Journal of Cardiology xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Journal of Cardiology

journal homepage: www.elsevier.com/locate/jjcc

Original article

Remnant lipoproteinemia predicts cardiovascular events in patients with type 2 diabetes and chronic kidney disease

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ARTICLE INFO

Article history:
Received 29 February 2016
Received in revised form 15 April 2016
Accepted 28 April 2016
Available online xxx

Keywords:
Remnant lipoproteins
Diabetes mellitus
Chronic kidney disease
Prognosis
Cardiovascular events

ABSTRACT

Background: Patients having type 2 diabetes mellitus (DM) and chronic kidney disease (CKD) are at high risk of cardiovascular events. Triglyceride-rich lipoprotein levels are synergistically increased in patients with DM and CKD. This study examined the predictive value of remnant lipoprotein levels for cardiovascular events in patients with DM and CKD.

Methods: Three hundred and sixty-five patients with type 2 DM and CKD were enrolled. Serum levels of remnant lipoproteins (remnant-like lipoprotein particles cholesterol; RLP-C) were measured by an immunoseparation method. All patients were followed prospectively for a period of 45 ± 23 months or until occurrence of one of the following events: cardiac death, non-fatal myocardial infarction, unstable angina requiring unplanned coronary revascularization, or ischemic stroke.

Results: During the follow-up period, 59 patients had cardiovascular events. Multivariate Cox analysis revealed that high levels of RLP-C (≥4.3 mg/dL; median value) were a significant risk factor for cardiovascular events, independent of traditional risk factors (HR: 1.30; 95% CI: 1.04–1.63; $p = 0.02$). The addition of high levels of RLP-C to traditional risk factors improved net reclassification improvement (NRI) and integrated discrimination improvement (IDI) (NRI 0.36, $p = 0.01$; and IDI 0.03, $p = 0.02$).

Conclusions: RLP-C is useful for risk assessment of future cardiovascular events in patients having type 2 DM and CKD.

Introduction

Diabetes mellitus (DM) is an important risk factor for cardiovascular disease as well as chronic kidney disease (CKD). Cardiovascular risk is synergistically increased when CKD is accompanied with DM [1]. Low estimated glomerular filtration rate (eGFR) was shown to be a predictor of cardiovascular events in diabetic patients [2]. In addition, CKD due to DM has particularly high risk of death prior to reaching end-stage renal disease (ESRD) when compared to other causes [3]. Thus, management of DM and CKD requires a multifactorial approach including dyslipidemia control.

We have previously shown that remnant lipoproteinemia had a predictive value for cardiovascular events in patients with type 2 DM [4]. High levels of triglyceride (TG)-rich lipoproteins are associated with type 2 DM due to increased hepatic lipogenesis caused by insulin resistance [5]. Also, there is an impaired clearance of TG-rich lipoproteins due to reduced activities of lipoprotein lipase and hepatic lipase in CKD [6]. Besides, there was evidence that the increase in intestinal cholesterol absorption might be an additional mechanism for remnant lipoproteinemia in patients having DM and CKD [7]. Remnant lipoproteins were also found to be increased even in ESRD patients undergoing hemodialysis [8]. In this context, levels of TG-rich lipoproteins including remnants may synergistically increase in patients with DM and CKD. Up to now, there were few studies investigating whether remnant lipoproteinemia may have a predictive value for cardiovascular events in patients having both DM and CKD.

In the past, it was difficult to assess levels of remnant lipoprotein as they have heterogeneous properties. However,

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http://dx.doi.org/10.1016/j.jjcc.2016.04.011
0914-5087/

a simple and reliable technique for measurement of remnant-like lipoprotein particles cholesterol (RLP-C) using immunoseparation method has been developed [9]. The present study was conducted to explore whether RLP-C may have predictive value for cardiovascular events in patients with DM and CKD.

Methods

Patients

This prospective study initially recruited 1409 patients who were admitted to the cardiology section of Yamanashi University Hospital from May 2007 to December 2015. All the patients had a routine measurement of lipid parameters including RLP-C. The inclusion criteria into this study were the concurrent diagnoses of type 2 DM and CKD. Type 2 DM was diagnosed by using American Diabetes Association (ADA) criteria, as indicated by a fasting plasma glucose concentration >7.8 mmol/L (126 mg/dL) or a 2-h plasma glucose concentration >11.0 mmol/L (200 mg/dL) after a 75-g oral glucose tolerance test or with glucose-lowering drug treatment [10]. CKD criterion was eGFR below 60 mL/min/1.73 m^2 for more than 3 months [11]. The staging of CKD was based on eGFR; stage III: 30–60 mL/min/1.73 m^2, stage IV: 15–30 mL/min/1.73 m^2, and stage V: <15 mL/min/1.73 m^2 [11]. This study excluded patients with renal artery stenosis detected using renal artery duplex ultrasound study. Renal artery stenosis was defined by a renal peak systolic velocity >200 cm/s and/or a systolic renal-to-aortic ratio >3.5. The other exclusion criteria were: (1) use of contrast media 3 months prior to enrollment; (2) polycystic kidney disease; (3) chronic inflammatory diseases; (4) major injury or surgery 3 months prior to enrollment; and (5) other serious diseases. Finally, a total of 383 patients were enrolled in the study according to these inclusion and exclusion criteria. All the patients gave written, informed consent for the study at enrollment. The study was approved by the ethics committee of Yamanashi University Hospital. The investigation conformed to the principles outlined in the 1975 Declaration of Helsinki.

