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Plasma C-Peptide Level and Continuous Glucose Monitoring-Derived Coefficient of Variation as a Predictable Risk Factor for Hypoglycemia in Koreans with Diabetes

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Hypoglycemia is one of the major limiting factors in intensive glycemic control, which is essential for preventing long-term microvascular and macrovascular complications in individuals with diabetes mellitus (DM) [1]. In addition to causing uncomfortable symptoms and fostering hypoglycemic fear, hypoglycemia is associated with several abnormalities that contribute to vascular risk, including arrhythmias, endothelial cell dysfunction, increased inflammation, and a prothrombotic environment [2]. If left untreated, hypoglycemia may progress to severe hypoglycemia (SH), defined as a hypoglycemic event that requires assistance from another person for recovery and leads to acute, severe cognitive impairment [3]. In 2019, the prevalence of SH events was 0.6%, with an incidence rate of 4.43 per 1,000 person-years, and approximately 23,000 SH events occur each year in Korea [4]. The relationship between SH and cardiovascular disease outcomes or mortality is supported by many large randomized clinical trials, cohort studies, and meta-analyses [5,6]. Therefore, early detection of high-risk patients and individualized education for hypoglycemia prevention are very important.

Assessing an individual's risk for hypoglycemia involves evaluating both clinical risk factors and relevant socioeconomic factors. Well-known clinical and biological risk factors for hypoglycemic events include older age, multimorbidity, cognitive dysfunction, chronic kidney disease (CKD) and end-stage kidney disease, cardiovascular disease, depression, neuropathy, and recurrent hypoglycemia [7,8]. Recently, with the increased use of continuous glucose monitoring (CGM) among individuals with DM, the episodes and duration of hypoglycemia have become more clinically apparent and easily measurable using the CGM-derived time below range (TBR) parameter [8]. This enables earlier intervention to facilitate behavioral and therapeutic changes that help avoid future episodes of hypoglycemia and SH. Therefore, CGM is recommended for insulin-treated individuals with DM, especially those using multiple daily insulin injections or continuous subcutaneous insulin infusion [9].

Although CGM reveals more instances of hypoglycemia, many of these episodes go unrecognized by individuals with type 1 DM (T1DM) and insulin-treated type 2 DM (T2DM). According to findings from the Hypoglycaemia-Measurement, Thresholds and Impacts (Hypo-METRICS) study, nearly two-thirds of CGM-detected hypoglycemic episodes were not recognized by patients, and over 40% of reported symptomatic events occurred at levels exceeding 70 mg/dL [10]. Moreover, for CGM-detected hypoglycemia below 54 mg/dL, 55% of epi-

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sodes in individuals with T1DM and 71% in those with T2DM were not accompanied by patient-reported symptoms [10]. These findings suggest that additional predictive markers in conjunction with CGM are necessary for the early detection of individuals at high risk for hypoglycemia in DM.

In general, increased glycemic variability is associated with a higher risk of hypoglycemia and SH. The percent coefficient of variation (%CV), which is calculated by dividing the standard deviation of glucose levels by the mean glucose level, is one indicator of glycemic variability measured by CGM. A %CV of 36% or greater corresponds to a relatively unstable glucose profile [11-13]. A *post hoc* analysis of the Intermittent-Scanning Continuous Glucose Monitoring to Glycemic Control Including Hypoglycemia and Quality of Life of Patients with Type 1 Diabetes Mellitus (ISCHIA) study, which investigated the association of %CV with clinical characteristics and CGM metrics, identified a discrimination threshold of approximately 40% to 42% for the risk of SH [14].

Recently, Kwon et al. [15] reported data from a large Korean cohort, comprising 1,185 adults with T1DM (n=196, 16.5%) and T2DM, who underwent professional CGM in an outpatient setting, to explore the predictive values of plasma C-peptide levels in comparison with the well-established predictor, CGM-defined CV, for hypoglycemia risk. The study conducted a receiver operating characteristic analysis of random C-peptide levels and CGM-defined CV for predicting a TBR (<70 mg/dL) greater than 4%. The optimal cut-off value for CGM-defined CV in T1DM was 36.0% (sensitivity, 87.0%; specificity, 72.5%; area under the curve [AUC], 0.89 [0.83–0.94]; P<0.001), and in T2DM, it was 30.6% (sensitivity, 87.0%; specificity, 72.5%; AUC, 0.82 [0.79–0.94]; P<0.001) [15]. In a subgroup analysis of participants with T1DM, the study confirmed that random C-peptide levels retained predictive value for a TBR (<54 mg/dL) greater than 1%. The optimal cut-off value for predicting a TBR (<54 mg/dL) greater than 1% in this group was 0.2 ng/mL, which was significantly lower than the corresponding value observed in participants with T2DM. Additionally, as CKD progressed, the researchers observed a negative correlation between plasma C-peptide levels and CGM-assessed CV, accompanied by a diminished predictive ability of plasma C-peptide levels for hypoglycemia. In contrast, the CGM-defined CV remained a reliable predictor of hypoglycemia across all stages of kidney function [15].

Indeed, hypoglycemia and glycemic variability—factors that HbA1c fails to capture—have been associated with adverse clinical outcomes in individuals with DM [16]. Current research demonstrates that combining various clinical factors yields a more accurate risk assessment than relying on a single parameter. CGM metrics such as TBR alone do not appear sufficiently accurate for predicting future episodes of hypoglycemia or SH. Therefore, it is recommended to combine TBR with other clinical measures—such as C-peptide levels in specific subgroups, traditional questionnaires for hypoglycemia detection, the updated Hypo A-Q awareness scale, or the %CV—in the absence of a singularly perfect measure [17,18].

CONFLICTS OF INTEREST

Seung-Hyun Ko is an executive editor of the journal. But she was not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

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