New risk factors of severe hypoglycemia

The number of elderly persons is increasing dramatically worldwide, especially in East Asia, and the average age of patients with diabetes has become older in this area. The quality of life of elderly patients with diabetes is easily impaired because of frailty and the development of physical disability. One of the major causes of these conditions is treatment-related severe hypoglycemia, which becomes a trigger for incidental falls, irreversible brain damage, cognitive dysfunction, cardiovascular events and fetal arrhythmia. Therefore, identifying the risk factors of severe hypoglycemia is critical for predicting and preventing severe hypoglycemia and its complications in individual patients. Various studies have investigated the risk factors for severe hypoglycemia, and have identified the type of diabetes, aging, sulfonylureas, insulin therapy, low glycated hemoglobin (HbA1c) values, long duration of diabetes and poor cognitive function as risk factors. A recent survey of the Japan Diabetes Society regarding treatment-related severe hypoglycemia confirmed that severe hypoglycemia was associated with old age, low glycated hemoglobin, medication of insulin and/or sulfonylureas, renal dysfunction, and a prior history of severe hypoglycemia in Japanese patients with type 2 diabetes[1].

Lee *et al.*[2] recently evaluated the risk factors for severe hypoglycemia in the Atherosclerosis Risk in Communities (ARIC) Study. The ARIC study is a prospective study that has been carried out since 1987–1989 in four USA communities. After 12 years of the study, 1,144 black and white individuals out of a total of 1,511 individuals who were diagnosed as diabetes or were taking diabetes medications were prospectively observed during a median follow-up period of 15.2 years. A total of 185 severe hypoglycemic events were identified through 2013 by International Classification of Diseases ninth revision codes from claims for hospitalization, emergency department visits and ambulance use. The Cox regression analysis showed that old age, black race, high fructosamine level, glucose-lowering medication, >300 mg/g urinary albumin excretion rate and poor cognitive function were identified as the isolated traditional risk factors of severe hypoglycemia. In addition to these factors, activities of daily living (ADLs) difficulty and the number of ADLs, but not instrumental ADLs (IADLs), were associated with severe hypoglycemia. As IADLs might be tightly associated with recognition function, the difficulty of IADLs was not solely determined as a risk factor of severe hypoglycemia after adjustment of cognitive function (Figure 1)[2].

The Atherosclerosis Risk in Communities study also showed that low 1,5-anhydroglucitol (1,5-AG) was a risk factor for severe hypoglycemia independent of average glucose levels (Figure 1)[2]. Hyperglycemia-induced increase of urinary glucose levels compete reabsorption of 1,5-AG via urinary tract and decrease serum 1,5-AG levels. Therefore, low 1,5-AG, a biomarker of glucose excursion, which reflects a long duration of high-glucose excursion, could be related to overtreatment for hyperglycemia and cause easily hypoglycemia. Indeed, higher HbA1c tended to be a risk factor for severe hyperglycemia, as well as lower HbA1c levels in type 2 diabetes patients[3]. The Diabetes Control and Complication Trial also reported that glucose variability determined from a standard deviation of a 7-point self-monitoring glucose measurement was associated with severe hypoglycemia in the intensive insulin treatment group for type 1 diabetes[4].

In 2016, the Japan Diabetes Society and the Japan Geriatrics Society recommended that the target level of glycemic control for elderly patients with diabetes should be changed from <7–8.5% according to the level of impaired cognitive function and difficulty of ADLs and IADLs with or without the use of insulin, sulfonylureas or glinides[5]. In addition, the lower limit of the target HbA1c level for these patients should range between 6.5 and 7.5% to prevent severe hypoglycemia. This recommendation was strongly confirmed by the results of the ARIC study and the Survey of Severe Hypoglycemia by the Japan Diabetes Society[1]. Therefore, the level of cognitive function and difficulty of ADLs should be evaluated routinely, and the target of glycemic goal should be decided according to these parameters and well-known traditional risks of severe hypoglycemia.

