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Risk Factors and Adverse Outcomes of Severe Hypoglycemia in Type 2 Diabetes Mellitus

Jae-Seung Yun, Seung-Hyun Ko

Division of Endocrinology and Metabolism, Department of Internal Medicine, St. Vincent's Hospital, College of Medicine, The Catholic University of Korea, Suwon, Korea

Hypoglycemia has been considered as a major barrier to achieving the proper glycemic target in type 2 diabetes mellitus patients. In particular, severe hypoglycemia (SH), which is defined as a hypoglycemic episode requiring the assistance of another person to raise the patient's glucose level, is a serious complication of diabetes because of its possible fatal outcomes. Recently, the recommendations for diabetes care have emphasized a patient-centered approach, considering the individualized patient factors including hypoglycemia. Many studies have been performed which analyzed the risk factors and clinical outcomes for SH. From the studies, researchers recommend that targeting a less stringent glycosylated hemoglobin level and selecting a safer class of drugs for hypoglycemia are appropriate for patients with a high risk of SH. Also, careful clinical attention to prevent hypoglycemia, including intensive education, is necessary to minimize the risk of SH and SH-related fatal outcomes.

Keywords: Diabetes mellitus, type 2; Hypoglycemia; Risk factors

INTRODUCTION

Hypoglycemia is common and may have serious clinical consequences for diabetes treatment. Hypoglycemia is categorized as either mild or severe according to the severity of the episode and whether requiring external assistance or being self-limiting [1]. In particular, severe hypoglycemia (SH) causes a significant burden on patients, their care-giver, and medical staff [2]. Although the prevalence and incidence of SH are relatively low, several studies have reported that SH can cause serious adverse outcomes, such as seizure, coma, myocardial infarction, residual neurological impairment, or death [3].

Tight control of blood glucose level in type 2 diabetes mellitus (T2DM) has benefits of reducing the risk for developing diabetic complications [4]. However, large randomized clinical trials failed to demonstrate that intensive glycemic control targeting a glycosylated hemoglobin (HbA1c) level of less than 6.5% improved the cardiovascular outcomes, and some pa-

tients rather experienced SH episodes, which is expected to be associated with cardiovascular events and mortality [5-7]. In this regard, many clinical practice guidelines including the American Diabetes Association, the European Association for the Study of Diabetes, and Korean Diabetes Association recommend a patient-centered care for diabetes management with individualized glycemic target according to patient's condition, and emphasize to avoid the potential risks of hypoglycemia [8]. Like other diabetic complications, prevention is the best cure for SH, and recognition of associated risk factors is the first step.

In this review, we will discuss the main risk factors and adverse clinical outcomes of SH in T2DM.

RISK FACTORS OF SEVERE HYPOGLYCEMIA

Intensive glycemic control

Many clinical practice guidelines for patients with T2DM rec-

Corresponding author: Seung-Hyun Ko ⓘ http://orcid.org/0000-0003-3703-1479
Division of Endocrinology and Metabolism, Department of Internal Medicine, St. Vincent's Hospital, College of Medicine, The Catholic University of Korea, 93 Jungbu-daero, Paldal-gu, Suwon 16247, Korea
E-mail: kosh@catholic.ac.kr

ommend targeting an HbA1c level less than 6.5% to 7.0% [9,10]. Although tight glycemic control contributed to reducing diabetic microvascular complications, it also resulted in a higher burden of treatment, higher costs, more adverse drug reactions, and an increased risk of hypoglycemia episodes. The largest trial was Action to Control Cardiovascular Risk in Diabetes (ACCORD) which registered over 10,000 patients and randomized them to receive either intensive (target HbA1c <6.0%) or conventional (HbA1c, 7.0% to 7.9%) treatment [6]. The ACCORD trial showed that the intensive treatment group had a significantly higher incidence of SH (16.2% vs. 5.1% during 3.5 years). In the Action in Diabetes and Vascular Disease (ADVANCE) study, the duration of diabetes and baseline HbA1c of registered patients were higher compared with the patients in ACCORD. In this trial, SH also showed a higher incidence in the group with intensive treatment compared to the group with conventional treatment (2.7% vs. 1.5% during 5.0 years) [7]. In Veteran's Affairs Diabetes Trial (VADT), the incidence of SH in the intensive treatment group was two times higher than in the conventional treatment group (8.5% vs. 3.1% during 5.6 years) [5]. Kelly et al. [11] and Ray et al. [12] assessed the effect of differential glycemic control on SH from a meta-analysis including five large randomized controlled clinical trials (UK Prospective Diabetes Study [UKPDS], PROspective pioglitAzone Clinical Trial In macroVascular Events [PROactive], ADVANCE, VADT, and ACCORD) and showed that intensive compared with standard glycemic control increased to almost double the risk of SH. From the results of ACCORD, ADVANCE, and VADT trials, 'one-size-fits-all' strict glycemic target has not been recommended. Nevertheless, a recent large-scale retrospective study showed that 20% of United State patients with T2DM received unnecessary intensive treatment, and the risk probability of SH was doubled with the intensive treatment group compared with the conventional treatment group in patients with a high comorbidity burden [13]. They emphasized the danger of not only a failure to intensify treatment but also a failure to deescalate treatment in response to low HbA1c levels. These studies suggested that a practical clinical approach might be to reduce HbA1c steadily to avoid SH.

