Cardiovascular Autonomic Dysfunction Predicts Severe Hypoglycemia in Patients With Type 2 Diabetes: A 10-Year Follow-up Study

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OBJECTIVE

The aim of this study was to investigate the development of severe hypoglycemia (SH) in the presence of cardiovascular autonomic neuropathy (CAN) in patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS

From January 2001 to December 2002, a total of 894 patients with type 2 diabetes were enrolled. A cardiovascular autonomic function test (AFT) was performed using the following heart rate variability parameters: expiration-to-inspiration ratio, response to Valsalva maneuver, and standing. From the results for each of the three tests (0 for normal, 1 for abnormal), a total AFT score of 1 was defined as early CAN, and an AFT score of ≥2 was defined as definite CAN.

RESULTS

The median follow-up time was 9.5 years. The mean age was 54.5 ± 10.1 years, and the mean duration of diabetes was 8.9 ± 6.3 years. One hundred ninety-six patients (31.4%) showed an abnormal cardiovascular AFT score at baseline. Sixty-two patients (9.9%) experienced 77 episodes of SH (1.33 per 100 patient-years). The number of SH events increased as the CAN score increased (23 patients [5.4%] with normal score; 17 patients [17.2%] with early CAN; and 22 patients [22.7%] with definite CAN; *P* for trends < 0.001). Cox proportional hazards regression analysis revealed that SH was associated with definite CAN (normal vs. definite CAN: hazard ratio 2.43 [95% CI 1.21–4.84]; *P* = 0.012).

CONCLUSIONS

Definite CAN was an independent prognostic factor for the development of SH in patients with type 2 diabetes.

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Diabetic cardiovascular autonomic neuropathy (CAN) is a common, insidious complication in diabetes, and it is significantly associated with conditions of cardiovascular morbidity and mortality, such as silent myocardial ischemia or life-threatening cardiac arrhythmia (1). CAN is manifested in a diverse spectrum of symptoms and signs, including resting tachycardia, orthostatic hypotension, and exercise intolerance (2). However, such manifestations are frequently not present in

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patients with diabetes who have cardiovascular autonomic dysfunction. Unlike other types of diabetic autonomic neuropathy, CAN is easily measured at the patient's bedside or on an outpatient basis using heart rate variability (HRV) during a Valsalva maneuver, deep breathing, and postural change; and reduced heart rate variation is the earliest indicator of CAN in patients with diabetes (3). Several studies have indicated that the prevalence of CAN ranges from 20 to 80% in patients with type 2 diabetes (3–5). Various factors, such as increased age, diabetes duration, the presence of microvascular complications, and glycemic control status, correlate with the development of CAN (3,6).

After the results of the Diabetes Control and Complications Trial and UK Prospective Diabetes Study were published, strict glycemic control has been emphasized for the prevention of diabetic microvascular and macrovascular complications in patients with diabetes. Contrary to expectations, recent large prospective clinical trials that assessed the clinical outcomes of an intensive glucose-lowering treatment revealed increased cardiovascular mortality with a risk of severe hypoglycemia (SH) in patients with type 2 diabetes (7–9). These studies also emphasized that hypoglycemia is regarded as a major barrier to achieving optimal glycemic targets in patients with type 2 diabetes (7–9).

Hypoglycemia is often accompanied by autonomic symptoms, which are tied to the perception of hypoglycemia. Adrenergic symptoms include palpitations, tremors, and anxiety; and cholinergic symptoms include sweating, hunger, and paresthesia (10). Heart rate and systolic blood pressure are typically increased during a hypoglycemia event, but may not be elevated in an individual who has experienced repeated recent episodes of hypoglycemia (11). The EURODIAB IDDM Complications Study has identified CAN as an independent risk factor for SH in patients with type 1 diabetes (12). It was suggested that counter-regulatory catecholamine responses and an awareness of hypoglycemia were impaired to a greater extent in type 1 diabetic patients with autonomic neuropathy (13). However, a relationship between CAN and SH has not yet been established in patients with type 2 diabetes.