The recent development of oral glucose medications, insulin analogs and insulin devices could contribute to a decrease in severe hypoglycemia. Among these developments, a predictive low glucose management system, which stops the insulin delivery of a insulin pump if hypoglycemia is predicted within a certain period, has recently been reported to reduce severe hypoglycemia in patients with type 1 diabetes[6]. On the contrary, high-risk patients with diabetes for severe hypoglycemia are increasing because of increasing number of elderly patients with impaired recognition function, difficulty of ADL renal dysfunction, and polypharmacy. We, therefore, evaluate these risk factors totally and select anti-diabetic medications with lower risk for hypoglycemia in each patient.

In conclusion, the ARIC study showed that glucose fluctuations and the level of ADLs could be associated with the incidence of severe hypoglycemia, as well as traditional risk factors, such as aging, black race, averaged glucose level (fructosamine), diabetes medication, albumin-
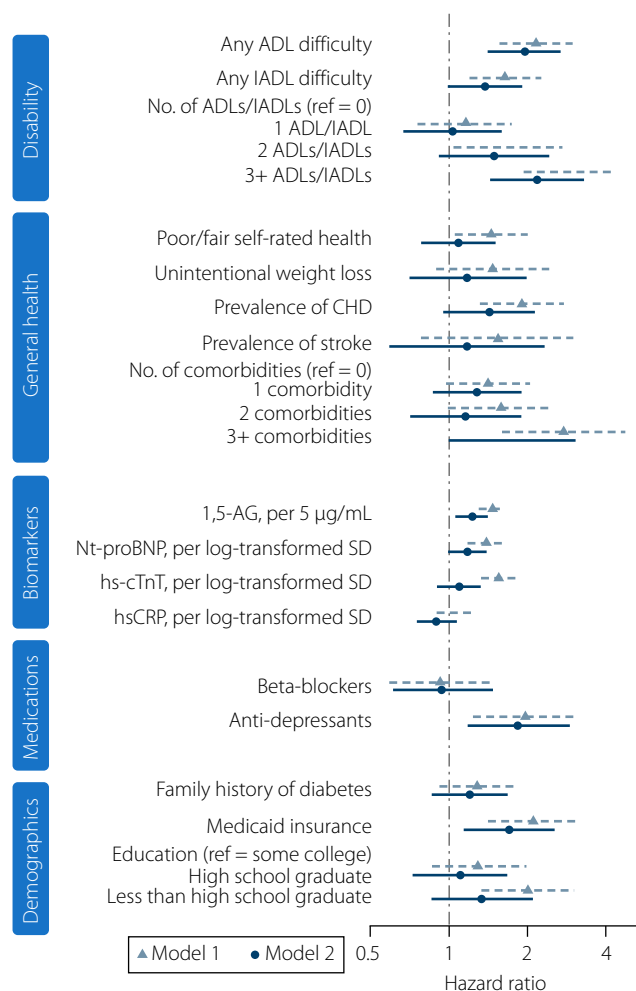
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Figure 1 | Adjusted hazard rations and 95% confidence intervals for non-traditional risk factors for hypoglycemia (*n* = 1,144; 169 people with hypoglycemia). Model 1 included age, sex and race. Model 2 included all variables in model 1 plus obesity, fructosamine, diabetes duration, diabetes medication, renal function and the albumin-to-creatinine ratio. 1.5-AG, 1,5-anhydroglucitol; ADL, activities of daily living; CHD, coronary heart disease; hsCRP, high-sensitive C-reactive protein; hs-cTnT, high-sensitivity cardiac troponin T; IADL, instrumental activities of daily living; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SD, standard deviation. Reproduced from the Atherosclerosis Risk in Communities (ARIC) study[2] with permission.

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to-creatinine ratio and cognitive function. These findings are very important for determining the target glucose level and to adequately select antidiabetic medication for individual elderly patients with type 2 diabetes.

DISCLOSURE