Antecedent hypoglycemia

The defective hormonal counter-regulatory response to hypoglycemia or failure to recognize the impending event of hypoglycemia is a well-known risk factor of SH [14,15]. Recurrent

hypoglycemia attenuates defenses against subsequent hypoglycemia and leads to hypoglycemia associated autonomic failure in patients with advanced T2DM. Here, recurrent hypoglycemia causes both defective glucose counter-regulation by attenuating the adrenomedullary epinephrine response, and hypoglycemia unawareness. Thus, hypoglycemia can trigger a vicious cycle of recurrent hypoglycemia. Quilliam et al. [16] suggested that a previous incidence of hypoglycemia was an independent predictor of SH in T2DM patients. In addition to traditional risk factors associated with hypoglycemia, they evaluated the increased rate of inpatient admission for SH after outpatient medical (odds ratio [OR], 7.88; 95% confidence interval [CI], 5.68 to 10.93) or emergency department visits (OR, 9.48; 95% CI, 4.95 to 18.15) for hypoglycemia in the previous 6 months. In another prospective cohort study, a history of SH was associated with a hazard ratio (HR) of 6.6 for subsequent SH episodes [17]. From our report, about 22.4% of patients with SH experienced previous hypoglycemic events within 3 months [18].

Most of these studies found that the association between antecedent hypoglycemia and SH showed that a prior history of hypoglycemia is one of the strongest predictors of all SH events [16,17,19]. The avoidance of hypoglycemia through careful management has been shown to reverse the defective glucose counter-regulatory hormone and hypoglycemia unawareness [20,21]. Therefore, strategic modulation of glycemic targets is a treatment option that should be considered in the month following an SH episode.

Renal impairment

Renal impairment is considered an independent risk factor of SH. The kidney has an important role in metabolizing circulating insulin, reabsorbing filtered glucose, contributing to gluconeogenesis, and excreting drugs and their metabolites with blood glucose lowering agents [22]. Therefore, kidney impairment reduces the ability to clear hypoglycemic agents, the degradation of insulin in peripheral tissues, gluconeogenesis, and insulin metabolism which can predispose a patient with chronic kidney disease (CKD) to hypoglycemia. In non-diabetic healthy people, the liver and kidney equally contribute to the increase in gluconeogenesis and glucose release into the circulation during the hypoglycemia [23,24]. However, the counter-regulatory response to hypoglycemia may be defected by impaired gluconeogenesis or a glycogen reserve deficiency caused by uremia-induced anorexia in patients with renal im-

pairment [25]. Also, CKD patients may be malnourished and experience muscle wasting, which decreases hepatic glycogen stores and the availability of gluconeogenic substrates. In the ACCORD trial, an albumin/creatinine ratio greater than 300 mg/g or a serum creatinine greater than 1.3 mg/dL was associated with a significantly increased risk of SH [26]. In AD-VANCE, for each μmol/L increase in serum creatinine, the risk of an SH event increased by 1% [27]. Davis et al. [17] suggested that the patients with estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 had a 3-fold increased risk of SH (HR, 2.90; 95% CI, 1.68 to 5.00; $P<0.001$). We also previously reported that the patients who had a macroalbuminuria level (urinary albumin excretion ≥300 mg/day) even with a normal eGFR level had an independently increased risk of SH with T2DM [19]. Not only decreased renal function but higher level of albumin excretion in patients with T2DM is needed to be paid attention for the development of SH.

Cognitive dysfunction

Hypoglycemia constitutes a threat to the overall health of the individual because the brain depends entirely on glucose as main metabolic energy source and rapidly malfunctions which causes neuroglycopenia [28]. Physiological defenses against a falling glucose concentration include behavior change via the central nervous system or its afferent or efferent connection, such as carbohydrate ingestion prompted by neurogenic symptoms. Due to this normal neurological response, hypoglycemia is overcome appropriately.

With increased number of old patients with advanced T2DM, people with T2DM accompanied by cognitive dysfunction become increase [29]. Moreover, the prevalence of dementia (Alzheimer or vascular dementia) has been reported higher in T2DM than that of general population [30]. Impaired cognitive function underlies much of the immediate morbidity associated with hypoglycemia [28]. Impaired cognitive function promotes erratic and irrational behavior, induces confusion and affects vision and balance, which can result in falls and accidents, and sometimes has more serious neurological consequences.

Cognitive dysfunction was evaluated as a risk factor for SH. In a *post hoc* analysis of the ACCORD trial (ACCORD-MIND), poor cognitive function (measured by Digit Symbol Substitution Test) increases the risk of SH (HR, 1.13; 95% CI, 1.08 to 1.18) in patients with T2DM [31]. In ADVANCE, severe, but not mild, cognitive dysfunction (measured by the Mini Mental

Status Examination) increased the risk of SH (HR, 2.10; 95% CI, 1.14 to 3.87) [29]. The relationship between cognitive status and SH was not different between the intensive and conventional treatment group in both trials [29,31]. To prevent hypoglycemia, intact cognitive function to regulate activity levels and dietary pattern, recognizing symptoms and responsiveness related with glycemic levels, predicting situations in which hypoglycemia may occur, and initiating appropriate mitigating actions are essential [32]. This is a demanding process that could cause greater difficulties for patients with severe cognitive impairment. These studies suggest that cognitive function should be evaluated when managing people with diabetes, and that for people in the lower range of cognitive function, health care providers should pay attention to the patients to prevent SH.

