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Investigation of MDA-LDL (malondialdehyde-modified low-density lipoprotein) as a prognostic marker for coronary artery disease in patients with type 2 diabetes mellitus

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ABSTRACT

Background: Although increased circulating levels of malondialdehyde-modified low-density lipoprotein (MDA-LDL) are associated with coronary artery disease (CAD), there is no direct evidence that increased MDA-LDL is a prognostic factor for CAD.
Methods: Forty-two patients (20 diabetic and 22 non-diabetic patients) who underwent percutaneous coronary intervention (PCI) were enrolled, and their baseline MDA-LDL levels were determined by immunoassay. Follow-up coronary angiography was performed at 2 to 7 months post-PCI. The patients were then divided into 2 groups, with in-stent restenosis (ISR) ($n = 13$) and without ISR ($n = 29$), and the baseline MDA-LDL levels were compared. We also studied 34 diabetics with CAD for up to 57 months until the onset of the next coronary event.
Results: In the diabetic patients, the mean MDA-LDL level was significantly higher in those with ISR than in those without ISR (151 +/− 61 vs. 90 +/− 26 U/l, $p = 0.010$). A baseline MDA-LDL value of 110 U/l for differentiating between diabetics with and without ISR was defined as the cut-off value. Kaplan–Meier analysis demonstrated that a circulating MDA-LDL of ≥110 U/l correlated significantly with a higher prevalence of cardiac events than MDA-LDL <110 U/l ($p = 0.032$).
Conclusions: Circulating MDA-LDL is a useful prognostic marker for future cardiac event in diabetic patients with CAD.

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1. Introduction

In recent years, oxidized LDL has attracted attention as a blood marker that is associated with coronary artery disease (CAD). Oxidized LDL plays important roles in the formation and development of the primary lesions of atherosclerosis. It is also known to damage vascular endothelial cells, facilitate expression of the adhesion factors of vascular endothelial cells, promote monocytic migration and facilitate the accumulation of lipids beneath the vascular endothelium through incorporation into monocyte-derived macrophages, which then form foam cells [1].

Recently, an ELISA technique was developed for the measurement of malondialdehyde-modified low-density lipoprotein (MDA-LDL), a representative form of oxidized LDL [2]. Clinical studies of the relationship between the blood MDA-LDL level and CAD have revealed the following. MDA-LDL levels were higher in CAD patients [3] and diabetic patients [4] than in the control subjects. There was a correlation between small, dense LDL (sdLDL), which is known to be a risk factor for CAD [5], and the MDA-LDL level, while the size of LDL particles correlated negatively with the MDA-LDL level [3,6–8]. The intima-media thickness correlated positively with the MDA-LDL level [3]. There was a positive correlation between the regression rate of coronary plaque volume as determined by the three-dimensional intravascular ultrasound technique and the regression rate of the MDA-LDL level after statin treatment [9]. An increased incidence of coronary in-stent restenosis (ISR) in type-2 diabetics after percutaneous coronary intervention (PCI) was related to an increased serum MDA-LDL level [10]. However, although many reports show that increased MDA-LDL is associated with CAD, no direct evidence has been presented that increased MDA-LDL is a prognostic factor for CAD.

This study prospectively investigated the relationships between the circulating MDA-LDL level and (1) ISR in patients who underwent PCI and (2) future cardiac events in CAD patients.

