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The impact of severe hypoglycemia on renal impairment in type 2 diabetes

Yu-Li Lee [a], Brian K. Chen [b], Kun-Der Lin [a], Rong-Wei Su [c], Mei-Yueh Lee [a], Pi-Jung Hsiao [a,d], Shyi-Jang Shin [a,d,e,*]

[a] Division of Endocrinology and Metabolism, Department of Internal Medicine, Kaohsiung Medical University Hospital, Taiwan
[b] Arnold School of Public Health, University of South Carolina, USA
[c] Graduate Institute of Healthcare Administration, Kaohsiung Medical University, Kaohsiung, Taiwan
[d] School of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan
[e] Center for Lipid and Glycomedicine Research, Kaohsiung Medical University, Kaohsiung, Taiwan

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ABSTRACT

Aims: Hypoglycemia has been reported to be associated with the development of microvascular events. Therefore, it is important to assess the impact of severe hypoglycemia on renal dysfunction in type 2 diabetes.

Methods: We conducted a retrospective cohort study in a large tertiary care hospital from 2004 to 2013. A total of 101 patients with type 2 diabetes from the outpatient department with a history of severe hypoglycemia were studied. A random sample of 101 patients with type 2 diabetes without any hypoglycemia was selected by matching values of baseline blood creatinine, age, sex and diabetic duration.

Results: Baseline blood creatinine (1.42 ± 0.75 mg/dL) significantly increased to 1.77 ± 1.26 and 1.93 ± 1.54 mg/dL, and baseline eGFR (44.37 ± 26.13 ml/min/1.73 m^2) decreased to 41.28 ± 27.70 and 37.64 ± 24.54 ml/min/1.73 m^2 at the onset of hypoglycemia and the follow-up visit in severe hypoglycemia group; while no significant changes were observed in the group without any hypoglycemia. Multiple linear regression analysis showed that severe hypoglycemia is an independent risk factor for increase in blood creatinine and decrease in eGFR in all patients with type 2 diabetes, and that baseline creatinine, longer diabetic duration and lower HbA1c are risk factors for the deterioration of renal impairment in the group with severe hypoglycemia.

Conclusion: Our results showed that severe hypoglycemia is associated with deterioration of renal function in type 2 diabetes with chronic kidney disease and the patients with higher baseline creatinine and a longer diabetic duration could be more vulnerable to aggravation of renal function impairment.

* *Corresponding author at*: Division of Endocrinology and Metabolism, Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan. Tel.: +886 7 3121101x5529; fax: +886 7 312 2810.
E-mail address: sjshin@kmu.edu.tw (S.-J. Shin).

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1. Introduction

Worldwide, the number of adults with diabetes was estimated at 382 million in 2013, a figure that is expected to increase to 592 million by 2035 [1]. Studies have suggested strict control of blood glucose as a means to prevent complications from diabetes mellitus, particularly microvascular complications such as diabetic nephropathy [2–6]. Yet hypoglycemia remains the most common and significant treatment-limiting adverse event in patients with diabetes [7], and is associated with recurrent morbidity in most people with type 1 diabetes and in many with type 2 diabetes [8]. A systematic review of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial, and the Veterans Affairs Diabetes Trial (VADT) reported that intensive glucose therapy increased the risk of severe hypoglycemia 2-fold relative to a control group [9]. A meta-analysis of 14 randomized clinical trials also showed that intensive glycemic control increased the relative risk of severe hypoglycemia by 30% [10]. Post hoc analyses of the ADVANCE trial also demonstrated that patients who experience severe hypoglycemia had significantly higher risks of major macrovascular and microvascular events [11]. A retrospective cohort study using electronic medical records showed that hypoglycemia is associated with higher risks of incident macrovascular and microvascular events in veterans with type 2 diabetes whose mean baseline HbA1c value was $10.7 \pm 2.6\%$ (93 ± 28.6 mmol/mol) [12]. A recent study reported that patients with type 2 diabetes who had severe hypoglycemia events are at risk for premature death and all-site cancer [13]. Together, these clinical trials suggested that it is necessary to assess the relationship between severe hypoglycemia and subsequent renal function impairment using biochemical measurements in clinical practice. Our study provided evidence of sequential serum creatinine and estimated glomerular filtration rate (eGFR) data to assess the impact of severe hypoglycemic events on renal dysfunction and on its aggravation in patients with type 2 diabetes.