The aim of this study was to investigate the development of SH in the presence of CAN using HRV measurements in patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS

From January 2001 to December 2002, 1,102 patients with type 2 diabetes, aged 25–75 years, were consecutively recruited, and a cardiovascular autonomic function test (AFT) was performed at The Catholic University of Korea-affiliated diabetes center at St. Vincent's Hospital (Gyeonggi-do, Republic of Korea). Patients were excluded if they had arrhythmia or any severe illness, such as heart failure, liver cirrhosis, alcoholism, severe infection, or malignancy. Patients with renal impairment (estimated glomerular filtration rate [eGFR] $<$60 mL/min/1.73 m^2) were excluded. The participants received follow-up care from January 2011 to December 2012. Two hundred forty-seven patients who did not receive follow-up care and 23 patients who died during the follow-up period were excluded from the analyses. The Catholic Medical Center Ethics Committee approved this study. All the participants provided signed, informed consent forms.

At the beginning of the study, the height, body weight, and systolic and diastolic blood pressure of each patient were measured. Hypertension was defined as systolic blood pressure $\geq$140 mmHg, diastolic blood pressure $\geq$90 mmHg, or the use of antihypertensive medications. A postprandial glucose sample was obtained 2 h after the breakfast meal. Fasting and postprandial plasma glucose levels were measured using an automated enzymatic method, and the A1C level was measured by high-performance liquid chromatography with a reference range of 4.4–6.4% (25–46 mmol/mol; Bio-Rad, Montreal, Quebec, Canada) every 6 months to evaluate the status of glycemic control during the follow-up period. The blood lipid concentrations for total cholesterol, triglycerides, and HDL were measured enzymatically using an automatic analyzer (model 736-40; Hitachi, Tokyo, Japan). The eGFR was used to determine the chronic kidney disease classification using the four-component Modification of Diet in Renal Disease equation (14).

Diabetic retinopathy was assessed from retinal photographs at baseline, and the findings were reviewed by one ophthalmologist. Diabetic retinopathy was classified as the absence or the presence of diabetic retinopathy. Diabetic nephropathy was considered if a patient showed microalbuminuria (30–300 mg/day) or macroalbuminuria ($\geq$300 mg/day) (15). The urinary albumin excretion rate was measured from a 24-h urine collection using immunoturbidimetry (Eiken, Tokyo, Japan).

Cardiovascular AFT was performed by one examiner using the Ewing method, which included a test for HRV, such as the expiration-to-inspiration (E/I) ratio, responses to the Valsalva maneuver, and postural change from lying to standing (16). The patients were asked to fast for 12 h before the AFT, and to avoid taking insulin, antidepressants, neuroleptic agents, caffeine, nicotine, antihistamines, or sympatholytic drugs (17).

The cardiovascular AFTs were performed during the recording of a continuous electrocardiogram, and the R-R intervals were recorded. For the E/I ratio, the subjects were asked to take deep breaths at a rate of six breaths per minute. During this deep breathing, the shortest R-R intervals during inspiration and the longest R-R intervals during expiration were measured. The mean values were calculated from the six inspirations and expirations, and the E/I ratio was calculated by dividing the mean value for the longest R-R intervals during expiration by the mean value for the shortest R-R intervals during inspiration (3,18). The "30:15 ratio" was the ratio of the longest R-R interval during beats 20–40 after standing, to the shortest R-R interval during beats 5–25 after standing. For the heart rate

response to the Valsalva maneuver, the ratio of the longest R-R interval to the shortest R-R interval was checked during forced exhalation into the mouthpiece of a manometer to 40 mmHg for 15 s. An E/I ratio below the age-related reference value (age 20–24 years, 1.17; 25–29 years, 1.15; 30–34 years, 1.13; 35–39 years, 1.12; 40–44 years, 1.1; 45–49 years, 1.08; 50–54 years, 1.07; 55–59 years, 1.06; 60–64 years, 1.04; 65–69 years, 1.03; and 70–75 years, 1.02), a Valsalva ratio of <1.2, and a posture ratio of <1.03 were considered abnormal (19). Each of the three ratios described above was scored as normal = 0 or abnormal = 1, for a total maximum score of 3. The staging of CAN was confirmed as follows: a score of 0 was defined as normal autonomic function; a score of 1 was defined as early CAN; and a score of at least 2 was defined as a definite diagnosis of CAN (20,21).

