Patients with CD36 Deficiency Are Associated with Enhanced Atherosclerotic Cardiovascular Diseases

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Aim: The clustering of dyslipidemia, impaired glucose tolerance and hypertension increases the morbidity and mortality from cardiovascular events. A class B scavenger receptor, CD36, is a receptor for oxidized LDL and a transporter of long-chain fatty acids. Because of the impaired uptake of oxidized LDL in CD36-deficient macrophages and from the results of CD36 knockout mice, CD36 deficiency (CD36-D) was supposed to be associated with reduced risks for coronary artery disease (CAD); however, CD36-D patients are often accompanied by a clustering of coronary risk factors. The current study aimed to investigate the morbidity and severity of cardiovascular diseases in CD36-D patients.

Methods: By screening for CD36 antigen on platelets and monocytes using FACS or the absent myocardial accumulation of ¹²³I-BMIPP by scintigraphy, 40 patients with type CD36-D were collected, the morbidity of CAD and their features of atherosclerotic cardiovascular diseases were observed. Screening for CD36-D in both CAD patients (n=319) and healthy subjects (n=1,239) were undergone.

Results: The morbidity of CAD was significantly higher in CD36-D patients than in the general population; 50% of patients (20 out of 40) had CAD identified by BMIPP scintigraphy and 37.5% (3 out of 8) by FACS screening, respectively. Three representative CD36-D cases demonstrated severe CAD and atherosclerosis. The frequency of CD36-D was three times higher in CAD patients than in healthy subjects (0.9% vs 0.3%, p<0.0001).

Conclusion: The morbidity of CAD is significantly higher in CD36-D patients suffering from severe atherosclerosis, implying that the status of CD36-D might be atherogenic.


Key words; CD36 deficiency, Long-chain fatty acid transporter, Atherosclerotic cardiovascular disease, Insulin resistance, Metabolic syndrome

Introduction

Patients with metabolic syndrome (MetS) are characterized by a clustering of coronary risk factors, such as dyslipidemia including hypertriglyceridemia and a low level of high density lipoprotein-cholesterol (HDL-C), impaired glucose tolerance and hypertension along with the accumulation of abdominal visceral fat. The morbidity and mortality of atherosclerotic cardiovascular events are significantly high in patients with MetS, and the reduction of abdominal visceral fat by diet and exercise therapy is very important for treatment of the clustering of these coronary risk fac-
tors and atherosclerotic cardiovascular diseases.

CD36 is an 88-kDa membrane glycoprotein belonging to a class B scavenger receptor. CD36 is expressed in a variety of cells and tissues including platelets, monocyte/macrophages, heart, skeletal muscle, adipose tissue and small intestines. CD36 is a receptor for oxidized low density lipoproteins (LDL) and a transporter of long-chain fatty acids (LCFA). CD36-deficient patients were first identified from subjects who were refractory to platelet transfusion. Kashiwagi et al. identified several genetic mutations of human CD36 deficiency (CD36-D). We previously investigated the metabolic phenotypes of CD36-D patients and reported that they (high fasting serum triglycerides level, low HDL-C level, fasting hyperglycemia, insulin resistance and hypertension) were frequently observed and clustered in patients with CD36-D, similar to those with MetS. It was later reported that the accumulation of these metabolic phenotypes is not due to the deposition of abdominal visceral fat, but to insulin resistance or impaired metabolism of lipoproteins and free fatty acids (FFA) in the postprandial state in patients with CD36-D. It is well known that these metabolic profiles are independent coronary risk factors in the general population; therefore, the status of human CD36-D was supposed to be atherogenic and the morbidity of atherosclerotic cardiovascular diseases might be high in patients with CD36-D.

In contrast, the status of human CD36-D was supposed to be anti-atherogenic since CD36 is a scavenger receptor for oxidized LDL when the foam cell formation of CD36-D macrophages by exposure of oxidized LDL is impaired. Nozaki et al. showed that the uptake of oxidized LDL was reduced by approximately 40% in macrophages from patients with CD36-D compared with normal controls. Janabi et al. showed that the responses of oxidized LDL-induced NF-kappa B activation and subsequent cytokine expression were impaired in monocyte-derived macrophages from CD36-D patients. Furthermore, there have been two reports by Febbraio et al. and Moore et al. concerning the atherogenicity of genetic disruption of CD36 in mice. Both reports showed that macrophage foam cell formation when treated with oxidized LDL was impaired when they crossed CD36 null mice with atherogenic apoE-null mice; however, atherosclerotic lesion development in CD36-apoE double knockout mice was different in these two reports. Febbraio et al. showed a 76.5% decrease in aortic tree lesion areas when mice were fed a Western diet and a 45% decrease in the aortic sinus lesion area when fed a normal diet in CD36-apoE double knock-
ed anti-human CD36 monoclonal antibody OKM5 (Ortho Diagnostic Systems) (final concentration: 2.5 μg/ml) or FITC-conjugated mouse IgG (final concentration: 2.5 μg/ml) for 30 minutes at 40°C and assayed on a FACScan® system (Becton Dickinson Co., Mountain View, CA) as previously reported9. Appropriate cell fractions for the analysis of monocytes were selected by a gating method with a two-dimensional display of forward scatter and side scatter of analyzed cells. We diagnosed patients with type I CD36-D whose CD36 antigen was not detected in either monocytes or platelets. Each subject gave written informed consent before participating in the study, and the ethics committee of Osaka University Hospital approved the study design.

