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High-density lipoprotein cholesterol and the risk of nephropathy in type 2 diabetic patients

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Abstract *Background and aims:* To date, few studies have demonstrated the impact of variations in blood pressure, blood glucose and lipid levels on the progression of diabetic nephropathy (DN) in type 2 diabetic patients. This study aimed to assess the associations of mean values and variability in metabolic parameters with the development of DN in type 2 diabetic patients.
Methods and results: A total of 864 patients who had participated in a comprehensive diabetic care program for at least for 3 years were studied. Patients were stratified into progressor ($n = 180$) and non-progressor groups ($n = 684$) according to the status of progression of DN during the follow-up period. By Cox regression analysis, a higher mean HDL-C level was observed to be a protective factor against the progression of DN [hazard ratio (95% CI): 0.971(0.953–0.989), $P = 0.002$] and a higher HDL-C variation was found to be associated with a higher risk [hazard ratio (95% CI): 1.177(1.032–1.341), $P = 0.015$] of DN progression. By the Kaplan–Meier survival curve, patients with a higher HDL-C level and lower HDL-C variability were found to have the lowest risk of development of nephropathy.
Conclusions: Our study demonstrated for the first time that type 2 diabetic patients under a standard disease management program who have a stable and a higher mean HDL-C level were associated with a lower risk of development of DN.

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Introduction

Diabetic nephropathy (DN) is not only the leading cause of end-stage renal disease but also represents a risk factor for all-cause and cardiovascular mortality [1]. To ameliorate diabetic complications, the American Diabetic Association (ADA) established clinical practice guidelines for the management of diabetic patients [2]. By way of the ADA's recommendations, strict metabolic control could effectively delay the initial development of DN in diabetic patients with normoalbuminuria [3]. Although there are clear treatment goals to be reached, it is difficult to maintain these targets for diabetic patients in real-world daily practice [4], and sometimes there are substantial fluctuations in metabolic control.

Instability in blood glucose and blood pressure, and perhaps the lipid profile, could be harmful to diabetic patients. According to data analyses from the Diabetes Control and Complications Trial (DCCT), Kilpatrick et al. [5] demonstrated that variability in A1C adds to the mean value of A1C in predicting the risk of nephropathy in type 1 diabetic (T1D) patients. Similarly, independent of A1C level, a systemic review also demonstrated that glucose variability could be a predictor of diabetic retinopathy, cardiovascular events, and mortality in type 2 diabetic (T2D) patients [6]. In addition to glycemic variability, one study found blood pressure instability to be a risk factor for DN in T1D patients [7]. Very recently, even in T2D patients with optimal metabolic control, Di Flaviani et al. [8] reported that variability in blood pressure and blood glucose is associated with endothelial and cardiovascular damage. These reports emphasize the importance of preventing substantial changes in blood glucose and blood pressure in diabetic patients.

A growing body of evidence indicates that dyslipidemia may be a risk factor for the progression of DN. In T1D patients, Tolonen et al. [9] reported that patients with high triglycerides are at greater risk of progression of DN. In T2D patients, Zoppini et al. [10] demonstrated that a higher high-density lipoprotein cholesterol level is associated with a lower incidence of chronic kidney disease. These results imply that dyslipidemia could be a risk factor for DN. As well as instability in A1C and blood pressure, lipids changes accompany medical treatment, but the impact of variability in lipids on the development of DN remains unknown. In order to investigate the effect of variability in lipids concurrently with A1C and blood pressure on the progression of DN in T2D patients, the current study was designed to analyze the effects of metabolic control in T2D patients participating in a disease management program for at least 3 years and assess their subsequent renal events.

Methods

Subjects

From October 2006 to May 2011, among 2711 T2D patients, a total of 864 (31.88%) T2D patients who had been enrolled into a comprehensive diabetic care program for at least for 3 years were included in this study. These participants were recruited from Tri-Service General Hospital and a specialized diabetic outpatient clinic [11—13]. In this program, patients were requested to return to the clinic every 3 months. At the time of enrollment, the patients' A1C, total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides and serum creatinine levels were assessed and their urine was examined for albuminuria. At subsequent follow-up assessments, A1C was measured quarterly, and total cholesterol, LDL-C, HDL-C and triglycerides were measured quarterly if ADA treatment goals were not met, then every 6 months if ADA treatment goals were met. Serum creatinine was measured yearly in diabetic patients with normoalbuminuria and microalbuminuria. Regarding diabetic patients with macroalbuminuria, serum creatinine was measured every 6 months in men with serum creatinine $<$ 1.5 mg/dL and women with $<$1.4 mg/dL and every 3 months in male patients with serum creatinine $\geq$ 1.5 mg/dL and female patients with $\geq$1.4 mg/dL. The diabetic patients were also regularly interviewed by certified diabetic educators and registered dietitians. The study was approved by the Institutional Review Board of Tri-Service General Hospital.

Definition of renal functional status

The status of DN was graded by the urine albumin-to-creatinine ratio (ACR). We collected overnight first-void urine samples for ACR measurement. Normoalbuminuria was defined as an ACR $<$ 30 mg/g, microalbuminuria as an ACR of 30 mg/g—299 mg/g, and macroalbuminuria as an ACR $>$ 300 mg/g on at least two of three samplings within a 6-month period. The progression of DN was defined as a shift to an advanced renal functional stage from the baseline. If patients were already found to be at the macroalbuminuric stage at baseline, their DN would be considered to have progressed if their serum creatinine doubled or if they were diagnosed with ESRD. If a patient was found to have a change in DN stage, he/she would undergo two additional ACR or serum creatinine measurements every 3 months to confirm the DN stage.

Biochemical and physical measurements

Body height, body weight and blood pressure were measured at scheduled clinic visits. Body mass index (BMI) was calculated by dividing weight (kg) by the square of height (m). Blood pressure was measured in the sitting position after 10 min of rest. Cardiovascular diseases were defined as any of the following events from medical records: acute coronary syndrome, coronary artery procedure (by-pass surgery or angioplasty), stroke and ischemic limb amputation. Blood samples were collected after at least 8 h of overnight fasting. A1C was measured in whole blood using ion exchange high-performance liquid chromatography (BIO-RAD®, VARIANTTM II Turbo, Hercules, CA). A biochemical automatic analyzer (Beckman-Coulter Inc. Fullerton, CA) was used to analyze blood samples and measure plasma glucose, total cholesterol, HDL-C, LDL-C and triglycerides. The serum levels of total cholesterol, LDL-C and triglycerides were measured by a standard enzymatic method. Serum HDL-C was measured by direct enzymatic methods using commercial kits (Cholestest®