Contents available at ScienceDirect

Diabetes Research and Clinical Practice

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

Malondialdehyde-modified LDL-related variables are associated with diabetic kidney disease in type 2 diabetes

Shoko Furukawa [a], *Hiroaki Suzuki* [a,*], *Kazuya Fujihara* [b], *Kazuto Kobayashi* [a], *Hitoshi Iwasaki* [a], *Yoko Sugano* [a], *Shigeru Yatoh* [a], *Motohiro Sekiya* [a], *Naoya Yahagi* [a], *Hitoshi Shimano* [a,c]

[a] *Division of Endocrinology and Metabolism, Department of Internal Medicine, Faculty of Medicine, University of Tsukuba, Tsukuba, Ibaraki, Japan*

[b] *Department of Hematology, Endocrinology and Metabolism, Niigata University Faculty of Medicine, Niigata, Japan*

[c] *International Institute for Integrative Sleep Medicine (WPI-IIIS), University of Tsukuba, Tsukuba, Ibaraki, Japan*

ARTICLE INFO

Article history:
Received 6 November 2017
Received in revised form
3 April 2018
Accepted 9 May 2018

Keywords:
Malondialdehyde-modified low-density lipoprotein
Type 2 diabetes
Albuminuria
Estimated glomerular filtration rate
Dyslipidemia

ABSTRACT

Background and aims: Oxidized low-density lipoprotein (oxLDL) causes the development of atherosclerosis and kidney injury. Although circulating oxLDL levels were reportedly increased in type 2 diabetic patients with macroalbuminuria, it remains unclear whether albuminuria or the reduced glomerular filtration rate (GFR) is independently associated with the circulating oxLDL level. This study aimed to elucidate the association between the stage of diabetic nephropathy and serum malondialdehyde-modified LDL (MDA-LDL) and the ratio of MDA-LDL to LDL-cholesterol (MDA-LDL/LDL).

Methods and results: This retroactive cross-sectional study used data from 402 patients with type 2 diabetes. Patients undergoing hemodialysis were excluded. Serum MDA-LDL levels were significantly increased with increases in severity of albuminuria (103 ± 44 U/L, 109 ± 54 U/L, and 135 ± 72 U/L for normoalbuminuria, microalbuminuria, and macroalbuminuria, respectively; P for trend = 0.020) but not according to the estimated GFR (eGFR). An increased MDA-LDL/LDL ratio was significantly associated with both increased albuminuria (35 ± 13, 37 ± 14, and 40 ± 15 for normoalbuminuria, microalbuminuria, and macroalbuminuria, respectively; P for trend = 0.003) and reduced eGFR (34 ± 13, 36 ± 13, 38 ± 12, and 51 ± 28 for grade 1, 2, 3 and 4, respectively; P for trend = 0.002). Multiple linear regression analysis showed that neither the albumin excretion rate nor eGFR but ln-transformed triglycerides and LDL-C levels were independent determinants of both serum MDA-LDL levels and MDA-LDL/LDL ratios.

Abbreviations: AER, albumin excretion rate: BMI, body mass index; CKD, chronic kidney disease; CVD, cardiovascular disease; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; EPA, eicosapentaenoic acid; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; ln AER, ln-transformed AER; ln HDL-C, ln-transformed HDL; ln TG, ln-transformed TG; MDA-LDL, malondialdehyde-modified low-density lipoprotein; MDA-LDL/LDL, MDA-LDL-to-LDL cholesterol ratio; oxLDL, oxidized low-density lipoprotein; TG, triglycerides

* Corresponding author at: Division of Endocrinology and Metabolism, Department of Internal Medicine, Faculty of Medicine, University of Tsukuba, Tsukuba, 1-1-1 Tennodai, Tsukuba, Ibaraki 305-8575, Japan.
E-mail address: hirosuzu@md.tsukuba.ac.jp (H. Suzuki).

https://doi.org/10.1016/j.diabres.2018.05.019
0168-8227/

Conclusion: Serum MDA-LDL levels and MDA-LDL/LDL ratios were increased in those with dyslipidemia associated with diabetic kidney disease.

1. Introduction

Diabetes mellitus is a high-risk state for atherosclerosis, leading to increased morbidity and mortality due to cardiovascular disease (CVD). It is also widely accepted that chronic kidney disease (CKD) presents a substantial risk for CVD. The presence of both diabetes and CKD is associated with a higher incidence of myocardial infarction and all-cause mortality compared with diabetes or CKD alone [1].

