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Original article

Long-term risk of stroke in type 2 diabetes patients with diabetic ketoacidosis: A population-based, propensity score-matched, longitudinal follow-up study

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ABSTRACT

Aim. – To investigate the long-term risk of stroke in type 2 diabetes (T2D) patients with previous episodes of diabetic ketoacidosis (DKA).
Methods. – This retrospective nationwide population-based cohort study was conducted using Taiwan's National Health Insurance database. Claims data from 2000 to 2002 were extracted for 3572 T2D patients with DKA and 7144 controls matched for age, gender, diabetes complications severity index, frequency of clinical visits and baseline comorbidities. Patients with type 1 diabetes (T1D), identified by glucagon C-peptide stimulation or glutamic acid decarboxylase (GAD) antibody blood tests and possession of a catastrophic illness certificate were excluded. All patients were tracked until a new stroke diagnosis, death or the end of 2011.
Results. – Of the 3572 selected patients, 270 with DKA and 404 of the 7144 controls were diagnosed with a new stroke, giving an incidence rate ratio (IRR) of 1.56 (95% CI: 1.34–1.82; $P < 0.0001$). DKA patients had a higher risk of ischaemic stroke than those without DKA (IRR: 1.62, 95% CI: 1.34–1.96; $P < 0.0001$), and DKA patients with hypertension and hyperlipidaemia were at even greater risk of stroke. Also, DKA patients were at particular risk for stroke during the first half-year following DKA diagnosis. After adjusting for patient characteristics and comorbidities, these patients were 1.55 times more likely to have a stroke than those without DKA (95% CI: 1.332–1.813, $P < 0.0001$).
Conclusion. – T2D patients with previous DKA have a higher risk of stroke, especially ischaemic strokes.
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Introduction

Stroke is a leading cause of death and disability in Taiwan [1]. Diabetes mellitus is an independent predictor of the incidence of ischaemic stroke [2], and chronic hyperglycaemia has been associated with infarct expansion and poorer functional outcomes [3]. One meta-analysis has associated diabetes with a two-fold increase in risk for vascular disease, independent of other conventional risk factors [4]. A hyperglycaemic crisis may further increase stroke risk. Wang et al. [5] reported that patients diagnosed with a hyperosmolar hyperglycaemic state (HHS) had a higher risk of ischaemic stroke the following year.

Diabetic ketoacidosis (DKA), a serious acute metabolic complication of diabetes, is characterized by uncontrolled hyperglycaemia, higher anion gap metabolic acidosis and increased total body ketone concentrations [6]. DKA is usually a consequence of absolute or relative insulin deficiency, increased concentrations of counter-regulatory hormones and peripheral insulin resistance [7]. In nationwide population-based studies, the mortality rate in children with DKA varied from 0.15% to 0.30% [8,9] whereas, in developing countries, it is higher, ranging from 3.4% to 13.4% [10–12]. In adults, the overall mortality rate is < 1%, but increases to > 5% in the elderly and in patients with concomitant life-threatening illnesses [6,13]. The morbidity and mortality in children and adolescents with DKA can mostly be attributed to intracerebral complications in the acute stage, the most common ones being cerebral oedema [14].

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Studies of subsequent stroke risk in type 2 diabetes (T2D) patients with DKA are scarce. One case study from Okamura et al. [15] reported the occurrence of acute infarction in a 79-year-old woman with DKA. However, while the current guidelines for the treatment of DKA focus on the acute phase, the long-term prognosis for T2D patients with previous episodes of DKA has rarely been addressed. It is also not known whether patients with T2D who have had DKA episodes are also at an increased risk of macrovascular complications or whether DKA can be considered a risk marker for long-term complications.

For these reasons, a population-based National Health Insurance (NHI) dataset in Taiwan was used to perform a longitudinal 10-year follow-up study to examine the relationship between DKA and the long-term risk of stroke in patients with T2D.

Materials and methods

Data sources

Taiwan launched its single-payer NHI programme on 1 March 1995. Its database now cover 99% of the country's population of 23.3 million, making it one of the largest and most complete population-based datasets in the world. These files, which are collected and made available by Taiwan's National Health Research Institutes, is known as the National Health Insurance Research Database (NHIRD). This database provides detailed information on the healthcare services provided to individual patients, including all payments for outpatient visits, hospitalizations, prescriptions and basic sociodemographic information, including gender and date of birth. For each outpatient visit or hospitalization, the submitted claims forms may contain as many as three to five diagnoses, as coded in the International Classification of Diseases, Ninth Revision (ICD-9), along with the prescribed drugs and doses, procedures and dates of these orders.