SH was defined as hypoglycemic episodes requiring the assistance of another person to actively administer carbohydrates, other resuscitative actions, hospitalization, or medical care in an emergency department (22).

For follow-up care, the patients who were enrolled in this study received routine medical treatment at intervals of 3–6 months on an outpatient basis. During their visit, the physician asked whether they had experienced severe hypoglycemic episodes or visited an emergency department as a result of SH. If a patient did not visit our clinic for any reason, we tried to contact the patient by telephone or electronic mail to evaluate the occurrence of SH. We also investigated the severe hypoglycemic events of patients in our emergency department each day. If patients reported their hypoglycemic episodes or visited our emergency department as a result of SH, we obtained clinical information, such as the presence of symptoms or signs, blood glucose levels, probable causes of events, and type and dosage of current hypoglycemic medications, from the patients' history and/or objective medical records and confirmed the occurrence of a severe hypoglycemic event.

Statistical Analyses

All results are expressed as the mean ± SD or percentage. The statistical analyses were performed using SAS version 9.2 (SAS Institute, Inc., Cary, NC). $P < 0.05$ was considered significant. To test the univariable relationships of the categorical variables, χ^2 tests were used, and independent Student *t* tests were used for the continuous variables. We used a Cox proportional hazards regression analysis to test the associations between the outcome (SH during follow-up) and the potential explanatory variables. The relationships were explored after adjusting for the following prognostic factors: sex, age, duration of diabetes, the presence of hypertension, mean A1C concentration, insulin treatment, the use of ACE inhibitors or angiotensin receptor blockers, the use of β-blockers, and the presence of diabetic microvascular complications. The results were reported as hazard ratios with 95% CIs.

RESULTS

The median follow-up time was 9.5 years. Among 1,102 patients who were recruited, 208 patients were excluded. Of the 894 patients who were enrolled the study, 624 patients (69.8%) completed the follow-up. At baseline, the total study population who completed the follow-up consisted of 252 men (40.4%) and 372 women (59.6%), a mean age of 54.5 ± 10.1 years, and a mean duration of diabetes of 8.9 ± 6.3 years. At the beginning of the study, 167 patients (26.8%) were receiving insulin treatment, and 384 patients (61.5%) were receiving sulfonylurea treatment. Compared with the 624 participants who completed the follow-up evaluation, the 270 patients who did not complete the follow-up

Table 1—Baseline characteristics of participants who reached follow-up

Characteristics	Participants with SH (*n* = 62)	Participants without SH (*n* = 562)	*P* value
Women (%)	67.7	58.7	0.230
Age (years)	61.2 ± 10.2	53.7 ± 9.8	<0.001
Diabetes duration (years)	12.9 ± 7.6	8.4 ± 6.0	<0.001
Hypertension (%)	50.0	39.0	0.093
Diabetes treatment (%)			
Insulin	46.8	24.6	<0.001
Sulfonylurea	48.4	63.0	0.025
Hypertension treatment (%)			
ACE inhibitor or ARB	32.3	25.4	0.246
β-Blocker	6.5	3.9	0.343
Diabetic retinopathy (%)	43.5	27.4	0.008
Diabetic nephropathy (%)			0.017
Normoalbuminuria	71.0	79.2	
Microalbuminuria	17.7	17.3	
Macroalbuminuria	11.3	3.5	
Fasting plasma glucose (mmol/L)	9.1 ± 3.5	9.2 ± 3.2	0.924
Postprandial 2-h plasma glucose (mmol/L)	16.7 ± 6.7	15.4 ± 5.3	0.107
eGFR (mL/min/1.73 m^2)	88.9 ± 24.1	97.6 ± 26.6	0.014
Baseline A1C (%)	9.1 ± 2.0	8.6 ± 1.9	0.054
Cardiovascular AFT (%)			
Abnormal E/I ratio	24.2	11.2	0.003
Abnormal Valsalva ratio	48.4	17.4	<0.001
Abnormal posture ratio	40.3	18.7	<0.001
Staging of CAN (%)			<0.001
Normal	37.1	72.1	
Early	27.4	14.6	
Definite	35.5	13.3	

