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Glycemic excursions are positively associated with changes in duration of asymptomatic hypoglycemia after treatment intensification in patients with type 2 diabetes

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ABSTRACT

Aim: The aim of this study was to examine the association between glycemic excursions and duration of hypoglycemia after treatment intensification in patients with type 2 diabetes (T2D).

Methods: Patients with T2D on oral anti-diabetes drug (OAD) with glycated hemoglobin (HbA1c) of 7.0–11.0% were switched to metformin monotherapy (500 mg thrice daily) for 8 weeks, followed by randomization to either glibenclamide or acarbose as add-on treatment for 16 weeks. Glycemic excursions were assessed as mean amplitude of glycemic excursions (MAGE) with 72-h ambulatory continuous glucose monitoring (CGM) before randomization and at the end of study. Hypoglycemia was defined as sensor glucose level of less than 60 mg/dl in two or more consecutive readings from CGM.

Results: A total of 50 patients (mean age 53.5 ± 8.2 years, male 48%, mean baseline HbA1c 8.4 ± 1.2%) were analyzed. Duration of hypoglycemia significantly increased after treatment with glibenclamide (from 5.5 ± 13.8 to 18.8 ± 35.8 min/day, $p = 0.041$), but not with acarbose (from 2.9 ± 10.9 to 14.7 ± 41.9 min/day, $p = 0.114$). Post treatment MAGE was positively associated with change from baseline in duration of hypoglycemia after treatment with either glibenclamide (β coefficient 0.345, $p = 0.036$) or acarbose (β coefficient 0.674, $p = 0.046$). The association remained significant after multivariate adjustment ($p < 0.05$ for all models).

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Conclusions: Post treatment glycemic excursions are associated with changes in duration of hypoglycemia after treatment intensification with OAD in patients with T2D. Glycemic excursions should be an important treatment target for T2D to reduce the risk of hypoglycemia.

1. Introduction

The micro- and macro-vascular complications associated with type 2 diabetes (T2D) can be prevented or delayed with intensive glycemic control [1,2]. Treatment guidelines [3–5] recommend a general target of glycated hemoglobin (HbA1c), usually of less than 7% (53 mmol/mol), for patients with T2D. However, an obvious disadvantage of HbA1c is that it does not provide information about short-term excursions in glucose levels, which have been associated with oxidative stress independent of HbA1c [6,7] and related to the pathogenesis of diabetes complications [8,9]. The importance of glycemic excursions in patients with diabetes is further supported by its association with incidence of micro- and macro-vascular diabetes complications [10–15].

Furthermore, glycemic excursions have been associated with risk of hypoglycemia, an important barrier in diabetes treatment, independent of levels of mean blood glucose or HbA1c [16–19]. In patients with type 1 diabetes, incidence of severe hypoglycemia was associated with an increase in standard deviation of self-monitoring of blood glucose [16,17]. Similar findings were noted in patients with T2D using data from self-monitoring of blood glucose [18] or continuous glucose monitoring (CGM) [19]. Hypoglycemia [20,21], even when it is asymptomatic [22,23], has been associated with adverse cardiovascular outcomes in patients with diabetes. Given that glycemic excursions have been associated with chronic diabetes complications and risk of hypoglycemia, they should be appropriately monitored in patients with diabetes [24–27].

Treatment guidelines have advocated the importance of individualization in diabetes management [28], including appropriate selection of treatment agents and target of glycemic control, and avoidance of hypoglycemia. The effect of glycemic excursions on risk of hypoglycemia after treatment intensification with oral anti-diabetes drug (OAD) has not been investigated in patients with T2D. The aim of this study was to examine the association between glycemic excursions and duration of hypoglycemia, as assessed with CGM, after treatment intensification with OAD in patients with T2D. We analyzed data from a previous trial [29] in which ambulatory CGM was conducted in patients with T2D on metformin monotherapy before and after treatment intensification with either glibenclamide (a sulfonylurea) or acarbose (an α-glucosidase inhibitor). With CGM, we assessed glycemic excursions as mean amplitude of glycemic excursions (MAGE) [30], and monitored asymptomatic hypoglycemia which may not be detected using self-monitoring of blood glucose.

2. Subjects, materials and methods

2.1. Study design

In this study we analyzed data from a previously published randomized trial [29]. The trial was a 24-week, randomized, open-label, parallel-group study, which was conducted in accordance with the Declaration of Helsinki in two medical centers in central Taiwan. The study protocol was approved by the institutional review board of study sites, and all patients provided informed consent prior to any study related procedures. Briefly, outpatients with T2D were eligible if they were aged 30–70 years, were on mono- or dual-OAD for more than 3 months, and had an HbA1c of 7.0–11.0% (53–97 mmol/mol). Patients were excluded if they were treated with insulin or drugs that promote weight loss, had impaired renal (serum creatinine concentration >132.6 μmol/l) or liver (aspartate aminotransferase or alanine aminotransferase 2.5 times the normal range) function, had a history of hemoglobinopathy or chronic anemia, or women of child-bearing potential without adequate contraception.

Subjects were treated with metformin monotherapy (500 mg thrice daily) for 8 weeks, followed by randomization in a 1:1 ratio to receive either glibenclamide (n = 26) or acarbose (n = 29) as add-on treatment for 16 weeks [29]. For the first 4 weeks of add-on treatment, the dosage was 2.5 mg thrice daily for glibenclamide (Veterans Pharmaceutical Plant, Veterans Affairs Commission, Executive Yuan, Taiwan), and 50 mg thrice daily for acarbose (Bayer Schering Pharma, Taiwan Branch). In the next 12 weeks, the dosage of glibenclamide and acarbose was doubled if it was tolerable. Six patients in glibenclamide group and one patient in acarbose group could not tolerate dose titration due to symptoms of hypoglycemia and abdominal distention, respectively. After an overnight fasting, blood samples were collected for the measurements of plasma glucose, insulin, and HbA1c before randomization and at the end of study. A total of 51 patients completed this study [29] and 50 of them were included in the analysis (one patient in acarbose group who did not complete CGM was excluded).

2.2. Assessment of glycemic excursions and duration of hypoglycemia

A Medtronic MiniMed Continuous Glucose Monitoring System (Northridge, CA, USA) was used for continuous interstitial glucose measurements on an ambulatory basis over a 72 h period [31] before randomization and at the end of study. The sensor was inserted on day 1 and removed on day 4 at mid-morning. Patients were instructed to calibrate the system using capillary blood glucose testing as advised by the