

Presence of Macroalbuminuria Predicts Severe Hypoglycemia in Patients With Type 2 Diabetes

A 10-year follow-up study

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OBJECTIVE—We investigated the factors that might influence the development of severe hypoglycemia in patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS—From January 2000 to December 2002, patients with type 2 diabetes aged 25–75 years without chronic kidney disease (estimated glomerular filtration rate ≥ 60 mL/min/1.73 m²) were consecutively recruited ($n = 1,217$) and followed-up in January 2011 and May 2012. Severe hypoglycemia (SH) was defined as an event requiring the assistance of another person to actively administer glucose, hospitalization, or medical care in an emergency department. We used Cox proportional hazard regression analysis to test the association between SH episodes and potential explanatory variables.

RESULTS—After a median 10.4 years of follow-up, 111 (12.6%) patients experienced 140 episodes of SH, and the incidence was 1.55 per 100 patient-years. Mean age and duration of diabetes were 55.3 ± 9.8 and 9.8 ± 6.5 years, respectively. The incidence of SH events was higher in older patients ($P < 0.001$), in those with a longer duration of diabetes ($P < 0.001$), in those who used insulin ($P < 0.001$) and sulfonylurea ($P = 0.003$), and in those who had macroalbuminuria ($P < 0.001$) at baseline. Cox hazard regression analysis revealed that SH was associated with longer duration of diabetes and the presence of macroalbuminuria (normoalbuminuria versus macroalbuminuria: hazard ratio, 2.52; 95% CI 1.31–4.84; $P = 0.006$).

CONCLUSIONS—The development of SH was independently associated with duration of diabetes and presence of macroalbuminuria, even with normal renal function in patients with type 2 diabetes.

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The importance of glycemic control in type 2 diabetes is well-recognized because strict glycemic control decreases the incidence and progression of diabetic microvascular and macrovascular complications (1–3). However, recent, large, prospective, clinical trials showing the clinical outcomes of intensive glucose-lowering treatment observed increased risk of severe hypoglycemia in patients with type 2 diabetes, and hypoglycemia is regarded as the main barrier to

achieving optimal glycemic targets in patients with type 2 diabetes (4–6).

During strict glycemic control, hypoglycemia is an inevitable clinical problem in both type 1 and type 2 diabetes, and all diabetic patients are exposed to the risk of hypoglycemia as long as they use glucose-lowering treatment. Hypoglycemia can impact patient quality of life, deter the pursuit of lowering blood glucose to the target range, and increase the risk of sustaining acute vascular events in

patients with comorbidities (7). The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial and the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) study have shown that intensive glucose control led to increases in macrovascular disease and cardiovascular events, although HbA_{1c} reached the target range, and hypoglycemia is supposed to contribute to the increased cardiovascular mortality in patients with type 2 diabetes (4,5). Therefore, prevention of hypoglycemic events and early detection of patients at high risk for hypoglycemia has important clinical implications in patients with diabetes.

The proportion of diabetic patients with development of severe hypoglycemia and the incidence of hypoglycemic episodes vary markedly between studies. Although most of the existing studies about severe hypoglycemia have been based on retrospective or cross-sectional data, hypoglycemic events in patients with type 2 diabetes are generally less frequent compared with those with type 1 diabetes (8). This finding suggests the relative preservation of β -cell function with counter-regulatory hormone responses and, consequently, a relatively lower prevalence of impaired hypoglycemia awareness in type 2 diabetes (8). With a steadily growing number of people with type 2 diabetes and increasing use of insulin or hypoglycemic agents for strict glycemic control, the number of cases of type 1 and type 2 diabetes with severe hypoglycemia have been increasing (9,10).

Irrespective of the type of diabetes or hypoglycemic treatment, risk factors for future development of hypoglycemic events in subjects with diabetes include advanced age, duration of diabetes, polypharmacy, history of previous hypoglycemia, and duration of insulin treatment (11). In addition, the presence of chronic kidney disease (CKD) is an important risk factor for the development of hypoglycemia (12). However, the association of the

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presence of albuminuria with future development of severe hypoglycemia in type 2 diabetic patients without CKD is not known.