These were the data extracted for T2D patients with DKA from a subset of the NHIRD referred to as the Longitudinal Cohort of Diabetes Patients (LHDB). This subset contains randomized selected data (120,000 patients/year) from patients with newly diagnosed diabetes mellitus (DM; ICD-9-CD: 250). DM was identified in the LHDB if the claimant had at least one diagnosis of DM or a prescription for antidiabetes medication, or had received a diagnosis of DM on at least two different visits or a diagnosis of DM on at least one visit plus a prescription for antidiabetes medication.

The institutional review board of Chi-Mei Medical Center approved the study protocol. The need for informed consent was waived because the dataset analyzed for this study was devoid of any identifiable personal information.

Study sample

For this retrospective cohort study, randomized selected data from patients newly diagnosed with T2D between 1 January 2000 and 31 December 2002 were collected from the NHIRD. Of these patients, those diagnosed with DKA (ICD-9 code: 250.1) during the 10-year follow-up period after a T2D diagnosis were selected to constitute the experimental group. The control subjects were those with a diagnosis of T2D without DKA during the follow-up period. Excluded were those with type 1 diabetes (T1D), which was identified by either glucagon C-peptide stimulation or glutamic acid decarboxylase (GAD) antibody blood tests and possession of a catastrophic illness certificate.

The included cases were those diagnosed as having DKA (DKA+ group) during an emergency room visit or hospitalization following a diagnosis of T2D. The controls (DKA– group; two patients for each DKA patient) were patients with a diagnosis of T2D, but without DKA during the follow-up period, randomly selected from the LHDB. The index date for the DKA+ group was the date that DKA was first diagnosed, and the same date was used as the index date for the controls. Patients in the control group who died before the index date were excluded.

The controls were matched with the DKA+ patients by age at the time of DM diagnosis ($\pm$ 30 days), time interval between DM diagnosis date to DKA index date, gender, diabetes complications severity index (DCSI), frequency of clinical visits (between the date of first DM diagnosis and index date) and selected comorbidities by propensity score. Matching by propensity score was done to reduce selection bias, as the method can account for the many confounding factors that may be present in an observational study with this number of variables. Propensity scores were obtained through a logistic regression model using the dependent variable as the odds of diagnosis of DKA and the confounding variables as independent variables. Afterwards, the SAS matching macro %OneToManyMTCH, as proposed by the Proceedings of the 29th SAS Users Group International (SUGI), was applied. The selected comorbidities were hypertension (401–405), renal disease (582, 583, 585, 586, 588), hyperlipidaemia (428), coronary artery disease (CAD: 410–414), liver cirrhosis (LC: 571.2, 571.5, 571.6, 789.5, 465.20), and atrial fibrillation and flutter (AF: 427.3). Any one of these comorbid conditions was included if the condition was diagnosed in an inpatient setting or mentioned in three or more ambulatory care claims coded 1 year before the index medical-care date. The number of episodes of DKA was defined as the number of times DKA was identified within 2 years of the index date.

Follow-up and outcome measures

The primary outcome of interest was the first hospitalization for acute stroke (ICD-9-CM codes: 430–431 for haemorrhagic stroke; 433–434 for ischaemic stroke; 435 for transient ischaemic attacks; and 436 for acute but ill-defined cerebrovascular disease). Follow-up time in person-years (PY) was calculated for each patient until the above stroke or disease was diagnosed, death or the end of 2011. Patients diagnosed with DM before the index date were excluded, as were also patients diagnosed as having a previous stroke (ICD-9-CM code: 430–438) before the index date.

Statistical analyses

Standardized difference scores [16] were used to assess the balance of measured variables between DKA+ and DKA– subjects in our matched sample, with a score ≥ 0.1 assumed to indicate imbalance [17]. All of the following analyses were performed using methods appropriate for the analysis of matching data when estimating the outcome effect. Incidence rate was calculated as the number of stroke cases during follow-up divided by PYs. The incidence rate ratio (IRR) was computed using conditional Poisson regression to estimate the risk of stroke between the DKA+ and DKA– groups. Moreover, Cox's proportional-hazards regression was performed to compute the risk of stroke between the DKA+ and DKA– groups while taking pair-matching into account. The SAS software procedures GENMOD (for conditional Poisson regression) and PHREG (for Cox's proportional-hazards regression with 2:1 matching) were used to analyze our matching cohort data. A Kaplan–Meier survival curve was estimated for both groups, and a stratified log-rank test was used to compare differences between the two cohorts, using a test described by Klein and Moeschberger [18]. A two-sided P value < 0.05 was considered significant. All statistical operations were performed using the SAS 9.4 statistical package (SAS Institute, Inc., Cary, NC, USA).

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