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ORIGINAL ARTICLE

Type 2 diabetes is associated with a worse functional outcome of ischemic stroke

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Abstract

AIM: To assess whether ischemic stroke severity and outcome is more adverse in patients with type 2 diabetes mellitus (T2DM).

METHODS: Consecutive patients hospitalized for acute ischemic stroke between September 2010 and June 2013 were studied prospectively (n = 482; 40.2% males, age 78.8 ± 6.7 years). T2DM was defined as self-reported T2DM or antidiabetic treatment. Stroke severity was evaluated with the National Institutes of Health Stroke Scale (NIHSS) score at admission. The outcome was assessed with the modified Rankin scale (mRS) score at discharge and with in-hospital mortality. Adverse outcome was defined as mRS score at discharge ⩾ 2 or in-hospital death. The length of hospitalization was also recorded.

RESULTS: T2DM was present in 32.2% of the study population. Patients with T2DM had a larger waist circumference, higher serum triglyceride and glucose levels and lower serum high-density lipoprotein cholesterol levels as well as higher prevalence of hypertension, coronary heart disease and congestive heart failure than patients without T2DM. On the other hand, diabetic patients had lower low-density lipoprotein cholesterol levels and reported smaller consumption of alcohol than non-diabetic patients. At admission, the NIHSS score did not differ between patients with and without T2DM (8.7 ± 8.8 and 8.6 ± 9.2, respectively; P = NS). At discharge, the mRS score also did not differ between the two groups (2.7 ± 2.1 and 2.7 ± 2.2 in patients with and without T2DM, respectively; P = NS). Rates of adverse outcome were also similar in patients with and without T2DM (62.3% and 58.5%, respectively; P = NS). However, when we adjusted for the differences between patients with T2DM and those without T2DM in cardiovascular risk factors, T2DM was independently associated with adverse outcome [relative risk (RR) = 2.39; 95%CI: 1.21-4.72, P = 0.012]. In-hospital mortality rates did not differ between patients with T2DM and those without T2DM (9.0% and 9.8%, respectively; P = NS). In multivariate analysis adjusting for the difference in cardiovascular risk factors between the two groups, T2DM was again not associated with in-hospital death.

CONCLUSION: T2DM does not appear to affect ischemic stroke severity but is independently associated with a worse functional outcome at discharge.

Key words: Ischemic stroke; Functional outcome; Severity; Mortality; Type 2 diabetes mellitus; Cardiovascular disease; Hyperglycemia; Cardiovascular risk; Dyslipidemia; Hypertension

Core tip: Even though type 2 diabetes mellitus (T2DM) is a major independent risk factor for ischemic stroke, it is unclear whether stroke severity and functional outcome differs between diabetic and non-diabetic patients. In the present study, T2DM was associated with worse functional outcome at discharge despite similar stroke severity at admission. The detrimental effect of T2DM on functional outcome was independent of the increased prevalence of cardiovascular risk factors in diabetic patients.

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a major independent risk factor for cardiovascular disease (CVD), including stroke[1]. In a meta-analysis of 102 prospective studies (n = 698782), patients with T2DM had 2.27 times higher risk for ischemic stroke[1]. Moreover, in the INTERSTROKE study, a case-control study in 22 countries worldwide, T2DM accounted for 5% of the population-attributable risk for stroke[2]. Given the rising prevalence of T2DM due to the epidemic of obesity, the number of patients suffering stroke due to T2DM is expected to further increase[3,4].

In contrast to the unequivocal association between T2DM and the increased risk for ischemic stroke, it is unclear whether patients with T2DM suffer more severe strokes or have worse outcome following stroke compared with subjects without T2DM[5-7]. Moreover, it is uncertain whether T2DM is independently associated with more severe stroke and with worse stroke outcome or if this relationship is due to the higher prevalence of other CVD risk factors in patients with T2DM, including hypertension, dyslipidemia and obesity[5-7].