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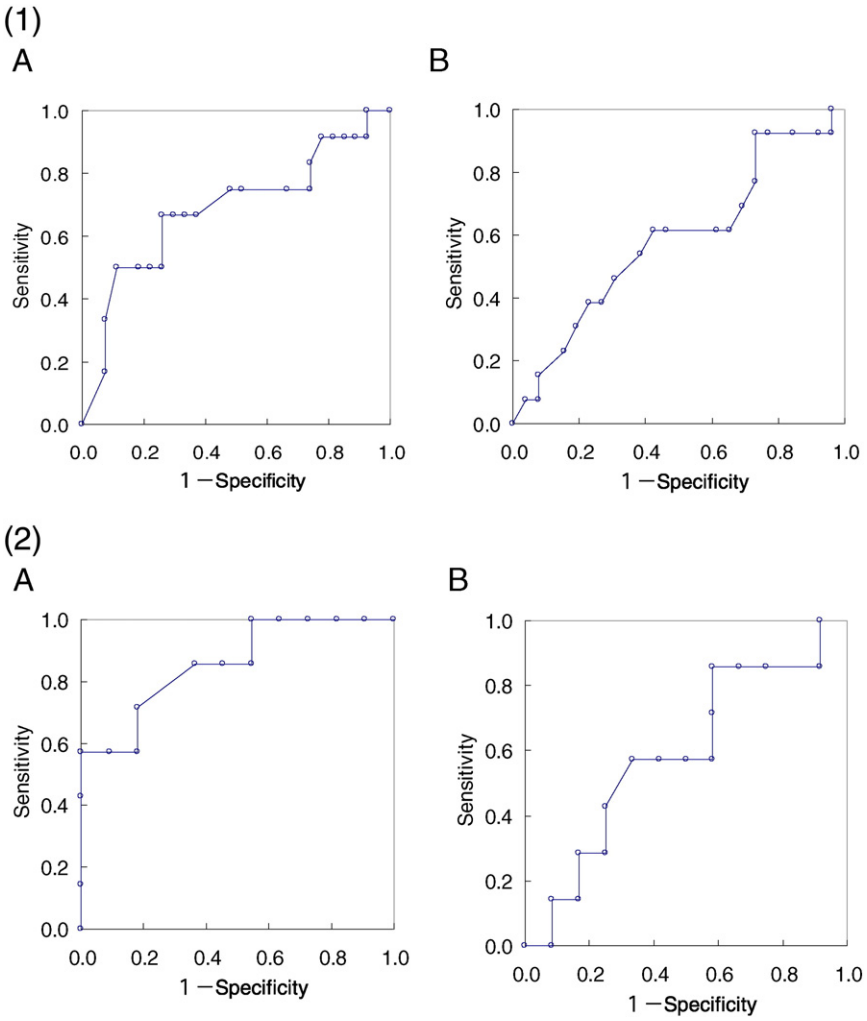

Fig. 1. (1) Receiver-operating characteristic curves of MDA-LDL for detection of in-stent restenosis in the whole group. A: Baseline (prior to PCI treatment). B: Follow-up (coronary angiographic evaluation 2 to 7 months after PCI). (2) Receiver-operating characteristic curves of MDA-LDL for detection of in-stent restenosis in the DM (+) group. A: Baseline (prior to PCI treatment). B: Follow-up (coronary angiographic evaluation 2 to 7 months after PCI).

2. Methods

2.1. Subjects

Forty-two consecutive patients (20 diabetics and 22 non-diabetics) who underwent stent implantation at PCI were prospectively studied. None of the patients received drug-eluting stents. The exclusion criteria were reduced left heart function (left ventricular ejection fraction ≤30%), unsuccessful PCI, renal insufficiency (serum creatinine ≥2 mg/dl), liver disease and/or malignant tumors. The study subjects received aspirin 100 mg/day (indefinitely following PCI), ticlopidine (for 1 month following PCI) and general treatment. None of the study subjects received intracoronary radiotherapy or experienced subacute in-stent thrombosis.

Ninety-one consecutive CAD patients (34 diabetic and 57 non-diabetic patients) were also studied prospectively. The diagnosis of CAD was based on a history of myocardial infarction, clinical symptoms including prolonged chest pain, and/or the presence of angiographically demonstrated coronary stenosis (obstructive lesions ≥50%). The exclusion criteria were reduced left ventricular function (left ventricular ejection fraction of 30% or lower), occurrence of ISR within 6 month after the initiation of observation, acute coronary syndrome (ACS), renal insufficiency (serum creatinine ≥2 mg/dl), liver disease, malignant tumors and/or acute death occurring within one month after the initiation of observation. The study subjects received standard treatment for risk factors of CAD (hypertension, diabetes mellitus, etc.) and

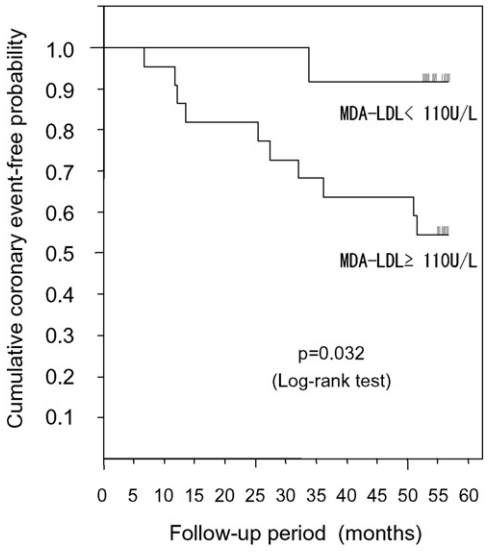

Fig. 2. Comparison of Kaplan–Meier curves for cumulative coronary event-free probability between subjects with the higher and the lower MDA-LDL levels in CAD (+) and DM (+) patients. The maximum duration of follow-up was 57 months, from the first measurement until the onset of the next coronary event, such as cardiac death, nonfatal myocardial infarction (MI), or refractory angina requiring PCI or coronary artery bypass grafting (CABG).

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