In this 10-year, prospective, longitudinal cohort study, we investigated the incidence and predisposing factors related to the development of severe hypoglycemic episodes among patients with type 2 diabetes, especially in those who had normal renal function.

RESEARCH DESIGN AND

METHODS—From January 2000 to December 2002, patients with type 2 diabetes aged 25–75 years were consecutively recruited and received follow-up from January 2011 to May 2012 at the University-affiliated Diabetes Center of St. Vincent's Hospital in South Korea. Patients were excluded if they were older than age 75 years, were mentally ill, were unable to undertake self-care behaviors, or had any severe illness, such as malignancy, severe infection, liver cirrhosis, or heart failure. Type 2 diabetic subjects who had impaired renal function [estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m²] also were excluded. This prospective cohort study was approved by the Catholic Medical Center Ethics Committee and conducted in accordance with the Declaration of Helsinki. All of participants provided signed written informed consent.

At the beginning of the study, patient height, body weight, and systolic and diastolic blood pressures were measured. Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or any use of antihypertensive medications (13). Diabetes treatment was categorized as using insulin, an oral agent (sulfonylurea, nonsulfonylurea), insulin added to an oral agent (sulfonylurea, nonsulfonylurea), or lifestyle modification alone.

Severe hypoglycemia was defined as hypoglycemia episodes requiring the assistance of another person to actively administer carbohydrate, other resuscitative actions, hospitalization, or medical care in an emergency department (14). We also included any episodes of severe hypoglycemia treated at home or in the workplace by family members or friends. We evaluated onset time, the main presenting symptoms of hypoglycemia, blood glucose (if recorded), and antecedent hypoglycemia during the past 3 months (including documented symptomatic hypoglycemia, asymptomatic

hypoglycemia, and probable symptomatic hypoglycemia). To identify predisposing factors related to severe hypoglycemia, we also evaluated the most plausible cause for each event based on the following options: missed meal; excessive activity; recent increase in insulin or oral hypoglycemic agent (within 2 weeks); concurrent illness; severe alcohol intoxication; or unknown cause (15). Death related to severe hypoglycemia was defined as death in which a low plasma glucose level had been identified in the emergency department and all other potential causes of death, e.g., infection, malignancy, pulmonary, suicide, or cardio-cerebrovascular events, had been excluded. We also included those patients in the severe hypoglycemia group.

All of the participants were followed-up every 3–6 months on an outpatient basis. When the patients visited the outpatient clinic, the physician asked whether they had experienced severe hypoglycemic episodes or visited an emergency department because of severe hypoglycemia. If a patient did not visit our clinic for any reason, then the diabetes education nurse tried to contact the patients by telephone or electronic mail to evaluate the occurrence of severe hypoglycemia. We also investigated severe hypoglycemic events of participants in our own emergency department every day.

Fasting and postprandial plasma glucose were measured using an automated enzymatic method, and HbA_{1c} was measured by high-performance liquid chromatography with a reference range of 4.4–6.4% (Bio-Rad, Montreal, Quebec, Canada). HbA_{1c} was measured every 6 months to evaluate the status of glycemic control during the follow-up period. Total cholesterol, triglycerides, and HDL cholesterol were measured enzymatically using an automatic analyzer (model 736–40; Hitachi, Tokyo, Japan). Fasting C-peptide was measured using a chemiluminescence immunoassay.