Follow-up study

A flow chart of patient enrollment and follow-up is shown in Fig. 1. After baseline data were obtained at our hospital, all study patients had monthly prospective follow-up investigations at out-patient clinic with the schedule and medication titration depending on attending doctors. The data were obtained every 3 months from the patients' primary physicians. These investigations were carried out for a period of up to maximum 80 months or until the occurrence of a major cardiovascular event that included cardiac death, non-fatal acute myocardial infarction (AMI), refractory unstable angina pectoris (uAP) requiring unplanned coronary revascularization, and ischemic stroke. uAP was diagnosed by the presence of acute ischemic symptoms lasting ≥20 min within the 48 h prior to hospital admission and consistent electrocardiographic changes without positive cardiac biomarkers [12]. AMI was diagnosed when creatine kinase-MB levels increased by at least 2 times the upper limit of normal or when troponin T levels were >0.1 ng/mL [12]. Cardiac death was confirmed by hospital records. Ischemic stroke was diagnosed if the patient had an appropriate clinical event lasting >24 h, and brain computed tomography/magnetic resonance imaging showed a finding compatible with ischemic infarction including atherothrombotic infarction and lacunar infarction [13,14].

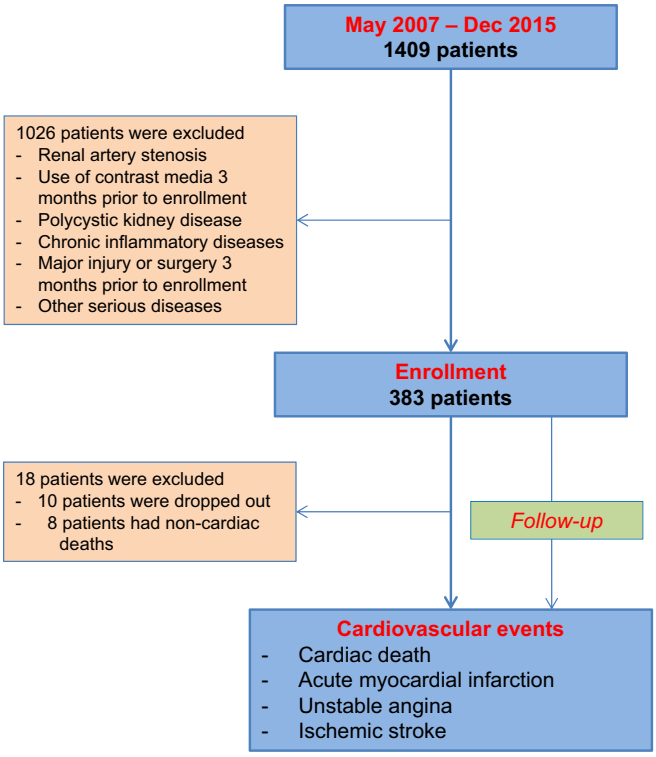

Fig. 1. Flow chart of patient enrollment and follow-up.

Laboratory examinations

Venous blood and urine sample were obtained after 12-h fasting at the discharge. Fasting serum TG concentration was measured enzymatically, and serum high-density lipoprotein cholesterol (HDL-C) concentration was measured by heparin-Ca^{2+}/Ni^{2+} precipitation. Low-density lipoprotein cholesterol (LDL-C) levels were calculated by Friedewald formula. Non-HDL-C was calculated as total cholesterol minus HDL-C. RLP-C levels were measured using immunoseparation assay as described previously [9]. Levels of total apolipoprotein (apo)B were determined by relevant immunoturbidimetric assays (Daiichi Chemicals, Tokyo, Japan). ApoAI levels were measured by the turbidimetric immunoassay system (Daiichi Pure Chemicals, Tokyo, Japan).

Creatinine levels in serum and urine were measured by an enzymatic method using an auto-analyzer (Mitsubishi Kagaku Iatron, Tokyo, Japan). Serum creatinine levels were measured on 2 days a week apart, with the average value being used in the analyses. eGFR was calculated as follow; eGFR (mL/min/1.73 m^2) = 194 × serum creatinine$^{-1.094}$ × Age$^{-0.287}$ (×0.739 if female) [15]. Urinary albumin levels were measured by immunonephelometry (Dade Behring, Marburg, Germany). Urine albumin to creatinine ratio (UACR) was calculated by dividing urinary albumin to urinary creatinine.

Statistical analysis

All descriptive data were expressed as either the mean value ± SD or median or frequencies (%). The predictive values of RLP-C levels were assessed by univariate and stepwise multivariate Cox proportional hazards models. Kaplan–Meier survival analysis was taken according to 2 groups based on the cut-off level of RLP-C [median value of RLP-C levels (4.3 mg/dL) in the study patients]. The additive effects of RLP-C on the predictive value were examined using C-statistic, category-free net reclassification improvement (NRI) and

Please cite this article in press as: Nguyen SV, et al. Remnant lipoproteinemia predicts cardiovascular events in patients with type 2 diabetes and chronic kidney disease. J Cardiol (2016), http://dx.doi.org/10.1016/j.jjcc.2016.04.011