Journal of Diabetes and Its Complications xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Journal of Diabetes and Its Complications

journal homepage: WWW.JDCJOURNAL.COM

Accelerated decline of renal function in type 2 diabetes following severe hypoglycemia

Tetsuro Tsujimoto [a,b,*], Ritsuko Yamamoto-Honda [a,c], Hiroshi Kajio [a], Miyako Kishimoto [a,c], Hiroshi Noto [a,c], Remi Hachiya [a], Akio Kimura [d], Masafumi Kakei [b,e], Mitsuhiko Noda [c,f]

[a] Department of Diabetes, Endocrinology, and Metabolism, Center Hospital, National Center for Global Health and Medicine, Tokyo, Japan
[b] Division of General Medicine, Jichi Medical University Graduate School of Medicine, Shimotsuke, Japan
[c] Department of Diabetes Research, Diabetes Research Center, National Center for Global Health and Medicine, Tokyo, Japan
[d] Department of Emergency Medicine and Critical Care, Center Hospital, National Center for Global Health and Medicine, Tokyo, Japan
[e] First Department of Comprehensive Medicine, Saitama Medical Center, Jichi Medical University School of Medicine, Saitama, Japan
[f] Department of Endocrinology and Diabetes, Saitama Medical University, Saitama, Japan

ARTICLE INFO

Article history:
Received 24 November 2015
Received in revised form 17 January 2016
Accepted 18 January 2016
Available online xxxx

Keywords:
Severe hypoglycemia
Type 2 diabetes
Blood pressure surge
Severe hypertension
Microvascular disease

ABSTRACT

Aims: This study aimed to evaluate whether the pronounced elevation in blood pressure during severe hypoglycemia is associated with subsequent renal insufficiency.
Methods: We conducted a 3-year cohort study to assess the clinical course of renal function in type 2 diabetes patients with or without blood pressure surge during severe hypoglycemia.
Results: Of 111 type 2 diabetes patients with severe hypoglycemia, 76 exhibited an extremely high systolic blood pressure before treatment, whereas 35 demonstrated no such increase (179.1 ± 27.7 mmHg vs. 131.1 ± 20.2 mmHg, $P < 0.001$). At 12 h after treatment, systolic blood pressure did not differ significantly (131.5 ± 30.7 mmHg vs. 123.5 ± 20.7 mmHg; $P = 0.39$). The estimated glomerular filtration rate (GFR) before and at the time of severe hypoglycemia did not significantly differ between both groups. A multivariate Cox proportional hazards regression analysis revealed that blood pressure surge during severe hypoglycemia was independently associated with a composite outcome of a more than 15 mL/min/1.73 m^2 decrease in the estimated GFR and initiation of chronic dialysis (hazard ratio, 2.68; 95% confidence interval, 1.12–6.38; $P = 0.02$).
Conclusions: Renal function after severe hypoglycemia was significantly worse in type 2 diabetes patients with blood pressure surge during severe hypoglycemia than those without blood pressure surge.

1. Introduction

Severe hypoglycemia can lead to the activation of the sympathoadrenal system and the release of counter-regulatory hormones, such as norepinephrine and epinephrine, resulting in significant changes to peripheral and central blood pressure, elasticity of blood vessels, and heart rate (Fisher, Gillen, Dargie, Inglis, & Frier, 1987; Hilsted et al., 1984). In fact, several studies have revealed that patients with diabetes exhibit blood pressure surges and severe acute hypertension during severe hypoglycemia (Feldman-Billard, Massin, Meas, Guillausseau, & Heron, 2010; Tsujimoto et al., 2014). Furthermore, because there was a delay between the occurrence of severe hypoglycemia out of the hospital and the initiation of emergency treatment, the blood pressure surge and severe acute hypertension might be sustained for several hours in some patients with diabetes.