Others

Age and the duration of diabetes are probably significant predictors for development of SH in those with T2DM. In the ACCORD study, the incidence of SH increased with age (HR, 1.03; 95% CI, 1.03 to 1.07) and duration (<5 years vs. ≥16 years; HR, 1.37; 95% CI, 1.09 to 1.73). In the Hong Kong Diabetes Registry, a 10-year increase in age was associated with a 2-fold higher risk of SH (HR, 1.92; 95% CI, 1.68 to 2.20) [33]. Previous reports suggested that the SH risk rose with a longer duration of insulin treatment [34-36]. These results supported that with advancing β-cell failure, people with long duration of T2DM progressively resemble those with type 1 diabetes mellitus in terms of the increased risk of hypoglycemia. Although the results of the association between body mass index (BMI) and hypoglycemia shown by previous studies are still controversial [17], several studies suggested that lower BMI was associated with an increased risk of SH [26,27,33]. Low BMI can represent the state of catabolism and malnutrition. Also, a linear correlation between BMI and β-cell mass has been reported in those with T2DM [37]. Thus, lower BMI patients can be vulnerable to hypoglycemic events. The studies reporting risk factors of SH are summarized in Table 1.

ADVERSE OUTCOMES OF SEVERE HYPOGLYCEMIA

SH and mortality

It has been reported that the patients with T2DM who had experienced SH showed an increased risk of mortality. In a 5-year follow-up study of the ADVANCE study, the mortality rate was

Table 1. Previous studies reporting risk factors of severe hypoglycemia

Study	Characteristic	Main finding

ACCORD (2010) [26]	Randomized controlled trial
	Follow-up duration: 3.5 years
	10,251 Participants with established cardiovascular disease or additional cardiovascular risk factors
		Total incidence of SH
		  Standard treatment: 3.5%; intensive treatment: 10.6%
		Hazard ratio (95% CI) for SH
		  Age (per 1 yr increase): 1.03 (1.02–1.05)
		  Diabetes duration (yr) ≤5 vs. >16: 1.37 (1.09–1.73)
		  Body mass index (kg/m^2) <25 vs. ≥ 30: 0.65 (0.50–0.85)
		  Albumin to creatinine ratio <30 vs. >300: 1.74 (1.37–2.21)
		  Serum creatinine (mg/dL) <1.0 vs. >1.3: 1.66 (1.25–2.19)

ADVANCE (2010) [27]	Randomized controlled trial
	Follow-up duration: 5.0 years
	11,140 Participants with a history of major macro-, or microvascular disease, or at least one other cardiovascular risk factors
		Total incidence of SH
		  Standard treatment: 1.5%; intensive treatment: 2.7%
		Hazard ratio (95% CI) for SH
		  Intensive treatment vs. standard treatment: 1.86 (1.40–2.40)
		  Age (yr): 1.05 (1.03–1.07)
		  Diabetes duration (yr): 1.02 (1.00–1.04)
		  Body mass index (kg/m^2): 0.95 (0.93–0.98)
		  Serum creatinine (μmol/L): 1.01 (1.00–1.01)
		  MMSE (per 1/30): 0.93 (0.87–0.99)

VADT (2009) [5]	Randomized controlled trial Follow-up duration: 5.6 years 1,791 Participants	Total incidence of SH Standard treatment: 3.1%; intensive treatment: 8.5%
Ray et al. (2009) [12]	Meta-analysis 5 Prospective RCT of 33,404 participants	Weighted averages of SH Standard treatment: 1.2%; intensive treatment: 2.3%

Kelly et al. (2009) [11]	Meta-analysis
	5 Prospective RCT of 27,802 participants
		Total incidence of SH
		  Standard treatment: 3.0%; intensive treatment: 8.1%
		Pooled RR for SH (95% CI)
		  Pooled RR: 2.03 (1.46–2.48)

Quilliam et al. (2011) [16]	Nested case-control study
	1,339 Cases and 13,390 controls
		Odds ratio for SH (95% CI)
		  Previous outpatient visit: 7.88 (5.68–10.93)
		  Previous emergency department visits: 9.48 (4.95–18.15)

Davis et al. (2010) [17]	Prospective study of 616 participants
	Follow-up duration: 6.4 years
		Multivariable hazard ratio (95% CI) for SH
		  History of SH: 5.66 (2.21–14.50)
		  eGFR <60 mL/min/1.73 m^2: 2.37 (1.37–4.15)

Miller et al. (2001) [19]	Cross sectional study
	1,055 Participants
		Odds ratio for hypoglycemia (95% CI)
		  Age (yr): 0.98 (0.97–1.00)
		  HbA1c at follow-up visit (per 1% increase): 0.87 (0.78–0.96)
		  Had hypoglycemia at baseline: 2.65 (1.80–3.80)

McCoy et al. (2016) [13]	Retrospective analysis 31,542 Patients with type 2 diabetes who achieved and maintained a HbA1c level less than 7.0%	Odds ratio for SH (95% CI) High clinical complexity and intensive treatment vs. low clinical complexity and standard treatment: 3.05 (1.99–4.67)

Punthakee et al. (2012) [31]	Randomized controlled trial
	Follow-up duration: 3.5 years
	2,956 Participants from ACCORD trial
		Hazard ratio (95% CI) for SH
		  DSST score lowest tertile vs. highest tertile: 1.13 (1.08–1.18)
		  MMSE score (decrease per 1/30 unit): 1.09 (1.03–1.15)

Kong et al. (2014) [33]	Prospective cohort study
	10,129 Participants from Hong Kong Diabetes Registry
		Hazard ratio (95% CI) for SH
		  Age (per 10 yr): 1.92 (1.68–2.20)
		  Body mass index (kg/m^2): 0.96 (0.93–0.99)
		  HbA1c (per 1%): 1.21 (1.13–1.29)
		  Chronic kidney disease: 1.91 (1.36–2.69)

ACCORD, Action to Control Cardiovascular Risk in Diabetes; SH, severe hypoglycemia; CI, confidence interval; ADVANCE, Action in Diabetes and Vascular Disease; MMSE, mini-mental state examination; VADT, Veteran's Affairs Diabetes Trial; RCT, randomized clinical trial; RR, relative risk; eGFR, estimated glomerular filtration rate; HbA1c, glycosylated hemoglobin; DSST, digital symbol substitution test.