Analysis of Clinical Profile and Atherosclerotic Cardiovascular Diseases in Patients with CD36-D

The presence or absence of atherosclerotic cardiovascular diseases was extensively investigated in patients with CD36-D based upon their medical history and symptoms. We assessed the severity of atherosclerotic cardiovascular diseases and risk factors of these patients. Blood pressure was determined in the sitting position, and peripheral venous blood was drawn in the fasting state after overnight fasting and centrifuged for serum separation. Serum levels of total cholesterol (TC), triglycerides (TG), and HDL-cholesterol (HDL-C) as well as fasting plasma glucose levels were measured by enzymatic methods as reported in our previous study9. HbA1c was measured by HPLC (Sekisui Medical Co., Tokyo, Japan). All samples were treated in accordance with the Helsinki Declaration. In some patients with CD36-D, coronary angiography was performed for an extensive evaluation of coronary artery atherosclerosis. In order to evaluate atherosclerotic lesions in arteries other than coronary arteries in detail, the thoracic and abdominal aorta and their branches were examined by aortic angiography or magnetic resonance angiography.

Prevalence of CAD in Patients with CD36-D Identified by Absence of Cardiac Uptake of 123I-BMIPP

In order to assess whether patients with CD36-D had a higher mortality and severity of CAD, we evaluated the morbidity of CAD in these patients by checking medical records. The diagnosis of CAD was established when a patient had coronary artery stenosis (≥ 75%) assessed by coronary angiography. The CAD patients were divided into 3 groups by their clinical course and results of coronary angiography: 1) acute or old myocardial infarction, 2) unstable angina, and 3) stable angina.

Prevalence of CAD in Patients with CD36-D Identified by Screening of CD36-D by FACS Analysis in the General Population

For the screening study of CD36-D by FACS analysis, normal healthy volunteers were recruited for over ten years in our laboratory and we found 8 patients with type I CD36-D. We traced their medical records, especially the result of coronary angiography, in order to confirm whether they were accompanied by CAD.

Prevalence of CD36-D in Patients with CAD and Healthy Subjects

In order to evaluate whether the frequency of CD36-D in patients with CAD is higher than in normal healthy subjects, we performed screening examinations in patients with CAD and healthy subjects. Patients with coronary artery stenoses (≥ 75%) were diagnosed with CAD by coronary angiography (n=319). Normal healthy volunteers were recruited using the following criteria: no ST-T abnormalities in ECG, no chest symptoms on effort and no significant coronary artery stenosis (≥ 75%) if they received coronary angiography (n=1,239). Their cell surface CD36 antigen on monocytes and platelets was analyzed by FACS analysis and type I CD36-D was diagnosed by an absence of CD36 antigen in both cells. Statistical significance was assessed by Pearson’s chi-square test using JMP 8 software (SAS Institute Japan, Tokyo, Japan).

Results

Case Presentations

Out of 40 patients with CD36-D, we experienced three representative cases of severe atherosclerotic cardiovascular diseases. The metabolic parameters of these patients are shown in Table 1, and compared with those of patients with CD36-D in our previous study9. As found in that study, these three cases were accompanied by hypertriglyceridemia and low HDL-C, and hypertension (Case 2 received anti-hypertensive drugs), while one case showed high fasting plasma glucose.

Case 1 is a 74-year-old man. At the age of 62, he suffered acute myocardial infarction. Coronary angiography demonstrated severe and diffuse stenoses in 3 major coronary arteries (Fig. 1A and 1B) and he underwent percutaneous coronary revascularization. At the age of 66, angiographic restenosis was detected in the right coronary artery (RCA) and left anterior descending artery (LAD), which were later revascularized successfully. At the same time, we found total oc-
Table 1. Metabolic Profiles of Three Cases of CD36-D Associated with Severe Atherosclerotic Cardiovascular Diseases

<table>
<thead>
<tr>
<th></th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>CD36-D (n = 40)*</th>
<th>Healthy subjects (n = 84)*</th>
</tr>
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<td>Age (year)</td>
<td>74</td>
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<td>73</td>
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<td>TG (mg/dl)</td>
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<td>152</td>
<td>156</td>
<td>178 ± 89</td>
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<td>HDL-C (mg/dl)</td>
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<td>34</td>
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<td>FPG (mg/dl)</td>
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<td>110 ± 22</td>
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<td>154</td>
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<tr>
<td>dBP (mmHg)</td>
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<td>86</td>
<td>53</td>
<td>80 ± 10</td>
<td>77 ± 18</td>
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</table>

*CD36-D (n=40) and healthy, age, sex, and BMI-matched controls (n=84) were quoted from our previous study (Reference 9).