The eGFR was used to determine CKD classification using the four-component Modification of Diet in Renal Disease equation (16). A simple urine dipstick test was used to screen for the presence of albuminuria. If the test for proteinuria was trace-positive or positive, then a quantitative macroalbuminuria test (24-h urine collection) was performed. If the dipstick test for proteinuria was negative, then a qualitative microalbuminuria test involving a spot urine sample was recommended. If the qualitative test was positive, then a

24-h urine collection sample was indicated to screen for microalbuminuria (17,18). The urinary albumin excretion (UAE) rate was measured from a 24-h urine collection using immunoturbidimetry (Eiken, Tokyo, Japan). Patients were classified into three groups by the standard diagnosis of diabetic nephropathy at enrollment: those with no diabetic nephropathy (UAE <30 mg/day); those with microalbuminuria defined as a UAE of 30–300 mg/day; and those with macroalbuminuria with UAE ≥300 mg/day (17,19). Patients who had undergone intense exercise within 24 h or had an infection, fever, congestive heart failure, or marked hypertension, all of which may elevate UAE over baseline values, were excluded.

Diabetic retinopathy was assessed from retinal photographs at baseline and the findings were reviewed by one ophthalmologist. Diabetic retinopathy was classified as the absence of diabetic retinopathy and the presence of diabetic retinopathy. Diabetic nephropathy was considered if patients with microalbuminuria or macroalbuminuria showed diabetic retinopathy (20).

Statistical analyses

All results are expressed as the mean ± SD, median (25th–75th percentiles), or proportions. χ^2 tests were used to test differences in the proportion of categorical variables, and independent Student *t* tests were used for evaluating the difference between the mean of two continuous variables. For parameters showing abnormal distributions, Wilcoxon rank sum test was performed. We used Cox proportional hazard regression analysis to test associations between the outcome (severe hypoglycemia episodes) and potential explanatory variables. The relationships were analyzed after adjustment for the following risk factors: sex; age; duration of diabetes; presence of hypertension; diabetic nephropathy; mean HbA_{1c} throughout the study; and use of insulin or sulfonylurea. The results are given as hazard ratios and 95% CIs. Statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC). *P* < 0.05 was considered significant.

RESULTS—Of the 1,271 patients who were enrolled in this study, 878 (69.1%) completed the follow-up evaluation (Fig. 1). The baseline characteristics of the subjects who completed follow-up are shown in Table 1. The total study population

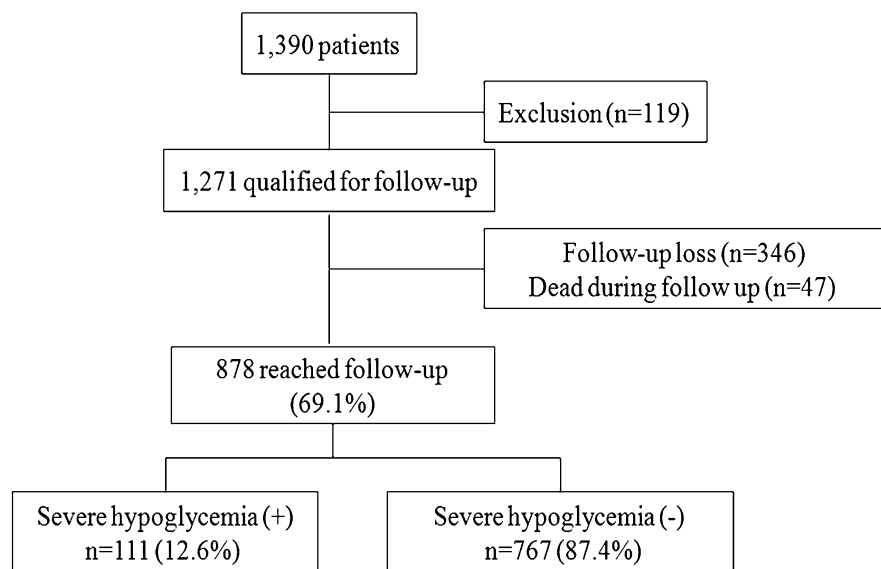


Figure 1—Study design summarizing sample recruitment and follow-up.