Oxidized low-density lipoprotein (oxLDL) has a pivotal role in the initiation and progression of atherosclerosis. oxLDL elicits foam cell formation, leading to increased release of inflammatory cytokines and chemokines from foam cells. It also stimulates medial smooth muscle cell migration into the intima, which was shown to be an important process for intimal thickening in atherosclerotic lesions [2]. Serum malondialdehyde-modified LDL (MDA-LDL), which is a type of oxidized LDL, was reported as a prognostic marker for future cardiac events in patients with stable angina and coronary stent implantation [3] or in diabetic patients with CAD [4]. The MDA-LDL-to-LDL cholesterol ratio (MDA-LDL/LDL) could predict the presence and development of coronary artery disease [5,6]. The MDA-LDL/LDL was independently associated with the coronary artery calcification score in patients with hemodialysis [7].

Recent studies have shown that oxLDL can contribute to the development of diabetic nephropathy through inducing injuries to podocytes [8], tubulointerstitial cells [9] and endothelial cells [10]. Production of collagen IV in mesangial cells was also reported as a contributor to the progression of diabetic nephropathy, which is stimulated by oxLDL-containing immune complexes [9]. Immunoglobulin G antibodies reacting with MDA-LDL lysine epitopes in circulating immune complexes were noted as a predictor of the development of macroalbuminuria in patients with type 2 diabetes [11]. Circulating oxLDL was reportedly increased in albuminuria in patients with diabetic nephropathy as well as in patients with end-stage renal diseases [12–14]. Although albuminuria was negatively correlated with the estimated glomerular filtration rate (eGFR) [15], there have been no studies on the association between oxLDL and eGFR in diabetes. Moreover, it is not clear whether albuminuria or eGFR is independently associated with circulating oxLDL levels.

To elucidate the association between the stage of diabetic nephropathy and serum MDA-LDL or the MDA-LDL/LDL, we conducted a cross-sectional study of patients with type 2 diabetes.

2. Methods

2.1. Study participants

We conducted a retrospective cross-sectional study using data on patients with type 2 diabetes who were admitted to the University of Tsukuba Hospital from January 2012 to December 2015. All patients had undergone a structured interview, physical examination, and laboratory analysis. We excluded data on patients undergoing hemodialysis, with the complications of diabetic ketoacidosis, hyperglycemia hyperosmolar syndrome, viral hepatitis, liver cirrhosis, malignancy, endocrine disorders affecting serum lipid levels, infectious diseases, inflammatory diseases, pregnancy, renal diseases other than diabetic kidney disease, and the use of systemic glucocorticoids, and who were under 20 years of age. Hypertension was defined as systolic blood pressure $\geq$140 mmHg and/or diastolic blood pressure $\geq$90 mmHg and/or the current use of antihypertensive agents. This retrospective study was approved by the Ethics Committee of the University of Tsukuba Hospital and conducted according to the Declaration of Helsinki.

2.2. Laboratory analysis

Blood samples were collected in the morning after an overnight fast within 3 days after admission. Plasma glucose and serum total cholesterol, high-density lipoprotein-cholesterol (HDL-C), triglycerides (TG), and creatinine levels were determined using an automated analyzer (7700 clinical analyzer; Hitachi High-Technologies Corporation, Tokyo, Japan). HbA1c was measured by high-performance liquid chromatography (Tosoh Corporation, Tokyo, Japan). Serum LDL-C levels were measured by a homogeneous assay (Sekisui Medical, Tokyo, Japan). Serum concentrations of MDA-LDL were quantitated by an enzyme-linked immunosorbent assay (Sekisui Medical, Tokyo, Japan). Albumin excretion rate (AER) was measured using 24-h urine specimens. eGFR was calculated using an equation modified for the Japanese: $eGFR = 194 \times sCre^{-1.0949} \times Age^{-0.287} \times 0.739$ (if female) [16]. AER and eGFR were categorized according to the 2012 Kidney Disease: Improving Global Outcomes clinical practice guidelines [17].

2.3. Statistical analysis

Continuous variables were expressed as mean ± SD or median and interquartile range based on distribution. Values of TG, HDL-C, and AER were log transformed due to their