. Nowadays, we treat patients far more aggressively with antihypertensive drug and statins, that each have been shown to lead to a stroke reduction up to 30% in diabetic patients.12–14 This does not necessarily mean that these drugs will alter the effect estimate of diabetes mellitus or impaired glucose tolerance itself. The risk reduction with antihypertensive medication is significantly larger in diabetic patients than in nondiabetics with hypertension. It is unknown, however, whether the effect of antihypertensive therapy also differs among the nondiabetic glucose categories. Statins are both effective in diabetic and nondiabetic patients. A meta-analysis of 14 randomized controlled trials among cardiovascular patients with diabetes mellitus, impaired fasting glucose and normal glucose levels, showed no difference in risk reduction of vascular events.
with statin therapy among these 3 glucose groups. Therefore, we do not think this will hamper external validity of our results.

The magnitude of the relative stroke risk estimate associated with impaired glucose tolerance in our study is similar to that found in a secondary prevention trial among patients with coronary heart disease. They also observed a J-shaped association between fasting glucose levels and stroke risk. The increased stroke risk in patients with impaired glucose tolerance could be explained by a similar metabolic mechanism that leads to vascular complications in diabetes mellitus.

The cardiovascular risk profile (obesity, hypertension, dyslipidemia, insulin resistance) is already worsening in this intermediate metabolic state, leading to a higher risk of stroke and other vascular events.

We found no association between impaired glucose tolerance and myocardial infarction or cardiac death. A study among patients with a recent myocardial infarction found a strong relationship between impaired glucose tolerance and vascular events, including myocardial infarction, but they did not examine the association with myocardial infarction separately. In the earlier mentioned secondary prevention trial among patients with coronary heart disease, impaired fasting glucose was related with a worse clinical outcome, but again no association with recurrence of myocardial infarction was observed. Disturbances in glucose metabolism may affect brain tissue more than myocardial tissue. The brain totally depends on glucose for its metabolic demands, whereas myocardial tissue can generate energy from other sources. In a normal, healthy situation, the brain is protected against disturbances in the glucose level by a counterregulatory mechanism. When this mechanism fails to maintain a normal glucose level during hypo- or hyperglycemia, the brain will be damaged. This might explain our finding that the intermediate metabolic stage of impaired glucose tolerance is associated with stroke and not with myocardial infarction or cardiac death. Furthermore, that the risk estimate for stroke in diabetic patients is higher than for myocardial infarction supports our findings as well.

In line with our results, previous studies found an increased risk of vascular disease in patients with low fasting glucose levels. One explanation might be frailty of these patients, which is supported by our finding that patients with low glucose levels weighed less than those with normal glucose levels. Furthermore, hypoglycemia is associated with focal and global brain damage and dysfunction. This again illustrates the vulnerability of the human brain compared with the heart.

Impaired glucose tolerance is like diabetes mellitus, an independent risk factor for stroke in nondiabetic patients with TIA or minor ischemic stroke. Low nonfasting glucose levels (<4.6 mmol/L) are also associated with an increased stroke risk. Intensive glucose control in both type 1 and type 2 diabetic patients seems to reduce stroke and other macrovascular events. New secondary prevention trials should be initiated to investigate whether intensive glucose control reduces stroke incidence in these patients.

Figure 2. HRs for stroke (A), myocardial infarction or cardiac death (B), and vascular events (C) by nonfasting glucose categories, adjusted for age, sex, hypertension, smoking, and minor stroke. Diabetic patients are included in the highest category (≥11.1 mmol/L). Bars represent 95% CI.
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References


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