consisted of 334 men (38.0%) and 544 women (62.0%) with a mean age of 55.3 ± 9.8 years and a mean duration of diabetes of 9.8 ± 6.5 years. At the beginning of the study, 250 (28.5%) patients were using insulin therapy, 657 (74.8%) were using an oral hypoglycemia agent, and 539 (61.4%) were receiving sulfonylurea treatment. The median follow-up time was 10.4 years. During the follow-up period, 111 patients (12.6%) experienced a total of 140 severe hypoglycemic episodes, for an incidence of 1.55 per 100 patient-years. The mean time from the enrollment date to the occurrence of the first severe hypoglycemic episode was 92.2 ± 34.6 months. The 878 participants who completed the follow-up evaluation did not differ from the 393 patients who did not complete follow-up, with respect to age (55.3 ± 9.8 vs. 56.5 ± 10.7 years; $P = 0.065$), sex ratio ($P = 0.464$), or duration of diabetes (9.8 ± 6.5 vs. 9.3 ± 7.2 years; $P = 0.287$), but had higher rates of hypertension ($P < 0.001$) and low HbA_{1c} ($8.8 \pm 2.0\%$ vs. $9.3 \pm 2.2\%$; $P = 0.001$). During follow-up, five patients (0.6%) died related to severe hypoglycemia.

There were no differences in the sex ratio, BMI, and presence of hypertension between the patients with and without severe hypoglycemia. However, the patients with severe hypoglycemia were older ($P < 0.001$), had a longer duration of diabetes ($P < 0.001$), and showed higher frequencies of diabetic nephropathy ($P < 0.001$) and diabetic retinopathy ($P < 0.001$) than the patients

without severe hypoglycemia at baseline. Moreover, the patients with severe hypoglycemia had significantly higher albuminuria than the patients without severe hypoglycemia. However, there were no differences in baseline fasting and postprandial glucose, creatinine level, eGFR, HbA_{1c}, lipid profile, or fasting C-peptide level between the two groups (Table 1).

Blood glucose at the hypoglycemia event was 40.1 ± 12.2 mg/dL and mean HbA_{1c} within 3 months from the hypoglycemic event was $7.3 \pm 1.0\%$. The main presenting symptoms of severe hypoglycemia were coma or stupor (49.1%), general weakness (26.8%), inappropriate behavior (10.2%), and seizure (1.9%). Presumptive attributed causes of severe hypoglycemia events were missed meals (41.5%), recent increase in medications (14.4%), concurrent illness (15.3%), increased activity (7.2%), alcohol abuse (4.5%), and unknown cause (17.1%). Hypoglycemia most frequently occurred in the morning (6:00 A.M.–11:00 A.M.; 54.3%). In addition, 60.0% and 37.3% of patients with severe hypoglycemia used insulin and sulfonylurea at the event, respectively. In particular, 24 (22.4%) patients with severe hypoglycemia experienced at least one event of antecedent hypoglycemia within the preceding 3 months, and 21 (18.9%) patients with severe hypoglycemia experienced severe hypoglycemia previously.

There were no significant differences in insulin dose by weight (0.56 ± 0.4 IU/kg vs. 0.42 ± 0.4 IU/kg; $P = 0.242$) or the frequency of sulfonylurea use

(23.0% vs. 41.8%; $P = 0.270$) at the severe hypoglycemic event between the groups with and without macroalbuminuria. The use of insulin at the time of the severe hypoglycemic event was higher in patients with macroalbuminuria than in those without macroalbuminuria (84.6% vs. 60.4%; $P = 0.049$). However, there were no significant differences in the mean HbA_{1c} level from the start of the study to the hypoglycemic event ($8.13 \pm 1.4\%$ vs. $8.28 \pm 1.4\%$; $P = 0.190$) or in HbA_{1c} levels during the 3 months before the severe hypoglycemic event ($7.38 \pm 2.3\%$ vs. $7.82 \pm 1.6\%$; $P = 0.168$) between the groups with and without macroalbuminuria. In addition, no statistically significant changes in insulin (30.0% vs. 17.3%; $P = 0.062$) or sulfonylurea use (7.5% vs. 9.6%; $P = 0.730$) from the time of enrollment to the end point were observed between the groups with and without macroalbuminuria.