Data are means ± SD unless otherwise stated. ARB, angiotensin receptor blocker.

evaluation did not differ with respect to age (54.5 ± 10.1 vs. 54.7 ± 10.6 years; *P* = 0.783), sex ratio (*P* = 0.997), the duration of diabetes (8.9 ± 6.3 vs. 7.9 ± 7.6 years; *P* = 0.063), the presence of hypertension (*P* = 0.290), or mean A1C concentration during the study (8.3 ± 1.3% vs. 8.3 ± 1.4% [67 vs. 67 mmol/mol]; *P* = 0.827).

During the follow-up period, a total of 77 SH episodes occurred in 62 patients (9.9%). The incidence of SH was 1.33 per 100 patient-years. The mean time from the enrollment date to the occurrence of the first SH episode was 76.9 ± 34.5 months. The patients with SH were older, had a longer duration of diabetes, and received more insulin treatment. Diabetic microvascular complications at baseline, such as retinopathy and nephropathy, were observed more frequently in the group with SH (Table 1).

In this study, 196 patients (31.4%) showed an abnormal cardiovascular AFT score at baseline. Abnormal AFT responses to deep breathing, the Valsalva maneuver, and changing from a lying to standing posture were shown in 78 subjects (12.5%), 128 subjects (20.5%), and 130 subjects (20.8%), respectively. Of the 196 patients who had abnormal AFT results, early CAN was diagnosed in 99 patients (15.9%), and definite CAN was diagnosed in 97 patients (15.5%). Among the patients with SH, an abnormal response to the Valsalva maneuver was observed in the largest number of patients (48.4%), and all of the AFT ratios (E/I, Valsalva, and posture ratio) revealed significantly more abnormalities in patients with SH than in those without SH (Table 1).

Patients with higher CAN scores were older, had diabetes for longer, were more likely to have hypertension, were more often treated with insulin or an ACE inhibitor, and had more diabetes complications (retinopathy and nephropathy). The patients with a higher score tended to exhibit higher levels in fasting and postprandial glucose and baseline A1C levels (Table 2). The development of SH increased as the CAN score increased (23 patients [5.4%] with normal autonomic function, 17 patients [17.2%] with early CAN, and 22 patients [22.7%] with definite CAN; *P* for trends <0.001). In the multivariable Cox proportional hazards regression analysis, the patients with definite CAN showed a 2.43 times higher risk of SH than those with normal autonomic function during the observation period after adjusting for sex, age, the duration of diabetes, the presence of hypertension, the mean A1C level, insulin treatment, ACE inhibitor or angiotensin receptor blocker use, β-blocker use, and the presence of diabetic microvascular complications (Fig. 1 and Table 3).

