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Higher serum triglyceride to high-density lipoprotein cholesterol ratio was associated with increased cardiovascular mortality in female patients on peritoneal dialysis

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Abstract *Background and aims:* High serum triglyceride to high-density lipoprotein cholesterol (TG/HDL-C) ratio has been found to be an independent predictor for cardiovascular events in the general population. We aimed to evaluate whether a high TG/HDL-C ratio was associated with an increased risk of mortality in patients on continuous ambulatory peritoneal dialysis (CAPD).
Methods and results: In this single-center retrospective cohort study, 1170 incident patients on peritoneal dialysis (PD) from 1 January 2007 to 31 December 2011 were recruited and followed up until 31 December 31 2013. The mean age was 47.4 ± 15.2 years, and 24.7% were diabetic. During a median of the 34.5-month follow-up period, 213 (18.2%) deaths occurred, 121 of which (56.8%) were caused by cardiovascular disease (CVD). The serum median TG/HDL-C ratio at baseline was 2.57 (range: 0.06–39.39). On multivariate Cox regression analysis, the highest quartile of the TG/HDL-C ratio (≥4.19) was associated with increased risk of all-cause mortality (hazard ratio (HR) 1.98, 95% confidence interval (CI), 1.17–3.36; $P = 0.011$) and CVD mortality (HR 2.28, 95% CI, 1.16–4.47; $P = 0.017$). For female patients, each one-unit higher baseline TG/HDL-C was associated with 13% (95% CI 1.06–1.22; $P = 0.001$) increased risk of CVD mortality, whereas such an association was not observed for male patients, (HR 1.00, 95% CI 0.92–1.08; $P = 0.977$).
Conclusions: A higher serum TG/HDL-C ratio was associated with an increased risk of all-cause and CVD mortality in PD patients. Moreover, the increased risk of CVD mortality was significantly higher in female than male PD patients.

Introduction

Both elevated serum triglyceride (TG) and reduced high-density lipoprotein cholesterol (HDL-C) levels are well recognized as risk factors of increased cardiovascular disease (CVD) [1]. Recently, a greater predictive power of detecting the risk of CVD was found by combining high TG and low HDL-C in a single marker instead of individual lipids [2]. Accumulated evidence indicated that the TG/HDL-C ratio is an independent predictor of all-cause mortality [3] and major cardiovascular (CV) events [4], and of fatal or nonfatal stroke [5] among healthy individuals, patients receiving coronary angiography therapy, and patients with a history of stroke.

Disturbances of lipid transport and metabolism are common complications of peritoneal dialysis (PD) [6]. The hallmark dyslipidemias in the PD population are

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hypertriglyceridemia and low serum HDL-C levels [7]. Factors contributing to this phenomenon may include glucose absorption from the dialysis fluid, which results in increased insulin levels and enhanced synthesis of TG in the liver, protein and lipoprotein loss into the dialysis fluid stimulating very low-density lipoprotein (VLDL) synthesis in the liver, and preferential loss of smaller "protective" HDL molecules [8,9]. However, there is a paucity of data on whether TG/HDL-C ratio is an independent predictor of mortality in PD patients. In this study, we attempted to test the hypothesis that higher TG/HDL-C ratios are associated independently with higher risks of all-cause and CVD mortality in PD patients.

Methods

Participants and study protocol

This was a retrospective observational cohort study. All incident PD patients at the First Affiliated Hospital, Sun Yat-sen University (SYSU) were recruited from 1 January 2007 to 31 December 2011. The inclusion criteria were ages $\geq$18 years and having received at least three consecutive months of continuous ambulatory peritoneal dialysis (CAPD) therapy. Patients who were catheterized in other hospitals, transferred from permanent hemodialysis (HD) or failed renal transplantation, or did not have baseline TG/HDL ratio were excluded. Conventional PD solutions (Dianeal 1.5%, 2.5%, or 4.25% dextrose; Baxter Healthcare, Guangzhou, China), Y-sets, and twin-bag systems were utilized in almost all of the CAPD patients. The study was conducted in compliance with the ethical principles of the Helsinki Declaration (http://www.wma.net/en/30publications/10policies/b3/index.html) and approved by the Human Ethics Committees of SYSU. Written informed consent was obtained from all participants before study entry.