Cox hazard regression analysis revealed that longer duration of diabetes (hazard ratio, 1.04; 95% CI, 1.01–1.07; $P = 0.017$) and the presence of macroalbuminuria at baseline (normoalbuminuria versus macroalbuminuria: hazard ratio, 2.52; 95% CI, 1.31–4.84; $P = 0.006$) conferred significantly higher risk of severe hypoglycemia after adjustment for baseline age, sex, presence of hypertension, duration of diabetes, presence of diabetic nephropathy, mean HbA_{1c}, use of insulin or sulfonylurea, use of ACE inhibitors or angiotensin receptor blockers, and the eGFR. Age also predicted the occurrence of severe hypoglycemia (Fig. 2 and Table 2).

CONCLUSIONS—In this prospective, longitudinal cohort study designed to investigate contributing factors to the development of severe hypoglycemia in patients with type 2 diabetes, we demonstrated that severe hypoglycemia occurred in older patients, those with longer-duration diabetes, and preexisting diabetic nephropathy patients, even without CKD.

Most previous reports have observed that the incidence of severe hypoglycemia in type 1 diabetes was much higher than in type 2 diabetes, although the reported incidence rates can be attributed to differences in study design, patient selection, duration of follow-up, degree of glycemic control, level of knowledge about hypoglycemia, type of medication, and definition of severe hypoglycemia (8). The studies reporting recorded rates of severe

Table 1—Baseline characteristics of participants

	Total	SH (+)	SH (−)	P
n	878	111	767	
Women, n (%)	544 (62.0)	75 (67.6)	469 (61.1)	0.193
Age, years	55.3 ± 9.8	61.0 ± 8.7	54.5 ± 9.7	<0.001
Diabetes duration, years	9.8 ± 6.5	13.1 ± 7.7	9.3 ± 6.1	<0.001
<5 years	259 (29.5)	16 (14.4)	243 (31.7)	
5–9 years	257 (29.3)	26 (23.4)	231 (30.1)	
≥10 years	362 (41.2)	69 (62.2)	293 (38.2)	
BMI (kg/m ²)	24.6 ± 3.3	24.1 ± 3.4	24.7 ± 3.3	0.073
Hypertension, n (%)	519 (59.1)	72 (64.9)	447 (58.5)	0.129
Diabetes treatment, n (%)				
Sulfonylurea	539 (61.4)	54 (49.5)	485 (63.6)	0.003
Insulin	250 (28.5)	52 (46.8)	198 (25.8)	<0.001
Antihypertensive medication, n (%)				
ACE inhibitor or ARB	245 (27.9)	32 (28.8)	213 (27.8)	0.816
Beta-blocker	35 (4.0)	8 (7.2)	27 (3.5)	0.063
Diabetic retinopathy, n (%)	123 (19.5)	26 (38.2)	97 (17.3)	<0.001
Diabetic nephropathy, n (%)				<0.001
Normoalbuminuria	681 (78.2)	71 (68.9)	610 (79.5)	
Microalbuminuria	150 (17.2)	20 (18.9)	130 (17.0)	
Macroalbuminuria	40 (4.6)	13 (12.3)	27 (3.5)	
Laboratory finding at baseline				
Fasting plasma glucose, mg/dL	171.7 ± 64.6	169.1 ± 68.3	172.0 ± 64.0	0.655
Postprandial 2-h plasma glucose, mg/dL	282.4 ± 92.0	301.3 ± 110.2	280.0 ± 89.2	0.095
Creatinine, mg/dL	0.77 ± 0.18	0.78 ± 0.16	0.77 ± 0.18	0.511
eGFR, mL/min/1.73 m ²	91.5 ± 24.4	87.4 ± 20.5	92.1 ± 24.9	0.059
HbA _{1c} , %	8.8 ± 2.0	9.0 ± 1.9	8.7 ± 2.0	0.237
Total cholesterol, mg/dL	182.7 ± 37.1	183.8 ± 38.2	182.5 ± 37.0	0.723
Triglyceride, mg/dL	157.4 ± 98.1	157.3 ± 80.6	157.5 ± 100.5	0.984
HDL, mg/dL	43.4 ± 10.8	43.7 ± 13.1	43.3 ± 10.4	0.789
LDL, mg/dL	108.8 ± 32.5	109.4 ± 30.9	108.7 ± 32.8	0.827
Fasting C-peptide, ng/mL	1.8 (1.2–2.5)	1.7 (1.2–2.5)	1.8 (1.2–2.5)	0.506
UAE, mg/day	10.0 (6.7–28.4)	13.7 (7.4–37.6)	10.0 (6.7–27.3)	0.019