Although the concept that hypoglycemia may aggravate the complication of diabetes existed before (Frier & Hilsted, 1985), several recent studies have reported associations between severe hypoglycemia and both higher mortality (Krinsley & Grover, 2007; Tsujimoto et al., 2015a) and an increased risk of cardiovascular disease (CVD) (Goto, Arah, Goto, Terauchi, & Noda, 2013; Tsujimoto et al., 2014; Zoungas et al., 2010). In addition, a recent study suggested that severe hypoglycemia may be associated with an increased risk of microvascular diseases (Zoungas et al., 2010). Although blood pressure surge and severe acute hypertension during severe hypoglycemia may result in endothelial damage (Lau et al., 1992; Mayer et al., 2011; Pretre & Von Segesser, 1997; Szczech et al., 2010), leading to higher risks of microvascular disease, such as renal dysfunction, the association between hypoglycemia-induced hemodynamic change

Conflict of interest: The authors have no potential conflicts of interest relevant to this article to report.

* Corresponding author at: Department of Diabetes, Endocrinology, and Metabolism, Center Hospital, National Center for Global Health and Medicine, 1-21-1 Toyama, Shinjuku-ku, Tokyo, 162-8655, Japan. Tel.: +81 3 3202 7181; fax: +81 3 3207 1038.
E-mail address: ttsujimoto@hosp.ncgm.go.jp (T. Tsujimoto).

http://dx.doi.org/10.1016/j.jdiacomp.2016.01.015

and microvascular disease remains unclear. The aim of this study was to assess whether a blood pressure surge during severe hypoglycemia can in fact induce or exacerbate renal insufficiency in patients with type 2 diabetes.

2. Methods

2.1. Study design and population

We conducted a cohort study at the National Center for Global Health and Medicine in Tokyo, Japan. Eligibility criteria included type 2 diabetes patients who had been transported to our hospital by ambulance and diagnosed with severe hypoglycemia between January 1, 2006 and March 31, 2012. These patients were assessed for serum creatinine levels upon arrival at the hospital and at least once after the initiation of treatment. The patients were followed-up for 3 years from the day of occurrence of severe hypoglycemia. Patients on chronic dialysis and with renal transplantation before the occurrence of the severe hypoglycemic event were excluded from the study, and those in cardiopulmonary arrest upon arrival were also excluded. In the present study, severe hypoglycemia was defined as the presence of any hypoglycemic symptoms that could not be resolved by the patients themselves and required medical assistance in the emergency department (American Diabetes Association, 2012). Blood glucose levels were usually measured at a central laboratory (81.1%, 90/111); however, in some cases, they were measured using a blood glucose meter (18.9%, 21/111).

We assessed patient demographic and baseline characteristics, systolic and diastolic blood pressure levels before and after the initiation of treatment for severe hypoglycemia, and the clinical course of renal function for 3 years. All data including the clinical records and laboratory results of patients were independently reviewed by at least two diabetologists. At events of disagreement between the two diabetologists, a third diabetologist was consulted to resolve the issue. Diabetes was confirmed when the patient had been previously diagnosed as having diabetes or was being treated with antidiabetic medicines, and type 2 diabetes was confirmed by a previous diagnosis or by the absence of a specific cause of diabetes and antibodies to glutamic acid decarboxylase. The present study was approved by the institutional review board of the National Center for Global Health and Medicine Hospital.

2.2. Blood pressure, renal function, and other measurements

Systolic and diastolic blood pressure levels of the patients were measured upon arrival and at 12 h after the initiation of treatment, provided that antihypertensive or vasopressor drugs were not used during that period. Serum creatinine levels were measured upon arrival, and estimated glomerular filtration rate (GFR) was calculated using the following formula, as recommended by the Japanese Society of Nephrology: estimated GFR (mL/min/1.73 m^2) = $194 \times \mathrm{Cre}^{-1.094} \times \mathrm{age}^{-0.287}$ ($\times 0.739$ if the patient is female) (Matsuo et al., 2009). Glycated hemoglobin (HbA1c) level was measured at the nearest time within 3 months of arrival.