19.5% in those who had experienced at least one episode of SH and 9.0% in those who had not (HR, 3.27; 95% CI, 2.29 to 4.65) [27]. Similarly, in retrospective epidemiological analyses from the ACCORD study, the mortality rates in participants who experienced at least one SH were also greater than those who had not experienced any episodes of SH across both study arms (HR, 1.41; 95% CI, 1.03 to 1.93) [38]. In VADT, a recent SH event was the strongest independent predictor of death at 90 days [39]. In the Outcome Reduction with an Initial Glargine Intervention (ORIGIN) trial, the incidence of all-cause mortality, cardiovascular mortality, and arrhythmic death in patients who had SH episodes was significantly higher than the incidence in people without SH during the median follow-up of about 6 years [40]. In a recent study from the Hong Kong Diabetes Registry, patients with SH had a three-fold higher incidence rate of mortality [33]. We also analyzed the prospective data from the hospital-based cohort for 10 years and reported that the experience of SH significantly increased the risk of all-cause mortality (HR, 2.64; 95% CI, 1.39 to 5.02) and cardiovascular mortality (HR, 6.34; 95% CI, 2.02 to 19.87) [41]. A possible potential mechanism of increased mortality during the SH event is considered to be mainly associated with cardiovascular complications. For example, it is possible that the association between SH and death may be related to increased risk of dysrhythmia, thrombogenesis, inflammation, and vasoconstriction [27].

Although the association of SH and increased mortality was reported consistently, a direct causal relationship and interaction with SH, intensive treatment, and mortality cannot be established with certainty. In both the ACCORD and ADVANCE studies, mortality in patients who experienced SH was higher in the group with conventional treatment than in the group with intensive treatment [27,38]. Also, recurrent hypoglycemia in the intensive treatment group did not associate with an increased risk of mortality [27]. There was no interaction between SH, treatment intensity, and mortality. It is possible that SH reflects the effects of health status or coexisting disease and relates unmeasured confounding factors to enhance mortality in an indirect way [27]. More delicate and longer-term studies are needed to clarify the relationship between intensive treatment, SH, and mortality.

SH and cardiovascular disease

There are several cardiovascular responses during hypoglycemia. Sympathoadrenal activation generates the release of a large amount of catecholamines, and in combination with sympathetic neural activation, hemodynamic changes affect a marker influence on the cardiovascular system [14,42]. Increased heart rate, changes in systolic and diastolic blood pressure, increased myocardial contractility, and changes in vascular elasticity related to hypoglycemia result in increased heart loading and interfere with coronary perfusion, especially in patients who have already had cardiovascular disease [43]. In addition, a previous report suggested that insulin-induced hypoglycemia provoked ischemic change in T2DM [44]. Catecholamine, other peptides including endothelin, or hormones which are released during hypoglycemia promote blood viscosity, platelet activation, and cell adhesion cause endothelial dysfunction, inflammation, and atherogenesis [45].

Hypoglycemia can affect cardiac repolarization, altered ST-segment and T-wave morphology and prolongation of the QT interval, which can be proarrhythmogenic [46,47]. Also, there is evidence to the fact that atrial, ventricular ectopic beats can be shown during asymptomatic hypoglycemia [44,48]. The report that ectopic beats were particularly prominent during the night when the participants were asleep is evidence to suggest that we take care of these patients to avoid hypoglycemia at night in patients undergoing diabetes care [49].

Clinical studies have shown the relationship between SH and cardiovascular disease. In the ADVANCE study, SH was associated with an increased risk of major macrovascular events (HR, 2.88; 95% CI, 1.19 to 4.19) [27]. In a systematic review and meta-analysis of cohort studies that included 903,510 patients with T2DM, SH was associated with a 2-fold increased risk of CVD [50]. Recent retrospective Japanese reports showed that SH was strongly associated with the risk of CVD (HR, 3.39; 95% CI, 1.25 to 9.18) and an additional updated meta-analysis from 10 studies also showed the same results (pooled relative risk [RR], 1.91; 95% CI, 1.69 to 2.15) [51]. However, it is unclear whether hypoglycemic adverse effects on the cardiovascular system persist [28]. It is also possible that SH reflects the effects of coexisting conditions and unmeasured or incompletely quantified confounding variables and is a marker of an increased risk of adverse clinical outcomes, rather than a direct cause [52].