ARB, angiotensin receptor blocker. Data are means ± SD, n (%), or median (interquartile range). P < 0.05 was considered significant.

hypoglycemia in type 1 diabetes showed that the incidence rates ranged from 11 to 150 per 100 patient-years (11,21–24), and this range was 2–35 per 100 patient-years in type 2 diabetes (11,22,25,26). In addition, recognized hypoglycemia and unrecognized hypoglycemia were more common and unavoidable complications in the intensive control group than in the standard group with type 2 diabetes (27). The incidence of severe hypoglycemia has considerably increased during the past decade, as estimated from severe hypoglycemic episodes occurring in subjects attending the emergency department and among patients treated by the emergency medical service (28,29). Some explanations, such as the implementation of

stringent goals for glycemic control with intensification of hypoglycemic therapy, accompanying comorbidities, and active monitoring of HbA_{1c} level, might have contributed to this sharp increase of severe hypoglycemic events in subjects with type 2 diabetes. Hypoglycemia also is associated with cardiovascular events and mortality, so prevention and identification of risk factors for hypoglycemia are clinically important issues for type 2 diabetic patients.

Severe hypoglycemia has several predictive risk factors, such as age, duration of diabetes, duration of insulin treatment, hypoglycemic events occurring in the preceding months, peripheral neuropathy, and, in particular, impaired kidney

function (11,12,24,30). The risk of hypoglycemia is a particular concern among patients with impaired renal function. In a national cohort of veterans observed during 1 year, the diagnoses of CKD and diabetes both were independent risk factors for hypoglycemia of any severity (12).

Our findings are consistent with previous observational studies implicating age and duration of diabetes as risk factors for severe hypoglycemia. However, most of the reported studies included patients who had impaired renal function already, which is associated with future development of severe hypoglycemia. In this present study, we excluded the subjects with CKD at baseline and followed-up our patients for >10 years. Interestingly, even without CKD, the presence of macroalbuminuria was an independent risk factor for future development of severe hypoglycemia in people with type 2 diabetes. To our knowledge, this is the first study to investigate macroalbuminuria as a risk factor for severe hypoglycemia. However, underlying mechanisms that could explain the presence of macroalbuminuria without CKD and increased risk of severe hypoglycemia need to be clarified.

Renal glucose release accounts for 20% of overall endogenous glucose release, which is responsible for ~40% of all gluconeogenesis (31). Therefore, the impaired kidney plays a complex and dynamic role in serum glucose control. Although the mechanism has not been fully addressed, reductions in the clearance of hypoglycemic agents, the degradation of insulin in peripheral tissues, gluconeogenesis, and insulin metabolism can predispose patients with CKD to hypoglycemia (32–34). In these patients, the counter-regulatory response to hypoglycemia may be limited by impaired renal gluconeogenesis or poor glycogen reserves caused by uremia-induced anorexia (35).