2.3. Study outcome

In the present study, the primary endpoint measure was the time to the first event of the composite outcome including a decrease of more than 15 mL/min/1.73 m^2 in estimated GFR and the initiation of chronic dialysis after the occurrence of severe hypoglycemia. Secondary composite outcomes included the following: 1) a decrease of more than 15 mL/min/1.73 m^2 in estimated GFR from the occurrence of severe hypoglycemia, the initiation of chronic dialysis, and death from any cause; 2) a decrease of more than 30 mL/min/1.73 m^2 in estimated GFR and the initiation of chronic dialysis after severe hypoglycemia; and 3) the initiation of chronic dialysis. The outcomes were independently checked from the clinical records by two diabetologists who were blinded to the characteristics of patients. The primary and secondary endpoints were independently reviewed by at least two diabetologists.

2.4. Statistical methods

Data are presented as number, percentage, mean with standard deviation, or median with interquartile range. Continuous variables were compared using t-tests or Wilcoxon rank sum tests. Categorical variables were compared using chi-square tests or Fisher's exact tests. The study patients were divided into two groups with or without blood pressure surge during severe hypoglycemia, according to a cut-off blood pressure of 160/80 mmHg, which is the approximate overall median value. Cox proportional hazards models were used to evaluate the association between blood pressure surge during severe hypoglycemia and subsequent impairment of renal function. Multivariate adjustments were made for age, sex, preexisting hypertension, history of ischemic heart disease, blood glucose level upon arrival, and duration of diabetes. Age was divided according to a cut-off of 70 years, which is the approximate overall median value. Diabetes duration was divided according to a cut-off of 10 years. Preexisting hypertension was defined as either a previous diagnosis of hypertension or the use of antihypertensive medications. History of ischemic heart disease was defined as a history of myocardial infarction or angina pectoris. Kaplan–Meier analyses were used to assess the primary and secondary endpoints, and groups were compared using the log-rank test. P values of <0.05 according to two-sided tests were considered to be statistically significant. All analyses were performed using Stata software, version 11.1 (Stata Corp, College Station, Texas, USA).

3. Results

We screened 59,602 patients who had been brought to the emergency department of the national center by ambulance. Of these patients, 293 were diagnosed with type 2 diabetes with severe hypoglycemia. We excluded one patient receiving chronic dialysis and 181 patients who have not had their serum creatinine levels examined upon arrival and at least once after the initiation of treatment. The study criteria were met by 111 patients with severe hypoglycemia. Clinical characteristics of type 2 diabetes patients upon arrival are presented in Table 1. Type 2 diabetes patients were divided into two groups with or without blood pressure surge according to a cut-off blood pressure of 160/80 mmHg as follows: 76 patients with blood pressure surge during severe hypoglycemia and 35 patients without blood pressure surge. The proportion of severe hypertension during severe hypoglycemia did not significantly differ in patients with and without preexisting hypertension (70.0% vs. 61.9%; $P = 0.47$). Systolic blood pressure levels in type 2 diabetes patients with and without blood pressure surge during severe hypoglycemia were 179.1 ± 27.7 mmHg and 131.1 ± 20.2 mmHg, respectively ($P < 0.001$). About 20% of the type 2 diabetes patients with blood pressure surge had a systolic blood pressure of more than 200 mmHg (18.4%, 14/76) and some of them had a systolic blood pressure of more than 230 mmHg (6.6%, 5/76). Estimated GFR of patients upon arrival was not found to be significantly different between type 2 diabetes patients with and without blood pressure surge during severe hypoglycemia (57.7 ± 29.1 mL/min/1.73 m^2 vs. 55.3 ± 31.1 mL/min/1.73 m^2; $P = 0.70$). In addition, the proportion of patients with an estimated GFR of <60 mL/min/1.73 m^2 did not significantly differ between both groups (53.9% vs. 60.0%; $P = 0.55$). The estimated GFR at the nearest time within 3 months before arrival was also not found to be significantly different (55.1 ± 24.2 mL/min/1.73 m^2 vs. 57.7 ± 28.2 mL/min/1.73 m^2; $P = 0.72$). Mean age, sex ratio, prevalence of preexisting hypertension, use of angiotensin II receptor blockers or angiotensin converting enzyme inhibitors, blood glucose level upon

Please cite this article as: Tsujimoto, T., et al., Accelerated decline of renal function in type 2 diabetes following severe hypoglycemia, *Journal of Diabetes and Its Complications* (2016), http://dx.doi.org/10.1016/j.jdiacomp.2016.01.015