Table 2—Baseline characteristics according to CAN staging

Characteristics	CAN staging: Normal (*n* = 428)	Early (*n* = 99)	Definite (*n* = 97)	*P* for trend
Women (%)	56.8	67.7	63.9	0.075
Age (years)	52.6 ± 10.0	59.1 ± 9.2	57.7 ± 9.2	<0.001
Diabetes duration (years)	7.5 ± 5.4	10.0 ± 7.0	14.0 ± 6.8	<0.001
<5 years (%)	41.9	29.3	8.2	
5–10 years (%)	30.1	29.3	21.6	
≥10 years (%)	28.0	41.4	70.2	
BMI (kg/m^2)	24.7 ± 3.1	25.0 ± 3.1	24.4 ± 3.8	0.641
Hypertension (%)	36.0	40.4	57.7	<0.001
Smoking (%)	23.1	20.2	22.7	0.819
Diabetes treatment (%)				
Insulin	17.3	38.4	56.7	<0.001
Sulfonylurea	68.2	53.5	40.2	<0.001
Hypertension treatment (%)				
ACE inhibitor or ARB	24.3	24.2	36.1	0.034
β-Blocker	3.7	3.0	7.2	0.200
Diabetic retinopathy (%)	16.6	44.4	68.0	<0.001
Diabetic nephropathy (%)	18.0	19.2	40.2	<0.001
Laboratory at baseline				
Fasting plasma glucose (mmol/L)	8.9 ± 3.0	9.2 ± 3.4	10.5 ± 3.8	<0.001
Postprandial 2-h plasma glucose (mmol/L)	14.9 ± 5.1	16.4 ± 6.3	17.6 ± 5.6	<0.001
Creatinine (μmol/L)	69.8 ± 15.9	67.2 ± 15.9	71.6 ± 17.7	0.870
eGFR (mL/min/1.73 m^2)	97.2 ± 24.6	98.8 ± 34.6	92.8 ± 24.8	0.260
Total cholesterol (mmol/L)	4.68 ± 0.91	4.82 ± 0.75	4.77 ± 1.12	0.246
Triglyceride (mmol/L)	1.72 ± 1.12	1.67 ± 0.83	1.89 ± 1.07	0.265
HDL (mmol/L)	1.11 ± 0.27	1.17 ± 0.28	1.10 ± 0.35	0.820
Baseline A1C (%)	8.4 ± 1.9	8.6 ± 1.8	9.4 ± 2.0	<0.001

Data are means ± SD unless otherwise stated. ARB, angiotensin receptor blocker.

CONCLUSIONS

In this long-term, prospective, observational cohort study, we demonstrated a significant relationship between diabetic cardiovascular autonomic dysfunction and the development of SH in patients with type 2 diabetes during an ~10-year follow-up period. We showed that a higher AFT score, especially a score indicating definite CAN, had a tendency to increase the risk of SH in patients with type 2 diabetes.

CAN is a well-known independent risk factor for cardiovascular events in patients with type 1 and type 2 diabetes (21,23). CAN has increased mortality by more than threefold, independent of traditional cardiovascular risk factors (21). By the use of various diagnostic criteria for CAN, the relative risk for mortality in subjects with CAN at baseline (abnormal AFT score ≥1) has been shown to be 2.14 (95% CI 1.83–2.51) compared with those whose baseline assessment was normal. In addition, an abnormal AFT score of ≥2 corresponded to a relative risk of 3.65 (95% CI 2.66–4.47) (2). In patients with type 1 diabetes, it has been reported

