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Serum lipoprotein(a) levels and diabetic nephropathy among Japanese patients with type 2 diabetes mellitus

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ABSTRACT

Aims: We aimed to evaluate the association between serum lipoprotein(a) [Lp(a)] levels and diabetic nephropathy among Japanese patients with type 2 diabetes mellitus.
Methods: This study included 581 patients with type 2 diabetes mellitus. Serum Lp(a) levels were divided into four groups; the cut-off points were at the 30th, 60th, and 90th percentile values on the basis of the distribution for all subjects. Diabetic nephropathy was defined as present when the urinary albumin-creatinine ratio was ≥33.9 mg/mmol creatinine and/or the estimated glomerular filtration rate was <30 ml/min/1.72 m^2. Adjustment was made for age, sex, body mass index, hemoglobin A_{1c}, duration of diabetes mellitus, current drinking, current smoking, hypertension, dyslipidemia, coronary heart disease, and stroke.
Results: Higher serum Lp(a) levels were significantly associated with a higher prevalence of diabetic nephropathy: the adjusted odds ratios (95% confidence intervals) for diabetic nephropathy in relation to serum Lp(a) levels of ≤6, 7–15, 16–38, and ≥39 mg/dl were 1.00 (reference), 2.74 (1.08–7.00), 3.31 (1.28–8.54), and 4.80 (1.57–14.60), respectively (*P* for trend = 0.004).
Conclusions: The results suggest that serum Lp(a) levels may be positively associated with diabetic nephropathy among Japanese patients with type 2 diabetes mellitus.

1. Introduction

Lipoprotein(a) [Lp(a)] is a complex particle that is composed of a low-density lipoprotein (LDL) molecule and apolipoprotein(a) [apo(a)] (Berg, 1963; Kronenberg & Utermann, 2013). Serum levels of Lp(a) are codominantly inherited and typically stable within individuals over time (Cobbaert & Kesteloot, 1992; Utermann, 1989), while they differ among individuals and different racial groups (Marcovina et al., 1996; Rifai et al., 1992). Higher serum levels of Lp(a) are currently considered to be a risk factor for coronary heart disease and stroke in both general (The Emerging Risk factors Collaboration, 2009) and diabetic populations (Hiraga et al., 1995; Kollerits et al., 2012; Qi & Qi, 2012; Ruiz et al., 1994). However, the association between serum levels of Lp(a) and diabetic microvascular complications is unclear. The relationship between serum levels of Lp(a) and diabetic nephropathy has been especially inconsistent. Three studies found that serum levels of Lp(a) were cross-sectionally positively associated with diabetic nephropathy among patients with type 2 diabetes mellitus in Western countries (Hernández et al., 1997; Lin et al., 2014; Toro et al., 2015). In Asian countries, one prospective study

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found that higher serum levels of Lp(a) were significantly associated with the progression of diabetic nephropathy among the patients exhibiting proteinuria with diabetes mellitus (Song et al., 2005), and four cross-sectional studies found a positive association between serum levels of Lp(a) and diabetic nephropathy among patients with type 2 diabetes mellitus (Chandni & Ramamoorthy, 2012; Deepa et al., 2002; Takegoshi et al., 1990; Tseng, 2009). In contrast, such a positive association was not found in other Western and Asian cross-sectional studies (Haffner et al., 1993; Heesen et al., 1993; Ling et al., 2011; Nagai et al., 1993; Reverter et al., 1994). To help clarify this discrepancy, we carried out a cross-sectional study of the relationship between serum levels of Lp(a) and diabetic nephropathy among Japanese patients with type 2 diabetes mellitus.

2. Subjects

The Dogo Study was a multicenter prospective cohort study that recruited 1051 Japanese patients with previously diagnosed type 2 diabetes mellitus (median age at recruitment, 61.6 years; range, 19–88 years; 61.0% men). Collaborating physicians who specialize in diabetes mellitus at 10 different hospitals were responsible for the diagnosis of type 2 diabetes mellitus, which were made according to the Japan Diabetes Society criteria (The Committee of the Japan Diabetes Society on the diagnostic criteria of diabetes mellitus, 2010). Excluded from our current analysis were 470 patients who had missing data on the variables under study. Thus, the final analysis sample consisted of 581 patients. The present study protocol received ethical approval from the ethics committee of Ehime University Graduate School of Medicine. Written informed consent was obtained from all patients enrolled in the study.

