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Lipid abnormalities associated with urinary albumin excretion rate in Taiwanese type 2 diabetic patients

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Background. The purpose of this study was to examine the lipid abnormalities associated with urinary albumin excretion rate (UAER) in type 2 diabetic patients.

Methods. A total of 275 (122 men and 153 women; aged 60.6 ± 11.1 years) patients were selected with stringent criteria to prevent confounders. Normoalbuminuria ($N = 152$) and albuminuria ($N = 123$) were defined as urinary albumin-to-creatinine ratio (ACR) of <30 and ≥30 μg/mg, respectively. Total cholesterol, triglycerides, low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol, and apolipoproteins A1 (ApoA1) and B (ApoB) were measured and non-HDL cholesterol calculated. The subjects were divided into four phenotypes based on triglycerides (<1.5 or ≥1.5 mmol/L) and ApoB (<1.2 or ≥1.2 g/L).

Results. Total cholesterol, ApoB, and non-HDL cholesterol were significantly ($P < 0.05$) higher in patients with albuminuria. For quartiles of the lipid parameters, prevalences of albuminuria showed significant association with ApoB and non-HDL cholesterol (P trend <0.05). After adjusting for age, systolic blood pressure and hemoglobin A_{1c} (HbA_{1c}) correlation coefficients between the natural logarithm (ln) ACR and lipid parameters, odds ratios for albuminuria, and standardized regression coefficients for ln ACR, were significant for total cholesterol, ApoB and non-HDL cholesterol in all subjects and in men, but only ApoB was significant in women. For patients with normoalbuminuria, frequencies of normotriglycerides/normo-ApoB, hypertriglycerides/normo-ApoB, normotriglycerides/hyper-ApoB, and hypertriglycerides/hyper-ApoB were 44.7%, 28.9%, 10.5%, and 15.8%, respectively; and were 30.1%, 19.5%, 15.4%, and 35.0% for patients with albuminuria ($P <$ 0.001). The respective adjusted odds ratio for albuminuria for the four phenotypes was 1.00, 1.04 (0.54 to 2.00), 2.25 (1.02 to 5.00), and 3.38 (1.75 to 6.53).

Conclusion. Increased UAER is associated with ApoB-containing lipoproteins and the phenotype of hypertriglycerides/hyper-ApoB is associated with the highest risk of albuminuria. The surrogate marker of non-HDL cholesterol for ApoB is more applicable to the diabetic men.

Key words: microalbuminuria, lipid profile, apolipoprotein B, non-HDL cholesterol, type 2 diabetes.

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Increased urinary albumin excretion rate (UAER), even in the early microalbuminuric range, is associated with progressive renal failure and increased cardiovascular morbidity and mortality in diabetic and nondiabetic patients [1–8]. The mechanisms linking increased UAER and increased risk of cardiovascular disease remain to be answered, but one of the mechanisms is its link with atherogenic lipoproteins. Although lipid metabolism has been extensively investigated in diabetes, little information is available concerning the lipid abnormalities associated with increased UAER, especially in the early stage without impairment in renal function. In a prospective study from the Steno Diabetes Center, the baseline total cholesterol but not high-density lipoprotein (HDL) cholesterol was an independent risk factor for microalbuminuria and overt diabetic nephropathy in type 2 diabetic patients [9]. However, apolipoprotein (Apo) levels were not measured in that study. Samuelsson et al reported that ApoB was associated with a declining glomerular filtration rate (GFR) [10], and that renal dyslipidemia was predominantly associated with the accumulation of ApoB-containing lipoproteins in both sclerotic and nonsclerotic glomeruli [11]. However, these studies evaluated patients with more advanced renal disease and not specifically in diabetic patients. A Japanese study showed that type 2 diabetic patients who progressed from normoalbuminuria to microalbuminuria after 2 years had significantly higher baseline triglycerides and ApoB levels [12]. However, this study did not evaluate the interaction between triglycerides and ApoB.

Assessments of the conventional lipid profile including total cholesterol, triglycerides, HDL cholesterol and low-density lipoprotein (LDL) cholesterol do not always appropriately reflect the atherogenicity associated with dyslipidemia in the diabetic patients. Instead, measurement of plasma ApoB may reflect the total number of

atherogenic lipoprotein particles, including very low-density lipoprotein (VLDL), LDL, intermediate-density lipoprotein (IDL), and lipoprotein(a) [13]. Because ApoB is not always measured in clinical practice, the National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATP III) recommended the calculation of non-HDL cholesterol as a surrogate marker [14]. However, Sniderman, Scantlebury, and Cianflone [15] suggested that lipid measurement should include ApoB (rather than the surrogate non-HDL cholesterol) and patients should be classified based on triglyceride and ApoB levels because hypertriglyceride/hyper-ApoB phenotype is more atherogenic and is characterized by high triglyceride, low HDL cholesterol and increased numbers of small, dense LDL particles [15]. To the best of our knowledge, whether this phenotype is associated with increased UAER in type 2 diabetic patients has not been examined. Therefore, the objective of this study was to evaluate the relationship between UAER and the measured lipid profile, including total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, ApoA1, and ApoB, the calculated non-HDL cholesterol, and the phenotype of hypertriglyceride/hyper-ApoB in type 2 diabetic patients.

