Glycosylated Hemoglobin and Functional Outcome after Acute Ischemic Stroke

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Background: Diabetes mellitus (DM) is associated to an increased incidence of cerebral and myocardial infarction which could be reduced by long-term maintenance of optimal glycemic values. The aim of the study was to evaluate in diabetic patients with ischemic stroke the chronic glycemic status and its relationship with functional outcome. *Methods:* We retrospectively identified consecutive diabetic patients hospitalized for acute ischemic stroke. Clinical and biochemical characteristics at admission were assessed. The outcome measures were the attainment of the recommended glycosylated hemoglobin A1 (HbA1c) level and the 3-month functional status according to the modified Rankin Scale score. *Results:* Among the 112 enrolled patients, 39 (34.8%) met the recommended goal of HbA1c less than 7%. Higher education level was predictive of good prestroke glycemic control (adjusted OR 1.32 per year [95% CI 1.15-1.51], $P < .001$). At the 3-month evaluation, 44 (39.3%) patients were classified as having a poor outcome. After categorization of HbA1c values into tertiles, a dose–response relationship with poor functional recovery was found ($P = .001$). The suboptimal prestroke glycemic status was an independent predictor of unfavorable outcome (adjusted OR 6.22 [95% CI 1.94-19.98] for HbA1c $\geq$7%, $P = .002$). *Conclusions:* The management of DM was suboptimal in nearly two thirds of diabetic subjects presenting with acute ischemic stroke. The glycemic control before stroke occurrence was an independent prognostic factor and HbA1c values above the recommended goals increased the risk of unfavorable 3-month outcome. The improvement of DM management may be an effective strategy to either decrease the burden of cerebrovascular disease or influence its clinical course. **Key Words:** Stroke—diabetes mellitus—glycosylated hemoglobin—cerebrovascular disease.

Introduction

Cerebrovascular disease is a growing determinant of health expenditures worldwide and a leading cause of

morbidity, cognitive impairment, and mortality which could be contained through an appropriate management of the associated risk conditions.[1] Since the early findings of the Framingham Study, several epidemiological surveys have reported that diabetes mellitus (DM) is one of the major independent vascular risk factors. In particular, diabetic patients have from 2.5- to 3.5-fold greater stroke incidence with respect to nondiabetic subjects.[2-4] Additionally, there is accruing evidence that long-term maintenance of glycemic values near the normal ranges could be advantageous to reduce the risk of cerebral and myocardial ischemic events.[5,6] In this respect, the glycosylated hemoglobin A1 (HbA1c), which reflects average glycemia over the preceding 6-8 weeks, is one of the most established and widely used indexes for monitoring glycemic

control over the time.[7] Although HbA1c has been clearly demonstrated to be a marker and a strong predictor of diabetic vascular damage and complications in diabetic patients,[8] its prognostic significance in the acute cerebrovascular disease still represents an intriguing issue deserving further investigations.

The aim of this study was to evaluate in patients with ischemic stroke and known DM the chronic glycemic status as by admission HbA1c value and its relationship with the 3-month functional outcome.

Materials and Methods

Participants and Study Outcome

We retrospectively identified consecutive patients hospitalized at the Stroke Unit of Università Politecnica delle Marche from January 2012 to January 2015 for acute ischemic stroke within 24 hours from symptoms onset. Demographics, past medical history, current medications and vascular risk factors, baseline stroke severity measured by the National Institutes of Health Stroke Scale (NIHSS),[9] admission blood glucose level, quantitative determination of plasma HbA1c (%) by high-performance liquid chromatography, and the 3-month modified Rankin Scale (mRS)[10] were collected from medical records. Stroke subtypes were rated according to the TOAST (Trial of Org 10172 in Acute Stroke Treatment) classification.[11] For the purpose of the study, only patients who had been functionally independent before the stroke onset and had an established diagnosis of DM at the time of hospital admission were included; DM was defined according to patients' self-report history or the use of hypoglycemic drug or insulin. Potential study subjects were excluded if they lacked a functional status assessment at 3 months from stroke onset, if they presented hemoglobin variants or conditions that could affect erythrocyte turnover as hemolysis and blood loss,[7] or if the HbA1c determination occurred more than 24 hours from admission.

The outcome measures were the attainment of the HbA1c level less than 7% as the individual goal recommended for prevention of vascular disease in subjects with DM[5,6] and the 3-month functional status prospectively assessed by clinical evaluation. According to the baseline severity-adjusted analysis (responder analysis) for dichotomization of outcome status, we considered as poor outcome status a 3-month mRS score of 2-6 if the baseline NIHSS score was less than or equal to 7 points, mRS score of 3-6 if the NIHSS score was 8-14 points, and mRS score of 4-6 if the NIHSS score was greater than or equal to 15 points.[12,13]

Statistical Analysis

Values are presented as mean ± standard deviation or median (interquartile range [IQR]) for continuous variables and as the number (percent) of subjects for categorical variables. The Student's *t*-test, Mann–Whitney *U*-test, or chi-square test, as appropriate, was used to test differences on each of the subjects' characteristics. Univariate and multivariable logistic regression models were performed to determine the independent predictors for the attainment of the recommended HbA1c goal; covariates included the baseline patient characteristics such as age, sex, education level (as a continuous variable), comorbid medical conditions (hypertension, dyslipidemia, atrial fibrillation, smoking habits, body mass index ≥30 kg/m², previous stroke, coronary artery disease, or myocardial infarction), baseline NIHSS score, stroke subtype (TOAST criteria), and admission blood glucose.

The relationship between the HbA1c and the 3-month functional outcome was evaluated. The HbA1c levels were categorized into tertiles with the lowest third as reference subgroup and firstly analyzed by the chi-square test for linear trend. The risk of poor outcome was estimated by logistic regression analysis after adjusting for the effect of the potential confounding variables. Model 1 was adjusted for age and sex; model 2 included all covariables in model 1 plus baseline NIHSS score, stroke subtype (TOAST criteria), thrombolytic treatment, admission blood glucose, and comorbid medical conditions (hypertension, dyslipidemia, atrial fibrillation, smoking habits, body mass index ≥30 kg/m², previous stroke, coronary artery disease, or myocardial infarction). The relationship between the achievement of the recommended HbA1c target goal and the 3-month outcome was also assessed. Odds ratios (ORs) and corresponding 95% CIs were reported. We used the variance inflation factor to assess the multicollinearity between the exposure variables and the likelihood ratio test to compare the fit of the models. As sensitivity analysis, logistic regression models were repeated using simple dichotomization of mRS score into 0-2 versus 3-6, instead of the baseline severity-adjusted dichotomization. Results were considered significant for *P* values < .05 (two sided). Data analysis was performed using STATA/IC 13.1 statistical package (StataCorp LP, College Station, TX).

Standard Protocol Approvals, Registrations, and Patient Consents

The study was approved by the local ethics committee and performed in accordance with the Declaration of Helsinki. The board allowed the study to be conducted without patients' consent because of the retrospective nature of the study.

Results

A total of 137 Caucasian patients admitted to our Stroke Unit for acute ischemic stroke and diagnosed with DM at the time of the index event were initially considered. Twenty-five patients were excluded for unavailable determination of the HbA1c and/or 3-month outcome. As