Occurrence and Predictors of Persistent Impaired Glucose Tolerance After Acute Ischemic Stroke or Transient Ischemic Attack

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Background: Impaired glucose tolerance is often present in patients with a transient ischemic attack (TIA) or ischemic stroke and doubles the risk of recurrent stroke. This impaired glucose tolerance can be transient, reflecting an acute stress response, or persistent, representing undiagnosed impaired glucose metabolism possibly requiring treatment. We aimed to assess the occurrence of persistent impaired glucose tolerance after a stroke or TIA and to develop a prediction model to identify patients at risk of persistent impaired glucose tolerance. *Methods:* Patients admitted to the stroke unit or TIA clinic of the Erasmus Medical Center with ischemic stroke or TIA and impaired glucose tolerance (2-hour postload glucose level of 7.8-11.0 mmol/L) were consecutively enrolled between July 2009 and June 2012. The oral glucose tolerance test was repeated after 3 months and patients were classified as having transient impaired glucose tolerance or persistent impaired glucose tolerance. We developed a prediction model by means of a multivariable logistic regression model. We calculated the area under the receiver operating characteristic curve (AUC) to quantify the performance of the model and the internal validity by bootstrapping. *Results:* Of the 101 patients included, 53 (52%) had persistent impaired glucose tolerance or progression to diabetes. These patients were older and more often had hypertension and used statins. A prediction model including age, current smoking, statin use, triglyceride, hypertension, previous ischemic cardiovascular disease, body mass index, and fasting plasma glucose accurately predicted persistent impaired glucose tolerance (bootstrapped AUC, .777), with statin use, triglyceride, and fasting plasma glucose as the most important predictors. *Conclusions:* Half of the patients with impaired glucose tolerance after a TIA or ischemic stroke have persistent impaired glucose tolerance. We provide a prediction model to identify patients at risk of persistent impaired glucose tolerance, with statin use, triglyceride, and fasting plasma glucose as the most important predictors, which after external validation might be used to optimize secondary prevention. **Key Words:** Stroke—TIA—impaired glucose tolerance—prediction model.
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Introduction

Impaired glucose tolerance is an intermediate metabolic state between normal glucose tolerance and diabetes mellitus, and is present in more than one third of the patients with a transient ischemic attack (TIA) or ischemic stroke.[1-10] This impaired glucose tolerance can be transient, reflecting an acute stress response, or persistent, representing undiagnosed impaired glucose metabolism.[11,12] Various studies have found that impaired glucose tolerance is still present after 3 months in 26%-71% of the patients.[5-7] In patients with a TIA or ischemic stroke, impaired glucose tolerance nearly doubles the risk of recurrent stroke.[13] It is therefore important to identify patients with persistent impaired glucose tolerance as they might benefit from long-term lifestyle intervention and/or treatment with glucose-lowering agents.[14-16]

We aimed to assess the occurrence of persistent impaired glucose tolerance in nondiabetic patients with an ischemic stroke or TIA. We developed a prediction model to identify patients at risk of persistent impaired glucose tolerance, based on clinical predictors available at the time of admission.

Methods

Study Population

Patients were derived from the Erasmus Stroke Study, a prospective registry that started in 2005 and collects clinical information and blood samples of all patients with neurovascular diseases admitted to Erasmus University Medical Center Rotterdam, The Netherlands. We prospectively studied all consecutive patients with ischemic stroke or TIA and impaired glucose tolerance (2-hour postload glucose levels between 7.8 and 11.0 mmol/L) admitted to the stroke unit or visiting our specialized TIA clinic between July 2009 and June 2012 within 2 weeks after symptom onset. Patients with pre-existent diabetes and patients with 2-hour postload glucose levels of 11.1 mmol/L or higher (indicating newly diagnosed diabetes mellitus) were excluded. Written informed consent was obtained from all patients signed by the participants or a first-degree relative, as approved by the Institutional Ethics Committee.

Clinical Data

Demographic data, vascular history and risk factors including statin use, laboratory assessments including lipid profile, and data on event characteristics were collected. Stroke severity was assessed with the National Institutes of Health Stroke Scale score. Stroke subtype was classified with the Trial of ORG 10172 in Acute Stroke Therapy classification.[17]

Glucose Assessments

In all patients, fasting plasma glucose and glycosylated hemoglobin levels were assessed on the second or third day of admission or when visiting the outpatient clinic, as part of standard clinical care. On the same day, an oral glucose tolerance test (OGTT) was performed according to the World Health Organization protocol.[18] After overnight fasting, patients drank a solution of 75 g glucose in 150 mL water, and 2-hour postload glucose levels were assessed. Impaired glucose tolerance was defined as 2-hour postload glucose levels between 7.8 and 11.0 mmol/L. Patients with fasting plasma glucose levels of 7.0 mmol/L or higher were diagnosed with diabetes and therefore excluded.

Outcome

At 3 months, all patients were invited to visit the outpatient clinic and were asked to undergo a second OGTT. The OGTT was repeated and based on the results patients were classified as having transient impaired glucose tolerance (2-hour postload glucose level of $<$7.8 mmol/L), persistent impaired glucose tolerance (2-hour postload glucose level between 7.8 and 11.0 mmol/L), or progression to diabetes (2-hour postload glucose level of $\geq$11.1 mmol/L).[1]

Statistical Analysis

Statistical analyses were performed with Stata/SE 12.1 for Windows (Statacorp, College Station, TX). Missing variables were imputed with single imputation using the baseline characteristics and the outcome variable. We compared clinical variables between glucose groups, with transient impaired glucose tolerance as a reference. Patients with persistent impaired glucose tolerance or progression to diabetes were grouped together as persistent disturbed glucose tolerance because of the small sample size. The differences between the glucose groups in categorical variables were tested with the χ^2 test and continuous variables with the Student t test. Non-normal distributed variables were compared with the Wilcoxon rank sum test. P values of less than .05 were considered statistically significant.

Model Development

Possible predictors of persistent impaired glucose tolerance included known risk factors for developing diabetes and other risk factors according to the previous literature: age, sex, ethnicity, current smoking, statin use, lipids (triglycerides, low-density lipoprotein [LDL], and high-density lipoprotein [HDL]), hypertension, previous ischemic cardiovascular disease, atrial fibrillation (paroxysmal), body mass index (BMI), TIA versus ischemic

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