Abbreviations: BMI, body mass index; TC, total cholesterol; TG, triglycerides; FPG, fasting plasma glucose; sBP, systolic blood pressure; dBP, diastolic blood pressure.

Fig. 1. Case 1, a 74-year-old male patient with CD36-D
At the age of 62, he suffered from acute myocardial infarction, and emergent cardiac catheterization revealed severe and diffuse stenosis in the triple coronary arteries (1-A, right coronary artery (RCA); 1-B, left coronary artery (LCA), respectively). Magnetic resonance angiography revealed total occlusion of bilateral femoral arteries (1-C and 1-D), total occlusion of left anterior tibial artery and severe stenosis of right anterior tibial artery (1-E).
clusion of bilateral femoral arteries (Fig. 1C and 1D), complete obstruction of the left anterior tibial artery and severe stenosis of the right anterior tibial artery by magnetic resonance angiography (MRA) (Fig. 1E). Up to the age of 73, the serum level of brain natriuretic peptide (BNP) gradually increased and left ventricular ejection fraction assessed by echocardiography gradually decreased, although repeated revascularization was undergone successfully. At the age of 74, $^{123}$I-BMIPP scintigraphy revealed no myocardial uptake of BMIPP, an analogue of LCFA, and he was diagnosed with type CD36-D by FACS analysis. Regarding his risk factors for cardiovascular diseases, he had a history of smoking and impaired glucose tolerance was observed by an oral glucose tolerance test (data not shown) in addition to the metabolic disorders shown in Table 1.

Case 2 is a 73 year-old man. He had a history of excessive alcohol consumption, but he had never smoked. For over 10 years he regularly attended Osaka University Hospital and received medical treatments for hypertension and intermittent claudication. At the age of 72, he suffered acute myocardial infarction. On emergent coronary angiography, total occlusion of RCA was identified (Fig. 2A and 2B), and thereafter coronary revascularization was performed successfully. At the same time, thoracic and abdominal aortography revealed total occlusion of the right common iliac artery (Fig. 2C), complete obstruction of the right femoral artery (Fig. 2D) and severe stenosis of the left femoral artery (Fig. 2E). Thus, we decided to start anticoagulant therapy. Left ventricular ejection fraction in echocardiography did not improve although coronary revascularization was successful; therefore, we tested whether LCFA metabolism was impaired by scintigraphy using $^{123}$I-BMIPP, an analogue of LCFA, and found marked reduction of myocardial uptake of $^{123}$I-BMIPP. He was finally diagnosed with type I CD36-D by FACS analysis. This was accompanied by moderate hypertension and dyslipidemia, including hypertriglyceridemia and low HDL-C, as shown in Table 1.

Case 3 is a 73 year-old woman. She had no history of smoking or regular alcohol intake. At the age of 64, she began to feel chest discomfort and muscle
At the age of 64, she felt chest discomfort and muscle fatigue of the bilateral legs after climbing stairs. Magnetic resonance angiography (MRA) of lower limbs revealed total occlusion of bilateral femoral arteries and severe stenosis of right common iliac artery and bilateral popliteal arteries (3-A). The following year she was hospitalized for refractory unstable angina, and diagnostic cardiac catheterization revealed severe stenosis of triple coronary arteries (3-B and 3-C). Thoracic and abdominal aortography revealed severe stenosis of trunks brachiocephalicus, right common carotid artery (3-D), abdominal aorta and left renal artery (3-E).

Fatigue of the bilateral legs after climbing stairs. MRA of the lower limbs revealed total occlusion of the bilateral femoral arteries and severe stenosis of the right common iliac artery and bilateral popliteal arteries (Fig. 3A); therefore, anticoagulant drugs and vasodilators were administered. The following year she was hospitalized because of refractory unstable angina. Emergent diagnostic cardiac catheterization and thoracic and abdominal aortography were performed, which revealed severe stenoses of triple coronary arteries (Fig. 3B and 3C), the brachiocephalic trunk, right common carotid artery (Fig. 3D), abdominal aorta and left renal artery (Fig. 3E). At the same time, the patient was diagnosed with type II diabetes, hypertension, hypertriglyceridemia and low HDL-C, and drug treatments were started for these diseases. After stent implantation in the left renal artery, coronary artery bypass graft surgery was performed and a saphenous vein graft was connected to the RCA and left circumflex coronary artery, and the left internal thoracic artery to LAD. At the age of 73, she began to complain of exertional dyspnea and the serum level of BNP gradually increased even though these grafts were patent and native coronary arteries remained intact, as assessed by coronary angiography. $^{123}$I-BMIPP scintigraphy revealed no myocardial uptake of BMIPP and she
was diagnosed with type I CD36-D by FACS analysis.