METHODS

Subjects

The study was approved by the Department of Health, Executive Yuan, Republic of China with subjects participating voluntary with their informed consent. In a diabetic clinic at the National Taiwan University Hospital, the demographic data and basic information of the patients have been collected for convenience of follow-up, when they attended the clinic for the first time. Among them, there were 777 diabetic patients (339 men and 438 women) aged 30 years or older with the diagnosis of type 2 diabetes mellitus. The patients were treated with either oral antidiabetic drugs or insulin at the time of recruitment. They did not show a history of diabetic ketoacidosis at the onset of diabetes mellitus, nor did they receive insulin treatment within 1 year of diagnosis. All of these patients were invited to participate in a health examination and a total of 610 patients (268 men and 342 women) (78.5%) actually participated. The distribution of age and gender between those who did not participate and those who participated were not different significantly. For those who did not participate and those who participated, the respective age was 62.0 ± 10.6 years and 63.3 ± 10.8 years, respectively; and the respective percentage of men was 42.5% and 43.9%. In order to evaluate the lipid abnormalities associated with UAER without the influence of potential confounders, the subjects recruited into the present study were selected from the 610 subjects based on the following stringent criteria: (*1*) nonsmoker and nonconsumer of alcoholic beverages; (*2*) no history of hypertension and not taking any antihypertensive agent; (*3*) no history or symptoms of congestive heart failure and not receiving treatment for such; (*4*) no use of lipid-lowering agents, antibiotics, hormone replacements, or vitamin supplements; (*5*) normal renal function [blood urea nitrogen (BUN) $\leq$8.6 mmol/L (24 mg/dL) and serum creatinine $\leq$106.1 μmol/L (1.2 mg/dL)]; and (*6*) no acute illness or fever. As a result, a total of 275 patients (122 men and 153 women) aged 60.6 ± 11.1 years were recruited.

Measurements of albumin-to-creatinine (ACR) and calculation of creatinine clearance

The subjects were advised not to participate in vigorous physical activity one day before the examination. Urinary specimen and blood samples were collected in the early morning after the subjects fasted for at least 12 hours. First-void and midstream urine was collected; this was followed by venous blood sampling. The concentration of urine albumin was quantitatively measured by means of particle-enhanced turbidimetric immunoassay (Biolatex, Logrono, Spain). The urine creatinine concentration was measured after 10× dilution on an automatic biochemistry analyzer (Cobas Mira S) (Roche Diagnostica, Basel, Switzerland) with reagents obtained from Randox Laboratories Ltd. (Antrium, UK). ACR was calculated by dividing the urinary albumin concentration in micrograms by the urinary creatinine concentration in milligrams. An ACR $\geq$30 μg/mg was defined as albuminuria, and <30 μg/mg as normoalbuminuria. Creatinine clearance (mL/min) was calculated from the Cockcroft-Gault formulae as: [(140 − age in years) ∗ body weight in kg]/(72 ∗ serum creatinine in mg/dL) [16]. For women, the calculated values were multiplied by 0.85 [16].

Measurements of lipid parameters

Serum samples were used to determine total cholesterol, triglycerides, HDL cholesterol, and LDL cholesterol levels on an automatic biochemistry analyzer (Cobas Mira S) (Roche Diagnostica) with reagents obtained from Randox Laboratories Ltd. Serum ApoA1 and ApoB were measured with reagents obtained from Raichem SPIA (Reagents Applications Inc., San Diego, CA, USA). A tenfold dilution was made before assay if the serum sample was turbid or triglyceride level was >4.48 mmol/L (400 mg/dL).

Non-HDL cholesterol was calculated as total cholesterol minus HDL cholesterol. The subjects were divided into four phenotypes based on the levels of triglyceride (<1.5 or $\geq$1.5 mmol/L) and ApoB (<1.2 or $\geq$1.2 g/L) as normotriglyceride/normo-ApoB, hypertriglyceride/normo-ApoB, normotriglyceride/hyper-ApoB, and hypertriglyceride/hyper-ApoB. The cutoffs followed