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Variability of triglyceride levels and incidence of microalbuminuria in type 2 diabetes

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BACKGROUND: Experimental and clinical studies have shown a strong association between hypertriglyceridemia and diabetic nephropathy. A variability of triglyceride (TG) levels has been reported in diabetes.

OBJECTIVES: To investigate the relationship of TG variability with the incidence of microalbuminuria (albumin excretion rate $>$ 20 μg/min), in patients with type 2 diabetes.

METHODS: A longitudinal, retrospective, observational study was performed on a consecutive series of 457 normoalbuminuric outpatients, with measurements of HbA_1c, lipids and microalbuminuria thrice per year with 6.8-year follow-up. TG variability, defined as standard deviation of TG (TG-SD) and TG-SD adjusted for the number of visits was calculated. A nested case-control sensitivity analysis was performed to validate the results of the primary cohort study.

RESULTS: Incident microalbuminuria (N = 124, 27.1%) was associated with higher median TG-SD (33.6 mg/dL vs 29.0 mg/dL, $P < .05$) and TG-SD adjusted for the number of visits (31.4 mg/dL vs 26.7 mg/dL, $P < .05$). At multivariate (Cox) analysis, logTG-SD and adj-logTG-SD were significant predictors of incident microalbuminuria (hazard ratio 2.1 [1.1–4.2], $P = .028$ and 1.5 [1.1–3.3], $P = .042$, respectively). In the case-control analysis, time spent with TG $>$ 150 mg/dL during the follow-up was significantly higher in cases vs controls (27.2 ± 19 vs 16.7 ± 12.5 months, $P < .05$) with hazard ratio 2.0 (1.1–5.1), $P < .05$, for adj-logTG-SD.

CONCLUSIONS: A higher intraindividual TG variability is a predictor of incident microalbuminuria in type 2 diabetes. In addition, time of exposure to elevated TG levels (>150 mg/dL) predicts incident microalbuminuria.

Diabetic nephropathy (DN) is the most common cause of end-stage renal disease in people with diabetes.[1] Chronic hyperglycemia and elevated HbA_1c levels play a key role in the development of this complication.[2] Other traditional risk factors (ie, advanced age, long duration of diabetes, hypertension) play a role in the development of DN. Epidemiological data confirm that a tight control of glucose and

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blood pressure are the pivotal modifiable key factors in preventing the onset and progression of chronic kidney disease in diabetes.[3–5]

It has been suggested that dyslipidemia is an additional risk factor for this complication.[6] A systematic review of studies assessing the association between lipids and diabetic microangiopathy showed that hypertriglyceridemia may induce the onset or progression of renal disease in diabetes.[7] A post-hoc analysis of large-scale, randomized, controlled trials with fenofibrate, showed a favorable effect of triglyceride (TG)-lowering treatment on the incidence and evolution of DN in type 2 diabetes.[8] In addition, data from recent observational cohort studies showed an independent association between TG levels and risk of DN.[9,10]

In the last decade, HbA_{1c} variability, expressed as the intrapersonal standard deviation (SD) of serially measured HbA_1c, has emerged as a new independent risk factor for the development of diabetic microvascular complications, both in type 2 and type 1 diabetes.[11,12] A recent prospective cohort study, the Renal Insufficiency And Cardiovascular Events study,[13] confirmed that HbA_1c is independently associated with the development of albuminuria in patients with type 2 diabetes.

Intraindividual lipid fluctuations have been observed in longitudinal studies both in type 1 and type 2 diabetes, with TG levels showing the highest variability.[14,15] The potential impact of this variability on the risk for microvascular complications of diabetes has not been explored so far.

Thus, the primary aim of this study was to assess the effect of TG intraindividual variability on the incidence of microalbuminuria in type 2 diabetes.

Methods

A longitudinal, retrospective, observational cohort study was performed on a consecutive series of normoalbuminuric patients with a clinical diagnosis of type 2 diabetes, aged ≥50 years, referred to our clinic between January 1 and March 31, 2007. Patients with known chronic kidney disease, dialysis, or renal transplantation at enrollment and a history of alcohol abuse were excluded from the study. Duration of diabetes, anthropometric data (height, weight, and waist circumference), current therapies, and smoking status were recorded at first visit; on the same occasion, blood pressure was measured in the sitting position using a mercury sphygmomanometer, considering the mean of 2 measures after a rest of 5 minutes. Patients were entered in a regular program of scheduled follow-up visits, with determinations of HbA_1c, serum creatinine, lipid profile, and microalbuminuria at least 3 times a year; measurement of microalbuminuria was repeated when urinary albumin excretion rate (AER) in 1 overnight urine collection was >20 μg/min and <200 μg/min. This program was part of the routine clinical management of type 2 diabetes at the time of the study. Data were collected up to the last available visit before January 31, 2014, with an average follow-up of 6.8 years. The first 2 years of follow-up (from first visit) were used for determination of TG variability, defined as SD of TG (TG-SD). Following Pidcoke et al,[16] we also categorized the patients as hypertriglyceridemic when over 50% of TG measurements in those 2 years were above 150 mg/dL. Patients who developed microalbuminuria, or who were lost at follow-up, during those first 2 years, were excluded from any further analysis. The incidence of microalbuminuria, defined as urinary AER in 2 overnight urine collections >20 μg/min and <200 μg/min, was then assessed in the subsequent follow-up of 4.8 years.

In addition, a nested case-control study was performed within the same cohort, comparing cases of incident microalbuminuria with 1:1 randomly selected controls matched for age (±2 years), gender, duration of diabetes (±2 years), and body mass index (±1 kg/m^2). In cases and controls, time spent with TG > 150 mg/dL during the 4.8-year follow-up was calculated, hypothesizing that TG levels remained constant from 1 determination to the following measurement.

All laboratory measures were performed in our central laboratory. HbA_1c determinations were performed by high-performance liquid chromatography, using a DCCT-standardized protocol (Menarini Diagnostics, Florence, Italy). Fasting glucose, total cholesterol, high-density lipoprotein cholesterol, and TG concentrations were automatically determined (Beckman Instruments, Brea, USA), whereas low-density lipoprotein cholesterol levels were calculated by the Friedewald formula for TG levels < 400 mg/dL, and directly measured when TG exceeded that threshold. Albuminuria was measured by immunonephelometry (Beckman Coulter, USA).

Average HbA_1c and HbA_1c variability was calculated for each patient as the intraindividual mean (HbA_1c-mean) and SD (HbA_1c-SD), respectively. In each patient, TG variability was calculated as the SD for TG levels (TG-SD) and then adjusted for the number of available determinations to avoid potential bias in the analysis (adj-TG-SD) according to the formula: $\text{adj} - \text{TG} - \text{SD} = \text{SD}/\sqrt{[n/(n-1)]}$. Patients with no available data on microalbuminuria after January 1, 2013, were excluded from the analysis, unless they had previously developed microalbuminuria during follow-up. All the patients gave their written informed consent before study participation.

All variables were checked by Kolmogorov–Smirnov test to evaluate their distribution. TG levels were log-transformed because values were not normally distributed. Unpaired Student's *t* test and Mann-Whitney tests were used for comparisons of normally and non-normally distributed continuous variables, whereas chi square tests were applied for between-group comparisons of categorical parameters. In the cohort study, survival analyses were performed with Kaplan–Meier method, and Cox regression was used for multivariate analysis. In the nested case-control study, a conditional logistic regression was applied. All statistical analyses were performed using SPSS 21.0.