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Non-linear associations of risk factors with mild hypoglycemia among Chinese patients with type 2 diabetes

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ABSTRACT

Aims: The present study aimed to examine the nonlinear associations between risk factors and mild hypoglycemia in Chinese patients with type 2 diabetes mellitus (T2DM).
Methods: From May 2013 to August 2013, we conducted a cross sectional survey of 6633 inpatients with T2DM and without severe hypoglycemia, aged 21–77 years, from 81 top tertiary hospitals in China. Mild hypoglycemia was defined as having hypoglycemia with symptoms in one month. Binary logistic regression analysis with restricted cubic splines was used to estimate odds ratio curves of non-linear risk factors for mild hypoglycemia.
Results: Increasing body mass index was associated with decreasing risk of mild hypoglycemia in a linear manner while age, duration of diabetes, glycated hemoglobin ($HbA1_c$), mean artery pressure and lipids were associated with mild hypoglycemia in non-linear manners. Age ≥40 years, duration ≥2 years, $HbA1_c$ ≥7.0–<11.5% (≥53–<102 mmol/mol), triglyceride ≥1.7–<3.6 mmol/L, low-density lipoprotein cholesterol (LDL-C) ≥2.6–<4.8 mmol/L, and high-density lipoprotein cholesterol (HDL-C) ≥1.2–<4.8 mmol/L were associated with increased risks of mild hypoglycemia.
Conclusions: Chinese T2DM patients with age ≥ 40 years, duration of diabetes ≥2–<6 years, $HbA1_c$ ≥7.0–<11.5% (≥53–<102 mmol/mol), LDL-C ≥2.6–<4.8 mmol/L, HDL-C ≥1.2–<4.8 mmol/L or triglyceride ≥1.7–<3.6 mmol/L were at particularly high risk for mild hypoglycemia.

1. Introduction

Good glycemia control plays a key role in management of type 2 diabetes mellitus (T2DM). Increased levels of glycated hemoglobin ($HbA1_c$) were associated with the risk of micro-vascular and macro-vascular diseases (Gerstein et al., 2005; Stratton et al., 2000). However, aggressive glycemic control is inevitably associated with increased risk of hypoglycemia, as reported in several large scale randomized controlled trials including the ADVANCE (Action in Diabetes and Vascular disease: preterAx and diamicroN modified release Controlled Evaluation) (Patel et al., 2008), ACCORD (Action to Control Cardiovascular Risk in Diabetes) (Gerstein et al., 2008) and VADT (Veteran Affairs Diabetes Trial)(Duckworth et al., 2009). Indeed, hypoglycemia is one of major limiting factors for tight glycemic control while post-hoc analysis of randomized clinical trial data suggested a strong association between hypoglycemia and vascular disease (Zoungas et al., 2010).

Hypoglycemia is the most common acute complication of T2DM (Barnett, Brice, Hanif, James, & Langerman, 2013) and affected many aspects of life of patients with T2DM (Bonds et al., 2012). Worries and fears of hypoglycemia greatly reduced patients' adherence to the prescribed anti-glycemia therapy (Williams et al., 2012). Mild hypoglycemia may result in a series of neurologic symptoms (Guettier & Gorden, 2006; Kearney & Dang, 2007), and impaired awareness to subsequent hypoglycemia (Amiel, Dixon, Mann, & Jameson, 2008)

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while severe hypoglycemia may lead to seizures or loss of consciousness (Bonds et al., 2012) and permanent cognitive impairment (Yaffe et al., 2013).

Intensive therapy for diabetes (Duckworth et al., 2011; Macisaac & Jerums, 2011; Okawa et al., 2013), use of some glycemic lowing drugs, e.g., insulin and sulfonylureas (Bolen et al., 2007; Zammitt & Frier, 2005) and some behavioral factors such as skipping meals (Sotiropoulos et al., 2005) were identified to be major risk factors for hypoglycemia. Studies also reported that excessive daytime sleepiness and depressive disorder were associated with hypoglycemia (Bordier et al., 2015; Inkster et al., 2013). Hypoglycemia was more often occurring in male than in female (Inkster et al., 2013; Simon et al., 2015). Use of self-monitoring blood glucose (SMBG) was associated with hypoglycemia but the increased use of SMBG was usually regarded as one of the consequences of hypoglycemia rather than the cause (Simon et al., 2015).

The associations of common clinical factors such as duration of diabetes and lipid profile with hypoglycemia were not well investigated. A "real-world" study reported that patients with incident hypoglycemia had higher $HbA1_c$ value at baseline (7.6 vs. 7.4%) (60 vs. 57 mmol/mol)(Tschope et al., 2012). In another "real-world" study, per 1% increase in $HbA1_c$ level was associated with 12% decreased risk of non-severe hypoglycemia (Simon et al., 2015). A retrospective study reported that incident rate ratio of symptomatic hypoglycemia was lower in patients with higher BMI (Giorda et al., 2015). The data from the Initial Glargine Intervention trial (ORIGIN) showed that per 1 kg/m^2 increase in BMI was associated with a 3% reduction in the risk of hypoglycemia (The ORIGIN Trial Investigators, 2015). Indeed, there are some paradoxes regarding the associations of $HbA1_c$, and BMI with hypoglycemia. It is counterintuitive that high $HbA1_c$ but not low $HbA1_c$ was associated with increased risk of hypoglycemia and low BMI but not high BMI was associated with increased risk of hypoglycemia. It remains to be determined who are at risk of hypoglycemia. The current study analyzed the data from a cross sectional survey of Chinese patients with T2DM from 81 top tertiary care hospitals in China and explored non-linear associations of risk factors with mild hypoglycemia using a non-linear approach.