The aim of the present study was to evaluate the association between T2DM and acute ischemic stroke severity and in-hospital outcome. Furthermore, we aimed to examine whether T2DM affects stroke severity and outcome independently from other CVD risk factors.

MATERIALS AND METHODS

We prospectively studied all patients who were admitted to our department with acute ischemic stroke between September 2010 and June 2013 (n = 482; 40.2% males, age 78.8 ± 6.7 years).

At admission, demographic data (age, sex), history of T2DM and other cardiovascular risk factors [hypertension, atrial fibrillation, smoking, alcohol consumption, family history of CVD, chronic kidney disease], history of concomitant CVD [coronary heart disease (CHD), previous stroke, congestive heart failure] and pharmacological treatment were recorded. T2DM was defined as self-reported T2DM or antidiabetic treatment. Anthropometric parameters (weight, height, waist and hip circumference, waist to hip ratio) and systolic and diastolic blood pressure were also measured. The severity of stroke was assessed at admission with the National Institutes of Health Stroke Scale (NIHSS) score.

Routine laboratory investigations were performed after overnight fasting on the first day after admission and included serum levels of glucose, total cholesterol, high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), creatinine, uric acid and HbA_{1c}. Low-density lipoprotein cholesterol (LDL-C) levels were calculated using Friedewald's formula[8]. Glomerular filtration rate (GFR) was estimated using the Modification of Diet in Renal Disease equation[9]. Chronic kidney disease was defined as estimated GFR < 60 mL/min per 1.73 m^2.

All patients underwent brain computed tomography at admission and a second brain computed tomography was performed if clinically indicated.

All patients without atrial fibrillation were treated with aspirin; clopidogrel was given to patients intolerant to aspirin. Patients who were on aspirin prior to stroke were switched to clopidogrel and *vice versa*. Patients with atrial fibrillation were treated with low-molecular weight heparin. All patients were given a statin. Antihypertensive agents were discontinued during the acute phase of stroke except beta-blockers. Most patients with T2DM were treated with insulin during the acute phase of stroke. No patient underwent thrombolysis.

The outcome was assessed with the modified Rankin scale (mRS) score at discharge and with in-hospital mortality. Adverse outcome was defined as mRS score at discharge ⩾ 2 or in-hospital death. The length of hospitalization was also recorded.

Statistical analysis

All data were analyzed with the statistical package SPSS (version 17.0; SPSS, Chicago, IL, United States). Data are presented as percentages for categorical variables and as mean and standard deviation for continuous variables. Differences in categorical and continuous variables between groups were assessed with the χ^2 test and one-way analysis of variance, respectively. Binary logistic regression analysis was performed to evaluate the independent association between T2DM and adverse outcome or in-hospital mortality after adjusting for the differences in CVD risk factors between patients with and without T2DM. In all cases, a two-tailed $P < 0.05$ was considered significant.

RESULTS

T2DM was present in 32.2% of the study population.

Table 1 Clinical characteristics of patients with type 2 diabetes mellitus and those without

	Patients with T2DM (n = 155)	Patients without T2DM (n = 327)	P
Age (yr)	78.3 ± 6.3	79.1 ± 6.9	NS
Males (%)	38.7	41.0	NS
Systolic blood pressure (mmHg)	150 ± 24	146 ± 25	NS
Diastolic blood pressure (mmHg)	81 ± 10	81 ± 14	NS
Hypertension (%)	88.4	78.6	0.013
Smoking (current/past, %)	12.9/22.6	11.6/20.5	NS
Package-years	17 ± 39	14 ± 33	NS
Atrial fibrillation (%)	38.7	34.6	NS
Alcohol consumption (units/wk)	0.7 ± 2.4	2.1 ± 11.7	0.045
Weight (kg)	77.0 ± 13.0	73.7 ± 13.8	0.04
Body mass index (kg/m^2)	28.1 ± 5.2	27.2 ± 5.1	NS
Waist (cm)	110 ± 9	101 ± 13	< 0.001
Waist/hip	1.00 ± 0.06	0.97 ± 0.08	NS
Overweight/obese (%)	44.1/26.9	38.5/25.0	NS
Family history of cardiovascular disease (%)	14.8	15.0	NS
Coronary heart disease (%)	35.5	23.9	0.01
Previous ischemic stroke (%)	44.5	37.9	NS
Chronic kidney disease (%)	36.9	33.5	NS
Chronic heart failure (%)	26.5	16.5	0.015

T2DM: Type 2 diabetes mellitus; NS: Not significant.