SH and cognitive dysfunction

The status of chronic hyperglycemia is associated with an increased risk of cognitive impairment [29]. Thus, cognitive dysfunction or dementia is one of the important clinical outcomes

in patients with T2DM. Although the mechanisms of progressive cognitive dysfunction in T2DM is probably multifactorial, hypoglycemic episodes may influence and provoke cognitive decline [53]. Studies on the relationship between hypoglycemia and dementia have been reported. However, the published results are inconsistent. One retrospective study showed that patients with single or multiple episodes had a stepwise increase in the risk of dementia (HR, 1.26; 95% CI, 1.10 to 1.49 in patients with one SH episode) (HR, 1.80; 95% CI, 1.37 to 2.36 in patients with two SH episodes) (HR, 1.94; 95% CI, 1.42

Table 2. Previous studies reporting adverse clinical outcomes of severe hypoglycemia

Study	Characteristic	Main finding
ACCORD (2010) [38]	Randomized controlled trial	Hazard ratio (95% CI) for mortality
	Follow-up duration: 3.5 years	SH group vs. non-SH: 1.41 (1.03–1.93)
	10,194 Participants with established cardiovascular disease or additional cardiovascular risk factors.	
ADVANCE (2010) [27]	Randomized controlled trial	Mortality rate
	Follow-up duration: 5.0 years	Non-SH group: 9.0%; SH group: 19.5%
	11,140 Participants with a history of major macro-, or microvascular disease, or at least one other cardiovascular risk factors	Hazard ratio (95% CI) for mortality SH group vs. non-SH group: 3.27 (2.29–4.65) Hazard ratio (95% CI) for macrovascular events
		SH group vs. non-SH group: 2.88 (1.19–4.19)
ORIGIN (2013) [40]	Randomized controlled trial	Hazard ratio (95% CI) for mortality
	Follow-up duration: 6.2 years	SH group vs. non-SH group: 1.74 (1.39–2.19)
	12,537 Participants with dysglycemia and high cardiovascular risk	Hazard ratio (95% CI) for cardiovascular mortality
		SH group vs. non-SH group: 1.71 (1.27–2.30)
		Hazard ratio (95% CI) for arrhythmic death
		SH group vs. non-SH group: 1.77 (1.17–2.67)
Kong et al. (2014) [33]	Prospective cohort study	Mortality rate
	10,129 Participants from Hong Kong Diabetes Registry	Non-SH group: 11.2%; SH group: 32.8%
Cha et al. (2016) [41]	Prospective cohort study	Hazard ratio (95% CI) for mortality
	Follow-up duration: 10.4 years	SH group vs. non-SH group: 2.64 (1.39–5.02)
	1,260 Participants	Hazard ratio (95% CI) for cardiovascular mortality
		SH group vs. non-SH group: 6.34 (2.02–19.87)
Goto et al. (2016) [51]	Retrospective cohort study	Hazard ratio (95% CI) for cardiovascular disease
	Follow-up duration: 2.3 years	SH group vs. non-SH group: 3.39 (1.25–9.18)
	58,223 Participants	
Goto et al. (2016) [51]	Meta-analysis	Pooled RR for cardiovascular disease (95% CI)
	10 Studies of 985,758 participants	Pooled RR: 1.91 (1.69–2.15)
Whitmer et al. (2009) [54]	Retrospective cohort study	Hazard ratio (95% CI) for dementia
	Follow-up duration: 4.8 years	1 Episode of SH group vs. non-SH group: 1.26 (1.10–1.49)
	16,667 Participants	2 Episodes of SH group vs. non-SH group: 1.80 (1.37–2.36)
		3 Or more episodes of SH group vs. non-SH group: 1.94 (1.42–2.64)
Lu et al. (2016) [58]	Prospective cohort study	Hazard ratio (95% CI) for falls
	Follow-up duration: 7.3 years	SH group vs. non-SH group: 1.57 (1.47–1.67)
	93,147 Participants (31,049 SH group, 31,049 non-SH group, 31,049 non-diabetes group)	

ACCORD, Action to Control Cardiovascular Risk in Diabetes; CI, confidence interval; SH, severe hypoglycemia; ADVANCE, Action in Diabetes and Vascular Disease; ORIGIN, Outcome Reduction with an Initial Glargine Intervention; RR, relative risk.

to 2.64 in patients with three or more SH episodes) [54]. Another prospective study (The Edinburgh Type 2 Diabetes Study) showed that both a history of hypoglycemia (adjusted OR, 2.04; 95% CI, 1.25 to 3.31) and incident hypoglycemia (adjusted OR, 2.45; 95% CI, 1.37 to 4.39) during the study were associated with greater cognitive decline during follow-up. The Taiwanese nationwide random sampling cohort study showed that the adjusted RR for dementia was 1.60 (95% CI, 1.19 to 2.14) in subjects with hypoglycemia compared to those without hypoglycemia [55].

SH can result in neurological sequelae, which may accelerate the process of dementia. Animal studies found that SH led to necrosis of neurons in the hippocampus and cortical regions [56]. Recurrent hypoglycemia can cause synaptic dysfunction, even in the absence of neuronal death [57]. SH also increases blood viscosity, and thrombogenic effects by releasing the catecholamines and other hormonal factors that can affect vascular compromise in the brain [45]. In consequence, SH induces focal neurological deficit and transient ischemic attacks, which may result in neuronal cell death [55].

Others

Previous studies reported the risk for fall and for fall-related injury among patients who experienced SH. In a Taiwanese cohort study, the adjusted HR was 1.57 for diabetes with a history of SH as compared to those without [58]. Another study reported an elevated risk of fall associated with a history of hypoglycemia (adjusted HR, 1.36; 95% CI, 1.13 to 1.65) [59]. In addition, the anxiety and depression presented in patients with hypoglycemia has been noted previously [60]. Frequent blood glucose testing, fear of hypoglycemia, and concern about driving or sleeping makes for a lower quality of life in patients who have experienced an SH event. The studies reporting adverse clinical outcomes of SH are summarized in Table 2.