2. Methods

2.1. Participants

As a quality improvement program, Chinese Hospital Association (CHA) conducted a survey among top tertiary hospitals in China from May 2013 to August 2013 to learn the profile of hypoglycemia control among patients with T2DM. A total of 81 top tertiary care hospitals in 27 cities from 21 provinces of China were invited and agreed to participate in the survey. The inclusion criteria were 1) patients with T2DM and admitted to the department of endocrinology; 2) Agreed to use a basal bolus plus meal time insulin intensive management scheme after admission; and 3) between 18 to 80 years of age. The exclusion criteria were 1) with liver dysfunction defined as alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 2.5 folds of the upper limits of the normal range, 0–40 U/L; 2) with renal dysfunction defined as serum creatinine ≥125 μmol/L in male and ≥110 μmol/L in female or chronic kidney disease (CKD); 3) during pregnancy or lactation; and 4) unable to communicate in a normal way.

During the survey period, 6713 inpatients with T2DM were consecutively recruited from the department of endocrinology of the 81 participating hospitals. Of note, severe hypoglycemia and mild hypoglycemia may have different risk factors and consequences (Giorda et al., 2015; The ORIGIN Trial Investigators, 2015) and only a small number of patients in our patients had severe hypoglycemia. We further excluded 80 patients with severe hypoglycemia defined as having one or more episodes of hypoglycemia that needed assistance from other people in three months prior to the survey and the remaining 6633 patients were included in the final data analysis.

The study was approved by the ethics committee of the People's General Army (PLA) Hospital Clinical Research Ethics Committee. The survey was conducted in accordance with the Declaration of Helsinki Principles and written informed consent was obtained before the data collection.

2.2. Data collection and clinical measurements

The fieldworker/s (either a postgraduate medical student or a research nurse) reviewed case notes of the inpatients and retrieved the demographic information and the results of clinical measurements and laboratory essays. The collected parameters included body weight, body height, and sitting blood presure (BP), self-monitoring of blood glucose (SMBG), HbA_{1c}, lipid profile, liver function and renal fucntion. Fasting blood was taken for measurement of HbA_{1c} and lipids including low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglyceride (TG). Use of drugs was documented in details, including antidiabetes drugs (oral antidiabetes drugs (OADS), glucagon-like peptide (GLP)-1 based drugs and insulin and combinations of these drugs), lipid lowering drugs (statins and other lipid lowing drugs), and antihypertensive drugs (renin angiotensin system inhibitors, calcium antagonists and β-receptor antagonists). Diabetes complications including micro- and macro-vascular complications and the reasons for this admission were also documented in details.

2.3. Definition of mild hypoglycemia

Hypoglycemia cannot be precisely defined using plasma glucose levels alone because thresholds for symptoms vary significantly between patients (Barnett et al., 2013) and usually, a definition by clinical picture alone was acceptable by most authorities (Amiel et al., 2008). In this survey, we used self-reported episodes to define hypoglycemia. Mild hypoglycemia was defined as having one or more episodes of hypoglycemia with symptoms (e.g., palpitations, hunger, sweating, tremulousness, weakness, fatigue, dizziness, and anxiety) in one month prior to the survey.

2.4. Statistical analysis

The Statistical Analysis System (SAS, version 9.3; SAS Institute, Inc., Cary, NC, USA) was used to analyze the data. All continuous variables were expressed as median (interquartile range, IQR). Categorical variables were expressed as numbers and percentages. Normal distribution of continuous variables was checked by using normality test. The categorical variables between patients with mild hypoglycemia and those without were compared using Chi-square test or Fisher's exact test where appropriate. Two-sample Wilcoxon rank test or Student t test where appropriate was used to compare continuous variables between two groups. Binary logistic regression was used to obtain odds ratios (ORs) and their 95% confidence intervals (95% CLs) of factors for mild hypoglycemia. A structured adjustment scheme was used to adjust for confounding effects of other variables. First, we estimated ORs of possible clinical risk factors for mild hypoglycemia in univariable logistic analysis. Then, we adjusted for demographic and clinical factors, antidiabetes treatment, diabetes complications, and use of lipid lowing drugs and antihypertensive drugs. P values less than 0.05 from two tailed tests were considered as being statistically significant.

Body mass index (BMI) was calculated as body weight in kilograms divided by squared body height in meters. As systolic BP (SBP) and diastolic BP (DBP) were highly correlated (correlation coefficient = 0.456, $P < 0.0001$), mean arterial pressure (MAP) calculated as $MAP = (SBP + 2 \times DBP)/3$ was used in the analysis to avoid potential co-linearity. Some previous studies reported unexpected associations of some demographic and clinical factors with hypoglycemia such as HbA_{1c} (Simon et al., 2015) and BMI (The ORIGIN Trial Investigators, 2015). To capture non-linear associations of age, duration of diabetes, MAP, HbA_{1c}, BMI and lipids, we used

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