The mean duration of T2DM was 11.1 ± 8.2 years and the mean HbA_{1c} in patients with T2DM was 7.6 ± 1.5. Clinical characteristics of patients with T2DM and patients without T2DM are shown in Table 1. Patients with T2DM had larger waist circumference and higher prevalence of hypertension, CHD and congestive heart failure than patients without T2DM but reported a lower consumption of alcohol than the latter. Laboratory characteristics of patients with T2DM and patients without T2DM are shown in Table 2. Patients with T2DM had higher serum TG levels and lower serum HDL-C levels than patients without T2DM but had lower LDL-C levels than the latter ($P < 0.01$ for all comparisons). Serum glucose levels were also higher in the former.

At admission, the NIHSS score did not differ between patients with and without T2DM (8.7 ± 8.8 and 8.6 ± 9.2, respectively; P = NS). The outcome of the 2 groups is shown in Table 3. The duration of hospitalization was comparable in patients with and without T2DM (6.9 ± 4.6 d and 6.7 ± 4.1 d, respectively; P = NS). The mRS score at discharge also did not differ between the two groups (2.7 ± 2.1 and 2.7 ± 2.2 in patients with and without T2DM, respectively; P = NS). The NIHSS score at discharge was also comparable in patients with and without T2DM (6.2 ± 6.4 and 6.0 ± 6.2, respectively; P = NS). Rates of adverse outcome were also similar in patients with and without T2DM (62.3% and 58.5%, respectively; P = NS). However, when we adjusted for the differences between patients with T2DM and those without T2DM in cardiovascular risk factors (weight, consumption of alcohol, prevalence of hypertension, CHD and congestive heart failure, and serum LDL-C, TG and HDL-C levels), T2DM was independently associated with adverse outcome [relative risk (RR) = 2.39; 95%CI: 1.21-4.72, P = 0.012]. In-hospital mortality rates did not differ between patients with T2DM and those without T2DM (9.0% and 9.8%, respectively; P = NS). In multivariate analysis adjusting for the difference in cardiovascular risk factors between the two groups, T2DM was again not associated with in-hospital death.

We also evaluated whether T2DM duration and glycemic control were associated with stroke severity and outcome. At admission, the NIHSS score did not differ between patients with T2DM duration > 10 years (n = 64, 41.3% of patients with T2DM), patients with T2DM duration ≤ 10 years and patients without T2DM (8.8 ± 9.0, 7.7 ± 8.2 and 8.6 ± 9.2, respectively; P = NS) or between patients with T2DM and HbA_{1c} > 9% (n = 28, 18.1% of patients with T2DM), patients with T2DM and HbA_{1c} ≤ 9% and patients without T2DM (8.4 ± 9.8, 10.6 ± 9.5 and 8.6 ± 9.2, respectively; P = NS). In univariate analysis, the duration of hospitalization, the mRS score at discharge and the rates of adverse outcome at discharge did not differ between patients with T2DM duration > 10 years, patients with T2DM duration ≤ 10 years and patients without T2DM. In multivariate analysis, both patients with T2DM duration > 10 years and patients with T2DM duration ≤ 10 years had higher risk for adverse outcome than patients without T2DM (RR = 2.66; 95%CI: 1.17-6.08 and RR = 2.60; 95%CI: 1.05-7.49, respectively; P = 0.030). The risk for adverse outcome did not differ between patients with T2DM duration > 10 years and patients with T2DM duration ≤ 10 years. In contrast, in-hospital mortality rates did not differ between patients with T2DM duration > 10 years, patients with T2DM duration ≤ 10 years and patients without T2DM in either univariate or multivariate analysis. The duration of hospitalization, the mRS score at discharge and the rates of adverse outcome at discharge and in-hospital mortality also did not differ between patients with T2DM and HbA_{1c} > 9%, patients with T2DM and HbA_{1c} ≤ 9% and patients without T2DM in either univariate or multi-

