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The association between abnormal heart rate variability and new onset of chronic kidney disease in patients with type 2 diabetes: A ten-year follow-up study

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ABSTRACT

Aims: We investigated the association between cardiovascular autonomic neuropathy (CAN) and the future development of chronic kidney disease (CKD) in patients with type 2 diabetes.

Methods: From Jan 2003 to Dec 2004, 1117 patients with type 2 diabetes without CKD (estimated glomerular filtration rate [eGFR] $\geq$60 ml/min/1.73 m^2), aged 25–75 years, were consecutively enrolled. A cardiovascular autonomic function test (AFT) was performed using heart rate variability parameters. The eGFR was measured at least more than once every year, and new onset CKD was defined as eGFR $<$ 60 ml/min/1.73 m^2 using a Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.

Results: Among the 755 (67.6%) patients who completed the follow-up evaluation for 9.6 years, 272 patients (36.0%) showed a CKD stage $\geq$3. The patients who developed CKD were older, had a longer duration of diabetes, had hypertension, received more insulin and ACE inhibitor/angiotensin receptor blocker (ARB) treatment, and exhibited lower baseline eGFR, HbA1c, and albuminuria levels. Compared to patients without CKD, more patients with CKD at follow-up had CAN at baseline. In a multivariate analysis, after adjustment for age, sex, diabetes duration, presence of hypertension, mean HbA1c, diabetic complications, use of

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insulin, ACE inhibitor/ARB, statin, and baseline eGFR, the development of CKD was significantly associated with the presence of CAN (HR 2.62, 95% CI 1.87–3.67, $P < 0.001$).
Conclusions: In this prospective, longitudinal, observational cohort study, we demonstrated that diabetic CAN was an independent prognostic factor for the future development of CKD in type 2 diabetes.

1. Introduction

Diabetic nephropathy is an important microvascular complication in patients with type 2 diabetes and occurs in 20–40% of patients with diabetes [1,2]. It is also the major cause of end-stage renal disease (ESRD), requiring renal replacement therapy, including dialysis or transplantation [3–5]. According to the increase in prevalence of diabetes, the prevalence of diabetic nephropathy and/or chronic kidney disease (CKD) is expected to be increased steadily. Thus, it is clinically important to identify patients at high risk of CKD to prevent further deterioration of renal function or renal failure.

Cardiovascular autonomic neuropathy (CAN) is a frequent, insidious, and clinically important form of diabetic autonomic neuropathy and can be easily measured using heart rate variability (HRV) during deep breathing, a Valsalva maneuver, and a postural change [6]. The manifestations of CAN include resting tachycardia, orthostatic hypotension, and exercise intolerance and may develop very early in diabetes [7]. The presence of CAN is closely associated with macrovascular complications, and its mortality is related to fatal cardiac arrhythmia, severe hypoglycaemia, and sudden death [8].

Previously, clinical and epidemiological studies have shown that impaired cardiovascular autonomic function is associated with diabetic nephropathy in patients with diabetes [9–13]. It was suggested that this association could be mediated by CAN-induced changes in renal hemodynamics and in the circadian rhythm of blood pressure and albuminuria [7,14–16]. However, most of these studies have been performed in type 1 diabetes, as assessed by only using albuminuria levels or cross-sectional studies, and there were few studies about the relationship between CAN and the development of CKD in patients with type 2 diabetes.

Thus, we performed a long-term prospective study to evaluate the relationship between the presence of CAN using HRV measurements and the development of a new onset CKD in patients with type 2 diabetes.

2. Materials and methods

2.1. Study population

From March 2003 to December 2004, 1117 patients with type 2 diabetes were consecutively recruited and received follow-up care from January 2013 to May 2014 at the University-Affiliated Diabetes Center of St. Vincent's Hospital in South Korea. Patients were excluded if they were older than 75 years and had type 1 diabetes, gestational diabetes, a history of arrhythmia or any severe illness, such as heart failure, liver cirrhosis, alcoholism, severe infection, or malignancy. Patients who had renal impairment (estimated glomerular filtration rate [eGFR] < 60 ml/min/1.73 m^2) were initially excluded. Among 1117 enrolled patients, 354 patients who were lost in follow-up care and 8 patients who died from a cause not related to renal dysfunction prior to the endpoint were also excluded from the analyses. The Catholic Medical Center Ethics Committee approved this study. Written informed consent was obtained from all participants.

2.2. Data collection

At the beginning of the study, a detailed questionnaire was used to obtain participants' information, including medical history, current cigarette smoking status, and use of medications. Hypertension was defined as a systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg, or current use of antihypertensive medications [17]. Blood samples were collected from all patients after they had fasted for 8–12 h, and standard lipid parameters (total cholesterol, triglyceride, high density lipoprotein-cholesterol), blood glucose, and HbA1c were measured. Fasting and 2-h postprandial plasma glucose levels were measured using an automated enzymatic method. HbA1c levels were determined using 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 determine the status of the glycaemic control during the follow-up evaluation. The urinary albumin excretion rate was measured by an enzyme immunoassay using immunoturbidimetry with 24-h urine collection (Eiken, Tokyo, Japan). Diabetic retinopathy was assessed from retinal images at baseline, and the findings were reviewed by a board-certified ophthalmologist and classified as the absence or presence of diabetic retinopathy.

2.3. Cardiovascular autonomic neuropathy assessment

A cardiovascular autonomic function test (AFT) was performed in all enrolled patients at baseline. Cardiovascular AFT was performed by one examiner using the Ewing method. The patients were asked to fast for 12 h before the AFT, and to avoid taking insulin, aspirin, antidepressants, antihypertensive, neuroleptic agents, caffeine, nicotine, antihistamines, nasal sprays, or sympatholytic drugs [18]. To perform the test, the patients remained supine and were asked to breathe deeply at the rate of one breath per 10 s for 1 min while being monitored by an electrocardiogram. The *E/I* ratio indicates the ratio of the mean of the longest R–R intervals during expiration to the mean of the shortest R–R intervals. For the heart rate