CONCLUSIONS

Hypoglycemia reduces the quality of life, raises medical costs, and sometimes can lead to fatal outcomes. Thus, identifying the risk factors to prevent SH is a critical issue in T2DM. Healthcare providers should recognize the importance of identifying the patients' risk factors. In order to minimize the adverse consequences of SH, high-risk patients with SH should receive an individualized glycemic target, safer drugs for hypoglycemia, and intensive education about hypoglycemia.

CONFLICTS OF INTEREST

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

REFERENCES

1. Workgroup on Hypoglycemia, American Diabetes Association. Defining and reporting hypoglycemia in diabetes: a report from the American Diabetes Association Workgroup on Hypoglycemia. Diabetes Care 2005;28:1245-9.

2. Fidler C, Elmelund Christensen T, Gillard S. Hypoglycemia: an overview of fear of hypoglycemia, quality-of-life, and impact on costs. J Med Econ 2011;14:646-55.

3. Cox DJ, Kovatchev B, Vandecar K, Gonder-Frederick L, Ritterband L, Clarke W. Hypoglycemia preceding fatal car collisions. Diabetes Care 2006;29:467-8.

4. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352:837-53.

5. Duckworth W, Abraira C, Moritz T, Reda D, Emanuele N, Reaven PD, Zieve FJ, Marks J, Davis SN, Hayward R, Warren SR, Goldman S, McCarren M, Vitek ME, Henderson WG, Huang GD; VADT Investigators. Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med 2009;360:129-39.

6. Action to Control Cardiovascular Risk in Diabetes Study Group, Gerstein HC, Miller ME, Byington RP, Goff DC Jr, Bigger JT, Buse JB, Cushman WC, Genuth S, Ismail-Beigi F, Grimm RH Jr, Probstfield JL, Simons-Morton DG, Friedewald WT. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 2008;358:2545-59.

7. ADVANCE Collaborative Group, Patel A, MacMahon S, Chalmers J, Neal B, Billot L, Woodward M, Marre M, Cooper M, Glasziou P, Grobbee D, Hamet P, Harrap S, Heller S, Liu L, Mancia G, Mogensen CE, Pan C, Poulter N, Rodgers A, Williams B, Bompoint S, de Galan BE, Joshi R, Travert F. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 2008;358:2560-72.

8. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, Peters AL, Tsapas A, Wender R, Matthews DR; American Diabetes Association (ADA); European Association for the Study of Diabetes (EASD). Management of hyperglyce-

mia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2012;35:1364-79.

9. Korean Diabetes Association. Treatment guideline for diabetes. 5th ed. Seoul: Gold Planning and Development; 2015.

10. American Diabetes Association. Standards of medical care in diabetes: 2016. Diabetes Care 2016;39(Suppl 1):S1-106.

11. Kelly TN, Bazzano LA, Fonseca VA, Thethi TK, Reynolds K, He J. Systematic review: glucose control and cardiovascular disease in type 2 diabetes. Ann Intern Med 2009;151:394-403.

12. Ray KK, Seshasai SR, Wijesuriya S, Sivakumaran R, Nethercott S, Preiss D, Erqou S, Sattar N. Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus: a meta-analysis of randomised controlled trials. Lancet 2009;373:1765-72.

13. McCoy RG, Lipska KJ, Yao X, Ross JS, Montori VM, Shah ND. Intensive treatment and severe hypoglycemia among adults with type 2 diabetes. JAMA Intern Med 2016;176:969-78.

14. Cryer PE. Mechanisms of hypoglycemia-associated autonomic failure in diabetes. N Engl J Med 2013;369:362-72.

15. Yun JS, Ko SH. Avoiding or coping with severe hypoglycemia in patients with type 2 diabetes. Korean J Intern Med 2015;30:6-16.

16. Quilliam BJ, Simeone JC, Ozbay AB. Risk factors for hypoglycemia-related hospitalization in patients with type 2 diabetes: a nested case-control study. Clin Ther 2011;33:1781-91.

17. Davis TM, Brown SG, Jacobs IG, Bulsara M, Bruce DG, Davis WA. Determinants of severe hypoglycemia complicating type 2 diabetes: the Fremantle diabetes study. J Clin Endocrinol Metab 2010;95:2240-7.

18. Yun JS, Ko SH, Ko SH, Song KH, Ahn YB, Yoon KH, Park YM, Ko SH. Presence of macroalbuminuria predicts severe hypoglycemia in patients with type 2 diabetes: a 10-year follow-up study. Diabetes Care 2013;36:1283-9.

19. Miller CD, Phillips LS, Ziemer DC, Gallina DL, Cook CB, El-Kebbi IM. Hypoglycemia in patients with type 2 diabetes mellitus. Arch Intern Med 2001;161:1653-9.

20. Davis M, Mellman M, Friedman S, Chang CJ, Shamoon H. Recovery of epinephrine response but not hypoglycemic symptom threshold after intensive therapy in type 1 diabetes. Am J Med 1994;97:535-42.

21. Widom B, Simonson DC. Intermittent hypoglycemia impairs glucose counterregulation. Diabetes 1992;41:1597-602.

22. Gerich JE. Role of the kidney in normal glucose homeostasis and in the hyperglycaemia of diabetes mellitus: therapeutic implications. Diabet Med 2010;27:136-42.