Table 2 Laboratory characteristics of patients with type 2 diabetes mellitus and those without

	Patients with T2DM (n = 155)	Patients without T2DM (n = 327)	P
Glucose (mg/dL)	145 ± 64	99 ± 27	< 0.001
LDL-C (mg/dL)	103 ± 43	116 ± 38	0.007
HDL-C (mg/dL)	43 ± 14	48 ± 15	0.002
Triglycerides (mg/dL)	136 ± 63	112 ± 44	0.001
Uric acid (mg/dL)	5.8 ± 1.8	5.7 ± 1.9	NS
eGFR (mL/min per 1.73 m^2)	67 ± 22	70 ± 23	NS

T2DM: Type 2 diabetes mellitus; NS: Not significant; LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol; eGFR: Estimated glomerular filtration rate.

Table 3 Severity of stroke and outcome of patients with type 2 diabetes mellitus and those without

	Patients with T2DM (n = 155)	Patients without T2DM (n = 327)	P
National Institutes of Health Stroke Scale score at admission	8.7 ± 8.8	8.6 ± 9.2	NS
Duration of hospitalization (d)	6.9 ± 4.6	6.7 ± 4.1	NS
Modified Rankin scale score at discharge	2.7 ± 2.1	2.7 ± 2.2	NS
Adverse outcome (%)	62.3	58.5	NS
In-hospital mortality (%)	9	9.8	NS

T2DM: Type 2 diabetes mellitus; NS: Not significant.

variate analysis.

DISCUSSION

The main findings of the present study are that the severity of ischemic stroke does not appear to differ between patients with T2DM and those without T2DM. In contrast, T2DM independently portends a more adverse functional outcome at discharge in this population.

The neurological deficit at admission, evaluated with the NIHSS, was almost identical in diabetic and non-diabetic patients in our study (8.7 ± 8.8 and 8.6 ± 9.2, respectively; P = NS). A few studies have compared stroke severity between patients with T2DM and without T2DM, yielding conflicting results[10-13]. The two largest studies (n = 233 and 611 patients with T2DM) reported no association between T2DM and stroke severity, in accordance with our findings[10,11]. In contrast, an early small study (n = 50 diabetic patients) suggested that stroke is more severe in patients with T2DM; however, stroke severity was evaluated with a non-validated neurological index[12]. Finally, in a more recent report (n = 102 diabetic patients), patients with T2DM had a less severe stroke at admission[13]. The latter study included younger patients and a higher percentage of males than the present study; it is possible that this might have contributed to the less severe stroke presentation in diabetic patients since T2DM appears to increase CVD risk more in women and in older subjects[1]. Indeed, among patients with T2DM who suffer an ischemic stroke, women have a less favorable prognosis than men[14]. Nevertheless, the discordant findings regarding the association between T2DM and ischemic stroke severity stress the need for larger studies to resolve these discrepancies.