3. Materials and methods

3.1. Clinical examination and laboratory measurements

A self-administered questionnaire inquired about duration of diabetes mellitus, current drinking, current smoking, use of antihypertensive medication, and use of anti-hyperlipidemic medication. Body mass index (BMI) was calculated as weight (kg) divided by the square of height (m^2). Current drinking was defined as present when subjects reported drinking habitually. Current smoking was defined as present when subjects reported smoking at least one cigarette per day. Blood pressure was measured with a cuff in the sitting position after a rest period of more than 5 min. Hypertension was defined as present when systolic blood pressure was ≥140 mmHg, diastolic blood pressure was ≥90 mmHg, or both, or when subjects were under anti-hypertensive treatment. Dyslipidemia was defined as present when serum levels of LDL cholesterol (LDL-C) were ≥140 mg/dl (≥3.62 mmol/l), those of triglyceride (TG) were ≥150 mg/dl (≥1.69 mmol/l), or those of high-density lipoprotein cholesterol (HDL-C) were <40 mg/dl (<1.03 mmol/l), or when subjects were under lipid-lowering treatment. Coronary heart disease and stroke were assessed by a self-administered questionnaire, medical records, and/or admission data. Blood samples were taken the morning after overnight fasting. Serum levels of Lp(a) were measured using an Lp(a) Latex Daiichi kit (Sekisui Medical Co. Ltd., Tokyo, Japan) via a turbidimetric latex agglutination method. Urine samples were taken once in the morning from the first void.

3.2. Assessment of diabetic nephropathy

The urinary albumin:creatinine ratio (UACR) was used to classify the participants as follows: 0–29.9 mg/g (0–3.3 mg/mmol) creatinine was classified as normoalbuminuria; 30–299 mg/g (3.4–33.8 mg/mmol) creatinine as microalbuminuria; and ≥300 mg/g (≥33.9 mg/mmol) creatinine as macroalbuminuria (Haneda et al., 2015). Estimated glomerular filtration rate (eGFR) was calculated using serum creatinine (mg/dl): $194 \times (\text{serum creatinine})^{-1.094} \times (\text{age})^{-0.287} \times (0.739$ if female) (Japan nephrology society, 2012). Diabetic nephropathy was defined as present when UACR was ≥300 mg/g (≥33.9 mg/mmol) creatinine and/or eGFR was <30 ml/min/1.73 m^2 (Haneda et al., 2015).

3.3. Statistical analysis

Study subjects were divided into four groups according to their serum levels of Lp(a). The cut-off points were at the 30th, 60th, and 90th percentile values on the basis of the distribution for all study subjects (≤6, 7–15, 16–38, and ≥39 mg/dl). Age, sex, BMI, hemoglobin A_{1c} (HbA_{1c}), duration of diabetes mellitus, current drinking, current smoking, hypertension, total cholesterol, LDL-C, HDL-C, TG, coronary heart disease, and stroke were selected *a priori* as potential confounding factors. Age, BMI, HbA_{1c}, duration of diabetes mellitus, total cholesterol, LDL-C, HDL-C, and TG were used as continuous variables. Estimations of crude odds ratios (ORs) and their 95% confidence intervals (CIs) for diabetic nephropathy in relation to serum levels of Lp(a) were performed using logistical regression analysis. Multiple regression logistic analyses were used to adjust for potential confounding factors. All statistical analyses were performed using SAS software package version 9.4 (SAS Institute Inc., Cary, NC, USA). Two-sided *P* values less than 0.05 were regarded as statistically significant.

4. Results

The distribution of the serum levels of Lp(a) among our patients was heavily skewed to the right in the present study (Fig. 1). Characteristics of participants are shown in Table 1. The median serum level of Lp(a) was 12.0 mg/dl (range, 1–184 mg/dl) and the prevalence of diabetic nephropathy was 9.3% among the 581 subjects. The serum levels of Lp(a) among patients with diabetic nephropathy were significantly higher than among those without diabetic nephropathy (16.0 mg/dl [interquartile range (IQR), 9.0–25.0 mg/dl] vs. 11.0 mg/dl [IQR, 5.0–22.0 mg/dl], respectively; P = 0.016). However, there is no significant difference between the serum Lp(a) levels among patients with and without previous coronary heart disease (11.0 mg/dl [IQR, 6.0–22.0 mg/dl]

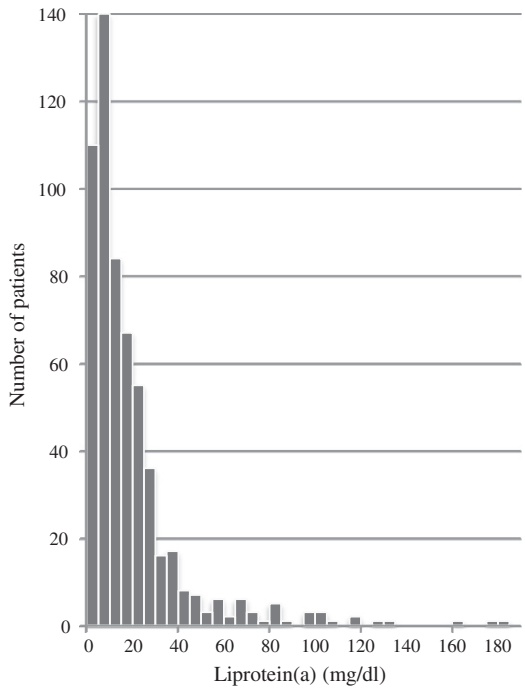

Fig 1. Distribution of serum levels of lipoprotein(a).