23. Gerich JE. Lilly lecture 1988. Glucose counterregulation and its impact on diabetes mellitus. Diabetes 1988;37:1608-17.

24. Cersosimo E, Garlick P, Ferretti J. Renal substrate metabolism and gluconeogenesis during hypoglycemia in humans. Diabetes 2000;49:1186-93.

25. Weir MA, Gomes T, Mamdani M, Juurlink DN, Hackam DG, Mahon JL, Jain AK, Garg AX. Impaired renal function modifies the risk of severe hypoglycaemia among users of insulin but not glyburide: a population-based nested case-control study. Nephrol Dial Transplant 2011;26:1888-94.

26. Miller ME, Bonds DE, Gerstein HC, Seaquist ER, Bergenstal RM, Calles-Escandon J, Childress RD, Craven TE, Cuddihy RM, Dailey G, Feinglos MN, Ismail-Beigi F, Largay JF, O'Connor PJ, Paul T, Savage PJ, Schubart UK, Sood A, Genuth S; ACCORD Investigators. The effects of baseline characteristics, glycaemia treatment approach, and glycated haemoglobin concentration on the risk of severe hypoglycaemia: post hoc epidemiological analysis of the ACCORD study. BMJ 2010;340:b5444.

27. Zoungas S, Patel A, Chalmers J, de Galan BE, Li Q, Billot L, Woodward M, Ninomiya T, Neal B, MacMahon S, Grobbee DE, Kengne AP, Marre M, Heller S; ADVANCE Collaborative Group. Severe hypoglycemia and risks of vascular events and death. N Engl J Med 2010;363:1410-8.

28. Frier BM. Hypoglycaemia in diabetes mellitus: epidemiology and clinical implications. Nat Rev Endocrinol 2014;10:711-22.

29. de Galan BE, Zoungas S, Chalmers J, Anderson C, Dufouil C, Pillai A, Cooper M, Grobbee DE, Hackett M, Hamet P, Heller SR, Lisheng L, Macmahon S, Mancia G, Neal B, Pan CY, Patel A, Poulter N, Travert F, Woodward M; ADVANCE Collaborative Group. Cognitive function and risks of cardiovascular disease and hypoglycaemia in patients with type 2 diabetes: the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial. Diabetologia 2009;52:2328-36.

30. Cukierman-Yaffe T, Gerstein HC, Williamson JD, Lazar RM, Lovato L, Miller ME, Coker LH, Murray A, Sullivan MD, Marcovina SM, Launer LJ; Action to Control Cardiovascular Risk in Diabetes-Memory in Diabetes (ACCORD-MIND) Investigators. Relationship between baseline glycemic control and cognitive function in individuals with type 2 diabetes and other cardiovascular risk factors: the action to control cardiovascular risk in diabetes-memory in diabetes (ACCORD-MIND) trial. Diabetes Care 2009;32:221-6.

31. Punthakee Z, Miller ME, Launer LJ, Williamson JD, Lazar RM, Cukierman-Yaffee T, Seaquist ER, Ismail-Beigi F, Sullivan MD, Lovato LC, Bergenstal RM, Gerstein HC; ACCORD Group of Investigators; ACCORD-MIND Investigators. Poor cognitive function and risk of severe hypoglycemia in type 2 diabetes: post hoc epidemiologic analysis of the ACCORD trial. Diabetes Care 2012;35:787-93.

32. Cox DJ, Kovatchev B, Koev D, Koeva L, Dachev S, Tcharaktchiev D, Protopopova A, Gonder-Frederick L, Clarke W. Hypoglycemia anticipation, awareness and treatment training (HAATT) reduces occurrence of severe hypoglycemia among adults with type 1 diabetes mellitus. Int J Behav Med 2004;11: 212-8.

33. Kong AP, Yang X, Luk A, Ma RC, So WY, Ozaki R, Ting R, Cheung K, Ho CS, Chan MH, Chow CC, Chan JC. Severe hypoglycemia identifies vulnerable patients with type 2 diabetes at risk for premature death and all-site cancer: the Hong Kong diabetes registry. Diabetes Care 2014;37:1024-31.

34. UK Hypoglycaemia Study Group. Risk of hypoglycaemia in types 1 and 2 diabetes: effects of treatment modalities and their duration. Diabetologia 2007;50:1140-7.

35. Akram K, Pedersen-Bjergaard U, Carstensen B, Borch-Johnsen K, Thorsteinsson B. Frequency and risk factors of severe hypoglycaemia in insulin-treated type 2 diabetes: a cross-sectional survey. Diabet Med 2006;23:750-6.

36. Henderson JN, Allen KV, Deary IJ, Frier BM. Hypoglycaemia in insulin-treated type 2 diabetes: frequency, symptoms and impaired awareness. Diabet Med 2003;20:1016-21.

37. Yoon KH, Lee JH, Kim JW, Cho JH, Choi YH, Ko SH, Zimmet P, Son HY. Epidemic obesity and type 2 diabetes in Asia. Lancet 2006;368:1681-8.

38. Bonds DE, Miller ME, Bergenstal RM, Buse JB, Byington RP, Cutler JA, Dudl RJ, Ismail-Beigi F, Kimel AR, Hoogwerf B, Horowitz KR, Savage PJ, Seaquist ER, Simmons DL, Sivitz WI, Speril-Hillen JM, Sweeney ME. The association between symptomatic, severe hypoglycaemia and mortality in type 2 diabetes: retrospective epidemiological analysis of the ACCORD study. BMJ 2010;340:b4909.