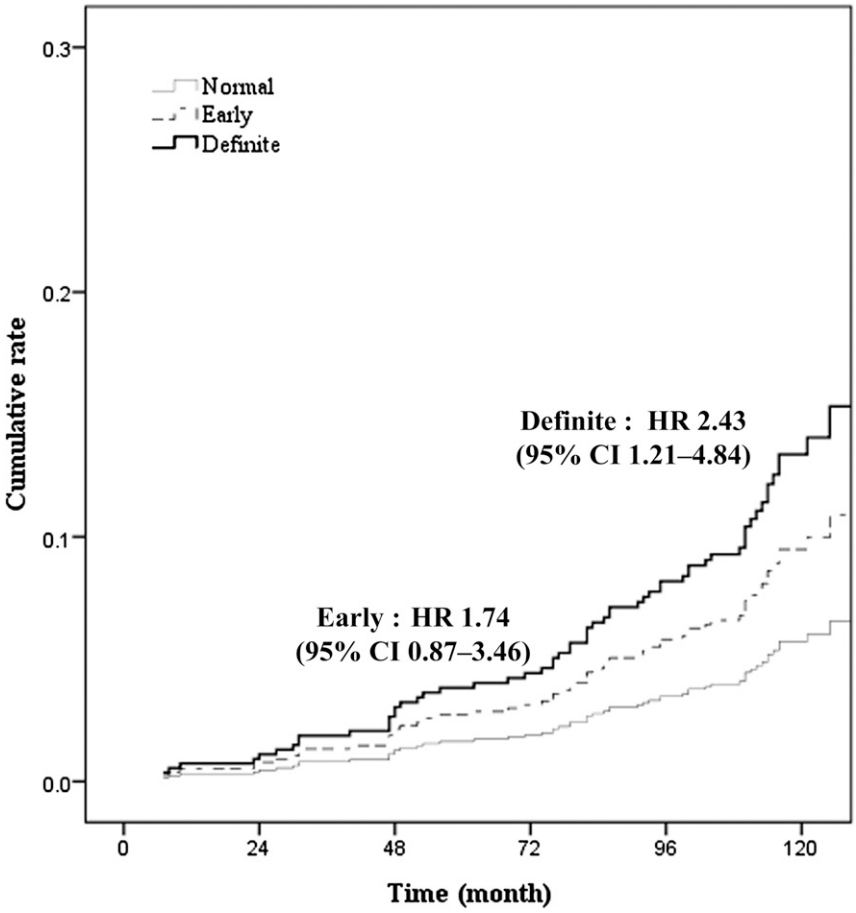

Figure 1—Cumulative incidence of SH according to the staging of cardiovascular autonomic dysfunction.

that existing diabetic autonomic neuropathy was associated with a fourfold increase in mortality (24). There may be a number of different pathogenic mechanisms that explain the association between CAN and the increased risk of mortality, such as renal failure, deadly arrhythmia, silent ischemia or infarction, or sudden death (25). Therefore, the early detection of CAN is clinically important to prevent cardiovascular morbidity and mortality in patients with diabetes.

There are various studies focused on the prevalence of diabetic CAN (3–5). The differences in these studies may result from a number of contributing factors including diverse definitions of CAN, different diagnostic methods, various characteristics of the study population, and variable cohort characteristics. According to our results, 31.4 and 15.5%, respectively, of the study subjects showed an abnormal AFT score and definite CAN at baseline, which were generally similar to the results of previous reports (26,27).

The most widely used type of test used for assessing for CAN is the cardiovascular autonomic reflex tests. The major benefits of these tests are that they are noninvasive, safe, and well-standardized methods with good sensitivity, specificity, and, reproducibility, which are easily performed in a clinical setting on an outpatient basis (3). Because of its clinical importance and applicability, current clinical practice guidelines recommend that patients with type 2 diabetes be screened for CAN at the time of their diabetes diagnosis (20,28,29). Based on the American Diabetes Association recommendations, the presence of one abnormal HRV test result suggests the development of early CAN, and at least two abnormal test results are required to confirm a definite diagnosis of CAN (20). We applied these updated American Diabetes Association criteria to classify the severity of cardiovascular autonomic dysfunction. Our study demonstrated that the frequency of an abnormal E/I ratio was lowest in the total population and SH groups.

Older age, a longer duration of diabetes, the presence of hypertension or microvascular complications, an unsatisfactory glycemic control status, and insulin treatment were associated with increasing severity of cardiovascular autonomic dysfunction. These clinical variables were mentioned as risk factors for impaired HRV in previous studies (2,20,30–32). As we reported previously (33), age, the duration of diabetes, insulin treatment, and impaired kidney function were related to the development of SH, and these factors could be confounding factors for the analysis. After adjusting all the variables, including the glycemic control status during the observation period, expressed as the mean A1C

Table 3—Multivariable Cox hazards regression model

	Hazard ratio (95% CI)		
Autonomic dysfunction	Model 1	Model 2	Model 3
Normal	1.00	1.00	1.00
Early	1.85 (0.96–3.58)	1.88 (0.97–3.66)	1.74 (0.87–3.46)
Definite	3.25 (1.79–5.89)*	2.74 (1.45–5.18)*	2.43 (1.21–4.84)*