The effect of acute hypoglycemia on renal function is to decrease GFR and renal plasma flow in healthy humans and in patients with diabetes (36,37). Additionally, the UAE rate is independently related to diabetic autonomic neuropathy in subjects with type 1 and type 2 diabetes, which is associated with hypoglycemia unawareness (38–40). Autonomic neuropathy has been known as an independent risk factor for severe hypoglycemia and is associated with impaired counter-regulatory catecholamine responses (40). Therefore, diabetic patients

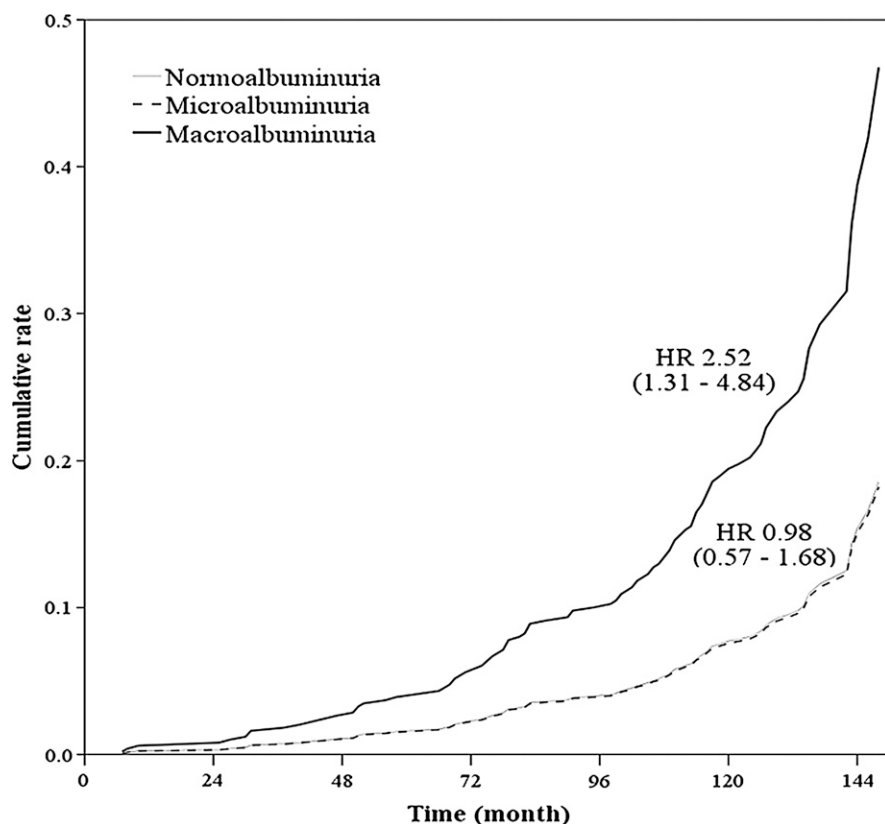


Figure 2—Cumulative incidence of severe hypoglycemia according to the presence of microalbuminuria or macroalbuminuria. HR, hazard ratio.

with macroalbuminuria, especially with frequent previous hypoglycemic episodes, might be vulnerable to renal injury, leading to CKD; combined with autonomic neuropathy, it could lead to severe hypoglycemia. The exact pathogenic mechanism should be investigated.

In this study, approximately half of severe hypoglycemia episodes were during the morning after skipping meals. A higher proportion of patients used insulin (66 patients; 60.0%) or sulfonylurea (41 patients; 37.3%) at the time of the hypoglycemic event among the patients with

severe hypoglycemia compared with those without. Importantly, 24 patients (22.4%) had experienced antecedent hypoglycemia of any degree (mild or moderate) within 3 months before severe hypoglycemic events. Therefore, diabetes education is needed in diabetic patients who experience frequent hypoglycemia, even if mild.