39. Seaquist ER, Anderson J, Childs B, Cryer P, Dagogo-Jack S, Fish L, Heller SR, Rodriguez H, Rosenzweig J, Vigersky R. Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and the Endocrine Society. Diabetes Care 2013;36:1384-95.

40. ORIGIN Trial Investigators, Mellbin LG, Ryden L, Riddle MC, Probstfield J, Rosenstock J, Diaz R, Yusuf S, Gerstein HC. Does hypoglycaemia increase the risk of cardiovascular events? A report from the ORIGIN trial. Eur Heart J 2013;34:3137-44.

41. Cha SA, Yun JS, Lim TS, Hwang S, Yim EJ, Song KH, Yoo KD, Park YM, Ahn YB, Ko SH. Severe hypoglycemia and cardiovascular or all-cause mortality in patients with type 2 diabetes. Diabetes Metab J 2016;40:202-10.

42. McAulay V, Deary IJ, Frier BM. Symptoms of hypoglycaemia in people with diabetes. Diabet Med 2001;18:690-705.

43. Sommerfield AJ, Wilkinson IB, Webb DJ, Frier BM. Vessel wall stiffness in type 1 diabetes and the central hemodynamic effects of acute hypoglycemia. Am J Physiol Endocrinol Metab 2007;293:E1274-9.

44. Lindstrom T, Jorfeldt L, Tegler L, Arnqvist HJ. Hypoglycaemia and cardiac arrhythmias in patients with type 2 diabetes mellitus. Diabet Med 1992;9:536-41.

45. Wright RJ, Frier BM. Vascular disease and diabetes: is hypoglycaemia an aggravating factor? Diabetes Metab Res Rev 2008; 24:353-63.

46. Koivikko ML, Karsikas M, Salmela PI, Tapanainen JS, Ruokonen A, Seppanen T, Huikuri HV, Perkiomaki JS. Effects of controlled hypoglycaemia on cardiac repolarisation in patients with type 1 diabetes. Diabetologia 2008;51:426-35.

47. Robinson RT, Harris ND, Ireland RH, Lee S, Newman C, Heller SR. Mechanisms of abnormal cardiac repolarization during insulin-induced hypoglycemia. Diabetes 2003;52:1469-74.

48. Gill GV, Woodward A, Casson IF, Weston PJ. Cardiac arrhythmia and nocturnal hypoglycaemia in type 1 diabetes: the 'dead in bed' syndrome revisited. Diabetologia 2009;52:42-5.

49. Chow E, Bernjak A, Williams S, Fawdry RA, Hibbert S, Freeman J, Sheridan PJ, Heller SR. Risk of cardiac arrhythmias during hypoglycemia in patients with type 2 diabetes and cardiovascular risk. Diabetes 2014;63:1738-47.

50. Goto A, Arah OA, Goto M, Terauchi Y, Noda M. Severe hypoglycaemia and cardiovascular disease: systematic review and meta-analysis with bias analysis. BMJ 2013;347:f4533.

51. Goto A, Goto M, Terauchi Y, Yamaguchi N, Noda M. Association between severe hypoglycemia and cardiovascular disease risk in Japanese patients with type 2 diabetes. J Am Heart Assoc 2016;5:e002875.

52. MacMahon S, Collins R. Reliable assessment of the effects of treatment on mortality and major morbidity, II: observational studies. Lancet 2001;357:455-62.

53. Strachan MW, Reynolds RM, Marioni RE, Price JF. Cognitive function, dementia and type 2 diabetes mellitus in the elderly. Nat Rev Endocrinol 2011;7:108-14.

54. Whitmer RA, Karter AJ, Yaffe K, Quesenberry CP Jr, Selby JV. Hypoglycemic episodes and risk of dementia in older patients with type 2 diabetes mellitus. JAMA 2009;301:1565-72.

55. Lin CH, Sheu WH. Hypoglycaemic episodes and risk of dementia in diabetes mellitus: 7-year follow-up study. J Intern Med 2013;273:102-10.

56. Puente EC, Silverstein J, Bree AJ, Musikantow DR, Wozniak DF, Maloney S, Daphna-Iken D, Fisher SJ. Recurrent moderate hypoglycemia ameliorates brain damage and cognitive dysfunction induced by severe hypoglycemia. Diabetes 2010;59:1055-62.

57. Duning T, van den Heuvel I, Dickmann A, Volkert T, Wempe C, Reinholz J, Lohmann H, Freise H, Ellger B. Hypoglycemia aggravates critical illness-induced neurocognitive dysfunction. Diabetes Care 2010;33:639-44.

58. Lu CL, Shen HN, Hu SC, Wang JD, Li CY. A population-based study of all-cause mortality and cardiovascular disease in association with prior history of hypoglycemia among patients with type 1 diabetes. Diabetes Care 2016;39:1571-8.

59. Signorovitch JE, Macaulay D, Diener M, Yan Y, Wu EQ, Gruenberger JB, Frier BM. Hypoglycaemia and accident risk in people with type 2 diabetes mellitus treated with non-insulin antidiabetes drugs. Diabetes Obes Metab 2013;15:335-41.

60. Strachan MW, Deary IJ, Ewing FM, Frier BM. Recovery of cognitive function and mood after severe hypoglycemia in adults with insulin-treated diabetes. Diabetes Care 2000;23:305-12.