Multivariable Cox regression models were adjusted as follows: Model 1: sex, age, diabetes duration; model 2: model 1 plus the presence of hypertension, mean A1C level, eGFR, diabetic retinopathy, and diabetic nephropathy; model 3: model 2 plus use of insulin, ACE inhibitors or angiotensin receptor blockers, or β-blockers. *$P < 0.05$.

level, a definite diagnosis of CAN remained as a predictable prognostic factor for the development of SH.

CAN has been primarily studied with respect to the risk for the occurrence of cardiovascular events. Our study reveals the clinical implication regarding an association between CAN and SH. Although debatable, it has also been suggested that increasing mortality due to autonomic dysfunction is associated with hypoglycemia, which is a major barrier for diabetes treatment (3,16,34). O'Brien et al. (34) showed that autonomic neuropathy might have a negative effect on survival, including impaired recognition of hypoglycemia and impaired recovery from hypoglycemia because of defective endocrine counter-regulatory mechanisms. According to the EURODIAB IDDM Complications Study, a combined autonomic deficit in heart rate and blood pressure responses to standing was associated with a modest increase in the risk of severe spontaneous hypoglycemia in patients with type 1 diabetes (12). Until now, no prior studies have demonstrated a relationship between CAN and SH in type 2 diabetic patients.

The pathogenic mechanism of SH has been known as hypoglycemia-associated autonomic failure (HAAF) (10). There is a difference in the concept between diabetic autonomic dysfunction and HAAF. Diabetic autonomic dysfunction is characterized as a systematic structural disorder that is clinically manifested by cardiovascular, gastrointestinal, and genitourinary symptoms. HAAF is a functional and reversible disorder caused by antecedent hypoglycemia that is reversed by an avoidance of hypoglycemia (35). Few studies have tried to demonstrate an association between diabetic autonomic dysfunction and HAAF. Ryder et al. (36) reported that autonomic dysfunction weakly correlated with hypoglycemic unawareness or a defective glucose counter-regulatory hormone. But the size of the patient population was too small and cross-sectional, and it did not show a clear causal relationship between the two variables.

In addition to the EURODIAB IDDM Complications Study mentioned earlier (12), other studies suggested that the adrenal response to hypoglycemia and hypoglycemic awareness have decreased in patients with autonomic dysfunction confirmed by standard CAN testing (13,37). Studies of the association between CAN and hypoglycemia have been performed predominantly in type 1 diabetic patients.

The major strength of this prospective study is the long-term ability to ascertain the relationship between CAN and SH in a large cohort of patients with type 2 diabetes. We tried to control representatively the factors that could affect cardiovascular autonomic function and SH, such as impaired kidney function.

There are some limitations to this study. First, we chiefly investigated the parasympathetic autonomic function of the cardiovascular reflex. The earliest clinical indicator of CAN is a decrease in the HRV in five noninvasive cardiovascular reflex test results (38). Among them, the heart rate response to deep breathing and posture is principally affected by parasympathetic activity. The three tests that we studied are widely recommended because of high reliability and good reproducibility (3). The test of orthostatic blood pressure may provide more detailed information about the association between severe autonomic neuropathy and SH. Second, there were 260 patients who did not receive complete follow-up, and there may be a selection bias caused by this dropout. Finally, this cohort study consisted of one Asian ethnic group. More studies are needed to apply this finding to other ethnic groups.

In summary, we demonstrated that diabetic CAN was an independent prognostic factor for the future development of SH in type 2 diabetic patients. Screening and regular follow-up of cardiac autonomic neuropathy and careful clinical attention to patient education concerning hypoglycemia are essential for patients with definite CAN to prevent SH and related mortality. Additional studies are needed to assure precise mechanisms and to apply these findings to other ethnic groups.

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