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■ Letter

Professional Continuous Glucose Monitoring Reveals Nocturnal Hypoglycemia in Patients with Type 2 Diabetes Mellitus and Cardiovascular Disease Treated with Oral Antidiabetics

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Dear Editor,

With great interest, we read the article by Kim et al.[1] "Frequency and severity of hypoglycemia in type 2 diabetes mellitus patients treated with a sulfonylurea-based regimen at university-affiliated hospitals in Korea: the naturalistic evaluation of hypoglycemic events in diabetic subjects study" and wanted to share our own findings regarding the occurrence of hypoglycemia in a cohort of patients with type 2 diabetes mellitus (T2DM) treated with oral antidiabetics.

Given the significance of hypoglycemia in patients with T2DM and cardiovascular disease treated with oral antidiabetics, we conducted a multi-center prospective observational study in primary care offices. The study analyzed 94 patients with T2DM treated with oral antidiabetics and monitored blood glucose with a professional continuous glucose monitoring (CGM) device (iPro2; Medtronic, Dublin, Ireland). The median hemoglobin A1C, age, T2DM duration, body mass index (BMI), and duration of CGM use were 7% (range, 5.8%–11.5%), 65 years (range, 40–83 years), 7 years (range, 1–36 years), 30.4 kg/m^2 (range, 21.3–1.5 kg/m^2), and 6 days (range, 1–7 days), respectively. Included patients had no subcutaneous therapy for diabetes (insulin or glucagon-like peptide 1 receptor agonists). One, two, three, and four oral antidiabetic agents were used in 33%, 41%, 23%, and 3% of the patients, respectively. Among the 50 patients treated with insulin secretagogues, the majority were treated with gliclazide (84%), while the remaining patients were treated with glimepiride or repaglinide. The dosages of glimepiride and repaglinide were converted to the approximate dose for gliclazide to achieve minimal equivalent dosages. Patients were divided into two groups; group 1 with known cardiovascular disease (n=20) and group 2 without (n=74). There were no significant differences in the hemoglobin A1C, age, T2DM duration, BMI, and or duration of CGM use among the groups. The percentage of patients treated with insulin secretagogues did not differ between the groups (40% of group 1 and 51% of group 2). The median dose of gliclazide was the same in both groups at 60 mg (range, 30–120 mg), meaning there were no confounders.

Both physician and patient were unaware of the CGM data until it was uploaded to the CareLink iPro software (Medtronic). Patients were instructed to keep a diary on food, activity, and therapy to help further interpretation of glucose deviations. Hypoglycemia was defined as at least 1% of the monitored period spent in the hypoglycemic range below 3.0 mmol/L (54 mg/dL) and/or an area under the curve registered under the mentioned blood glucose cut-off value. Nocturnal hypoglycemia was defined by a timeframe between 11

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PM and 6 AM.

The mean percentage of time spent in nocturnal hypoglycemia in group 1 and group 2 were 2.40% (range, 0%–4.96%) and 0.72% (range, 0%–3.17%), respectively. The Mann-Whitney U-test showed a significant difference in the time spent in nocturnal hypoglycemia among the groups (P=0.040), contrary to daytime hypoglycemia (P=0.178). Self-reporting of nocturnal hypoglycemic symptoms was irrelevant as none of the patients reported this during the night.

In our study, we found that in a cohort of patients with T2DM treated with oral antidiabetics, nocturnal hypoglycemia, based on the cut-off value of 3.0 mmol/L, was more prevalent in patients with cardiovascular disease. We used this cut-off value based on the International Hypoglycemia Study Group definition of blood glucose level <3.0 mmol/L as serious, clinically important hypoglycemia and their recommendation to include the value in reports of clinical trials.[2] There are multiple known links between nocturnal hypoglycemia and cardiovascular disease in diabetes. Nocturnal hypoglycemia can be potentially dangerous, even in healthy adults, as neuroendocrine counterregulatory responses start at a lower plasma glucose level during sleep than during wakefulness.[3] Attenuated sympathoadrenal responses to hypoglycemia can also be caused by sleep.[4] Furthermore, an association between physiological sleep and the occurrence of vascular events, cardiac arrhythmias, and sudden death exists even without diabetes.[5] The Action to Control Cardiovascular Risk in Diabetes trial indicated that patients with T2DM and a glucose concentration <2.8 mmol/L have higher mortality.[6]

In short, we found that patients with cardiovascular disease and T2DM treated with oral antidiabetics experienced nocturnal hypoglycemia lasting an average of 10 minutes (2.4% of 7 hours). As with this study, in everyday practice such events often remain unrecognized by both patients and physicians. The majority of such vulnerable T2DM patients treated with oral antidiabetics are seen only in primary care. As stated in the manuscript by Kim et al.,[1] a higher incidence of hypoglycemia may reflect challenges for diabetes management in family practice settings where an in-depth knowledge of diabetes management may be less likely. There is a rising body of evidence on the adverse effects of hypoglycemia on cardiovascular health and we recommend using professional CGM devices in primary care to identify patients who are at a greater risk for nocturnal hypoglycemia.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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