2. Subjects and methods

Patients with type 2 diabetes and severe hypoglycemia were recruited from the outpatient department of endocrinology and metabolism using electronic medical and pharmacy records at Kaohsiung Medical University Hospital. Patients who were ever hospitalized for severe hypoglycemia from January 1, 2004 to September 1, 2013 were selected. Severe hypoglycemia was defined as an event requiring assistance of another person [14]. Records of 122 patients who were admitted with severe hypoglycemia as the only reason were selected for initial review. Baseline demographical and laboratory records prior to the severe hypoglycemic attack, at the onset of severe hypoglycemia, and at a follow-up visit of more than three months to one year after the severe hypoglycemia were required for inclusion. Demographic and laboratory data, including age, sex, body mass index (BMI), diabetes duration, blood pressure, HbA1c, antebicum (AC) glucose, and total cholesterol, triglyceride, LDL-cholesterol, HDL-cholesterol, anti-diabetic agents, antihypertensive agents and antilipidemic agents, were collected for analysis. Twenty-one patients with non-diabetes-related nephropathy or uropathy, cancer, liver cirrhosis, and pyuria were excluded from the study. The final sample was 101 patients with severe hypoglycemia. The Kaohsiung Medical University Hospital Institutional Review Board approved this study (KMUH-IRB-20120305).

To understand the natural changes of blood creatinine and eGFR in patients with type 2 diabetes who did not experience any hypoglycemia events, we randomly selected from the outpatient department from January 1, 2004 to September 1, 2013 matched for age, sex, HbA1c, baseline blood creatinine and the proportion of patients with a diabetic duration >10 years. We measured blood pressure, body mass index (BMI), blood creatinine, GPT, total cholesterol, triglyceride (TG), LDL-cholesterol, HDL-cholesterol, glucose, HbA1c and eGFR at baseline, at the time of the severe hypoglycemic event (3.48 ± 2.52 and 3.57 ± 2.20 months after the baseline visit), and at the time of follow-up (11.53 ± 7.21 and 11.12 ± 3.97 months) in the group with severe hypoglycemia and the group without any hypoglycemia, respectively. We estimated the glomerular filtration rate by using the abbreviated MDRD equation [15]: estimated GFR $(\mathrm{ml/min/1.73\ m^2}) = 186 \times (\text{creatinine}/88.4) \times -1.154 \times (\text{age}) - 0.203 \times (0.742, \text{if female})$.

3. Statistical analysis

We compared differences in means for the continuous variables at different time points by using repeated-measures ANOVA, the post hoc Tukey's test, Bonferroni adjustment at time points ($P = 0.025$). The Chi-square test and Student t test were used to explore categorical variables and continuous variables respectively. Multiple linear regression models were used to estimate the risk factors for the increase of blood creatinine concentration and the reduction of eGFR at the follow-up visit. We controlled for a vector of covariates, including patient demographics and baseline characteristics. The two-tailed significance level was set at 0.05. All analyses were conducted using PASW statistical software version 18.0.

4. Results

In Table 1, age, sex, diabetes duration, proportion of patients with hypertension and hyperlipidemia, mean baseline blood glucose, HbA1c, creatinine, estimated GFR, systolic and diastolic BP, GPT, total cholesterol, TG, LDL-c, and HDL-c are shown to be not significantly different in the patients with severe hypoglycemia and those without any hypoglycemia. However, the proportions of patients with coronary artery disease, stroke and CHF, and insulin injection were higher in the patients with severe hypoglycemia than those without hypoglycemia.

At the onset of severe hypoglycemia in the group with severe hypoglycemia, blood glucose dropped to 38.13 ± 18.13 mg/dL and blood creatinine increased from 1.42 ± 0.75 to 1.77 ± 1.26 mg/dL, eGFR decreased from