Even though the rates of adverse outcome at discharge did not differ between diabetic and non-diabetic patients in unadjusted analyses in our study, binary logistic regression analysis adjusting for differences in CVD risk factors between the 2 groups identified an independent association between T2DM and adverse outcome (RR = 2.39). Therefore, our findings suggest that T2DM has a detrimental effect on ischemic stroke and that this association is not fully explained by the increased prevalence of other CVD risk factors in diabetic patients. Indeed, several studies suggested that hyperglycemia per se predicts worse outcomes in patients with ischemic stroke[15]. On the other hand, administration of insulin to maintain normoglycemia in these patients does not appear to improve functional outcome or to reduce in-hospital mortality[16,17]. Moreover, there is a paucity of studies that assessed the relationship between T2DM and functional outcome at discharge in acute ischemic stroke[13,18-20]. Both studies that adjusted for confounding variables reported a worse outcome in diabetic patients[18,19], whereas both studies that reported only unadjusted analyses did not identify any difference in functional outcome between patients with T2DM and patients without T2DM[13,20]. Accordingly, more studies are needed to evaluate whether T2DM affects functional outcome and to clarify the pathogenetic mechanisms underpinning this association.

In-hospital mortality rates did not differ between diabetic and non-diabetic patients in our study. This lack of difference was observed both in unadjusted analyses and when we adjusted for confounding variables. Some previous studies with only unadjusted analyses reported similar findings[13,20], whereas in-hospital mortality was higher in diabetic patients in a recent large study when multivariate analysis was performed[19]. Notably, in the latter study, mortality rates were identical in patients with and without T2DM in univariate analyses. Therefore, it is possible that

our study lacked the statistical power to detect a difference in mortality rates between diabetic and non-diabetic patients because of the low case-fatality rate.

Our study has some limitations. Although diabetic patients had poorer short-term functional prognosis in our population, previous studies showed that the subgroup of diabetic patients with lacunar infarction shows a better outcome[21,22]. However, magnetic resonance imaging is not available in our institution and imaging of the intra- or extracranial arteries was also not performed in all patients. Therefore, we cannot determine the frequency of the different stroke subtypes in our population. Moreover, the location of stroke, which may influence the functional outcome, was not systematically recorded. Finally, since we did not evaluate urinary albumin excretion in all patients, we were not able to evaluate the effects of albuminuria on stroke severity or outcome.

In conclusion, T2DM does not appear to affect ischemic stroke severity but is associated with worse functional outcome at discharge. This detrimental effect of T2DM on short-term stroke outcome appears to be independent of the increased prevalence of CVD risk factors in diabetic patients. Accordingly, management of hyperglycemia might have beneficial effects in patients with acute ischemic stroke but this remains to be established in prospective controlled trials.

COMMENTS

Background

Type 2 diabetes mellitus (T2DM) is a major independent risk factor for cardiovascular disease, including ischemic stroke. However, it is unclear whether stroke is more severe in patients with T2DM than in non-diabetic patients and whether the outcome of ischemic stroke is less favorable in the former.

Research frontiers

There is active research in the field of the potential role of strict glycemic control in the management of diabetic patients during the acute phase of ischemic stroke. Therefore, it is important to clarify whether hyperglycemia *per se* exerts a detrimental effect on stroke outcome.

Innovations and breakthroughs

The present study suggests that patients with T2DM have a less favorable functional outcome than non-diabetic patients even though stroke severity does not differ between the two groups. The adverse effect of T2DM on stroke outcome also appears to be independent of the increased prevalence of other cardiovascular risk factors in patients with T2DM (*e.g.*, hypertension, dyslipidemia, obesity) and appears to be mediated by hyperglycemia *per se*.

Applications

Since hyperglycemia appears to be associated with worse functional outcome in diabetic patients admitted with acute ischemic stroke, it is possible that strict glucose control might improve the outcome of this population. However, randomized controlled trials are needed to validate this hypothesis.

Terminology

In the present study, stroke severity was evaluated with the National Institutes of Health Stroke Scale, a comprehensive index of neurological deficit; a higher NIHSS signifies a more severe stroke. Functional outcome was assessed with the modified Rankin Scale (mRS), which quantifies disability and ranges from lack of symptoms (mRS = 0), no disability despite symptoms (mRS = 1), to progressively more severe disability (mRS = 2-5) and death (mRS = 6); adverse outcome was defined as mRS $\geqslant$ 2, *i.e.*, dependency or death.

Peer review

The study is important especially when from different populations.

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