To investigate confounding factors potentially involved in the development of severe hypoglycemia, particularly those related to intensive glycemic control for patients with diabetic nephropathy to prevent further progression of nephropathy, we performed further analyses of glycemic control status and diabetes medications. At the time of the hypoglycemic event, the groups with and without macroalbuminuria showed no differences in HbA_{1c} levels or significant changes in diabetes medication that might have affected the development of severe hypoglycemia. Multivariate analysis after adjustment for insulin treatment and diabetes control during the study also showed that macroalbuminuria was a risk factor for the development of severe hypoglycemia. However, the use of insulin at the time of the severe hypoglycemic event was higher in patients with macroalbuminuria than in those without macroalbuminuria. Therefore, the increase in severe hypoglycemia might be related to this more aggressive treatment, including higher insulin use and less sulfonylurea use with a lower HbA_{1c} in patients with macroalbuminuria as a potential confounding factor of this study.

The main strength of this study is the prospective ascertainment of severe hypoglycemic events in a large cohort of people with established type 2 diabetes for >10 years, especially in patients with normal renal function. There are some limitations to this study. First, our definition of severe hypoglycemia limited the hypoglycemia episodes to those requiring hospitalization or emergency care and self-reporting, and it could have underestimated the incidence of severe hypoglycemia. Second, we diagnosed diabetic nephropathy using 24-h urine collection samples according to American Diabetes Association recommendation published in 1994, instead of spot urine samples. Third, our study potentially is biased because of the patients who dropped out. We could not evaluate the development of severe hypoglycemic events in patients who did not follow-up. Finally, the cohort analyzed in this study consisted

Table 2—Associations between risk factors and severe hypoglycemia

	Hazard ratio (95% CI)	P value
Sex, female	1.07 (0.69–1.65)	0.773
Age, per 10 years	1.93 (1.49–2.50)	< 0.001
Hypertension, yes vs. no	1.16 (0.72–1.89)	0.539
Diabetes duration, per year	1.04 (1.01–1.07)	0.019
Diabetic nephropathy		0.017*
Normoalbuminuria	1.00	
Microalbuminuria	0.98 (0.57–1.68)	0.944
Macroalbuminuria	2.52 (1.31–4.84)	0.006
Mean HbA _{1c} , %		
<7.0	1.00	
≥7.0	0.94 (0.54–1.63)	0.820
Insulin use, yes vs. no	1.29 (0.72–2.30)	0.396
Sulfonylurea use, yes vs. no	0.78 (0.46–1.31)	0.344
ACE inhibitor/ARB use, yes vs. no	0.78 (0.47–1.29)	0.332
eGFR	1.00 (0.99–1.01)	0.853

ARB, angiotensin receptor blocker. *P for trend.

solely of ethnic Asians. To ensure that the conclusion of our study is equally applicable to other ethnicities, further studies are needed.

In conclusion, we demonstrated that the presence of macroalbuminuria was an independent risk factor for future development of severe hypoglycemia in type 2 diabetic patients without CKD. Therefore, to reduce mortality caused by hypoglycemia, greater clinical attention and diabetes education are advised to minimize the risk of severe hypoglycemia. Such guidelines would include education on skipping meals, excessive exercise, and the importance of using the correct dose of medication for patients with type 2 diabetes, especially those who are old or have a long duration of diabetes or diabetic nephropathy. Additional studies are needed to determine the mechanisms underlying our findings.

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J.-S.Y. analyzed data, wrote the manuscript and interpreted data. Su.-Hy.K. collected and reviewed data. Su.-He.K. reviewed and edited the manuscript. K.-H.S. reviewed and edited the manuscript and contributed to discussions. Y.-B.A. researched data and reviewed the manuscript. K.-H.Y. reviewed the manuscript and contributed to discussions. Y.-M.P. contributed to statistical analysis, data interpretation, and discussions. Se.-H.K. designed the study, collected and researched data, interpreted data, and wrote the manuscript. Se.-H.K. is the guarantor of this work and, as such, had full access to all the data in this study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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