All patients were followed up until death, transfer to HD, kidney transplantation, transfer to another center, or censoring on 31 December 2013. Baseline data at the first 1–3 months after the initiation of CAPD were collected, including demographics (age (years), gender, cause of end-stage renal disease (ESRD), major comorbidities (CVD, hypertension, and diabetes), body mass index (BMI) (kg/m^2)), and biochemical data (hemoglobin, serum albumin, serum creatinine, albumin-corrected calcium, serum phosphorus, total cholesterol, TG, HDL-C, and low-density lipoprotein cholesterol (LDL-C)), which were measured in the center laboratory of the First Affiliated Hospital of SYSU. The comorbidity score was determined according to the Charlson Comorbidity Index (CCI) [10]. The glomerular filtration rate (GFR) was measured as the mean of urea and creatinine clearance, calculated from 24 h urine collections and indexed for body surface area. We adapted the guideline of the International Society for Peritoneal Dialysis (ISPD) to evaluate and manage patients for the dyslipidemia. Patients were required to return to our center at least quarterly for an overall medical evaluation or they were interviewed by telephone monthly with primary nurses for assessing general conditions and concomitant medications. Quarterly visits and monthly telephone contacts were performed for clinical purposes not specifically for this study.

Study definitions

The primary outcomes were all-cause and CVD mortality. CV events contributing to CVD mortality included acute myocardial infarction, atherosclerotic heart disease, cardiomyopathy, cardiac arrhythmia, cardiac arrest, congestive heart failure, cerebrovascular accident, ischemic brain damage, anoxic encephalopathy, and peripheral vascular disease, determined by the PD follow-up panel composed of PD primary nurses and professors. CVD was defined as a history of angina pectoris, myocardial infarction, angioplasty, coronary artery bypass, heart failure, or stroke. Patients who reported current use of insulin or an oral hypoglycemic agent and/or who had a clinical diagnosis of type 1 or type 2 diabetes mellitus (T2DM) were considered to have diabetes mellitus (DM). Hypertension was recorded if the patient took antihypertensive drugs or had two separate blood pressure measurements $\geq$140/90 mmHg.

Statistical analysis

TG/HDL-C was calculated as TG divided by HDL-C (expressed in milligrams per deciliter). Non-HDL-C was calculated by subtraction of HDL-C from total cholesterol, and analyzed as a continuous variable. Participants were stratified into quartiles (Qs) of TG/HDL ratio: Q1 $<$ 1.68, 1.68 $\leq$ Q2 $<$ 2.57, 2.57 $\leq$ Q3 $<$ 4.19, and Q4 $\geq$ 4.19. The results were presented as frequencies and percentages for categorical data, and mean $\pm$ standard deviation for continuous variables. Chi-squared, one-way ANOVA or Kruskal–Wallis tests were used to test for the differences in categorical or continuous factors among different categories of the TG/HDL-C ratio. Furthermore, logistic analysis was conducted to assess the risk factors for high TG/HDL-C ratio. Survival was calculated using the Kaplan–Meier method, and the differences between distributions of survival were assessed by a log-rank test. The association between TG/HDL-C ratio and mortality was examined in a Cox regression model. Statistical significance was defined as $P < 0.05$ using two-tailed tests. Statistical analyses were performed using SPSS, version 13.0 for Windows (SPSS Inc.).

Results

Study population

In total, 1319 incident PD patients were catheterized at our PD center, of whom 17 were younger than 18 years of age, five patients were transferred from failed renal transplantation, 49 patients were from permanent HD, and 68 patients were on PD $<$ 3 months. Of the 1180 remaining patients, 1170 patients with available baseline TG/HDL-C ratio were finally enrolled in this study (mean age 47.4 $\pm$ 15.2 years; 58.9% men; 24.7% with diabetes) (Fig. 1). The most common primary renal disease is chronic