Number of Risk Factors for CAD in Patients with CD36-D and Healthy Control Subjects

We compared the number of risk factors for CAD in patients with CD36-D (n=40) and healthy, age-, sex-, and BMI-matched controls (n=84) from our former study (Reference 9). Diabetes mellitus, hypertension and dyslipidemia were counted as risk factors for CAD. Patients with CD36-D had more risk factors for CAD than healthy subjects (patients with CD36-D vs healthy subjects: 1.20 ± 0.80 vs 0.76 ± 0.72 risk factors, p<0.005), and were associated with multiple risk factors for CAD.

Frequency of CAD in Patients with CD36-D

The frequency of CAD was examined among 40 patients with CD36-D who were identified by an absence of cardiac uptake of 123I-BMIPP. As shown in Table 2, the frequency of CAD in CD36-D patients was significantly high (50%, 20 of 40 CD36-D patients). Furthermore, in 20 CD36-D cases of CAD, coronary stenoses with high severity, acute or old myocardial infarction and unstable angina pectoris were observed in 65% (13 of 20 patients with CD36-D). These data suggest that CD36-D patients are accompanied by enhanced atherosclerotic cardiovascular diseases. By a screening study of FACS analysis, we found 8 patients with type I CD36 deficiency. Three patients (37.5%) out of 8 had coronary artery stenoses by coronary angiography.

Prevalence of CD36-D in Patients with CAD and Healthy Subjects

In order to investigate whether CD36-D may increase the prevalence of CAD, we also compared the morbidity of CD36-D between healthy subjects (n=1,239) and patients with CAD diagnosed by coronary angiography (n=319). As shown in Table 3, the frequency of CD36-D in patients with CAD was approximately 3-fold higher than in healthy subjects [CAD patients vs healthy subjects, 0.94% (3/319) vs 0.32% (4/1239)]. The statistical significance was assessed by Pearson’s chi-square test, and the frequency of CD36-D was significantly higher in patients with CAD (p<0.0001). These data suggest that patients with CD36-D are susceptible to CAD.

Discussion

In patients with CD36-D, compared with healthy CD36-positive controls, metabolic phenotypes such as high TG levels, low HDL-C levels, high fasting glucose and hypertension were observed more frequent-
ly. Furthermore, we also found that patients with CD36-D are accompanied by insulin resistance, postprandial hyperlipidemia, and high levels of remnant lipoprotein cholesterol and FFA. These coronary risk factors were clustered in each CD36-D patient, which may appear to be partly similar to the profiles of patients with MetS. Another report showed that Pro90Ser CD36 mutation was associated with elevated FFA levels. These profiles have been shown to be independent coronary risk factors by many clinical investigations; however, the morbidity of atherosclerotic cardiovascular diseases in patients with CD36-D has not been clarified beside the reports of Ma et al. and Yasunaga et al. Ma et al. showed that a common haplotype at the CD36 locus was associated with high FFA levels and increased cardiovascular risk in Caucasians. Yasunaga et al. reported a 45-year-old male CD36-D patient with acute coronary syndrome without major cardiovascular risk factors. Emergency coronary angiography demonstrated 90% stenosis at segment 7 of LAD. We compared the number of risk factors for CAD in patients with CD36-D and healthy subjects (Fig. 4). Patients with CD36-D had more risk factors for CAD than healthy subjects and were associated with multiple risk factors for CAD. We also suggested that the clustering of coronary risk factors might increase the morbidity of cardiovascular disease in patients with CD36-D compared with healthy subjects.

In the current study, we investigated for the first time whether the morbidity of atherosclerotic cardiovascular diseases in CD36-D patients is higher. The clinical observations of three representative CD36-D patients were demonstrated in detail for those whose atherosclerotic lesions of not only coronary arteries but also the aorta and its branches could be assessed. As demonstrated in Table 1, dyslipidemia, hypertension and hyperglycemia were clustered in these three cases. Aortography and MRA revealed severe and multiple stenoses and occlusion of the aorta, its branches and arteries of lower limbs. We also found that atherosclerotic lesions were relatively long (up to 8-10 cm) and their collateral circulation was developed sufficiently. It was suggested that multiple and sequential stenoses along with long distance occlusion were not due to acute thrombotic occlusion but to chronic progression of atherosclerotic plaques. These three patients were rather older than the average CD36-D patients and were associated with multiple risk factors; therefore, we could not exclude the possibility that aging and the simple clustering of risk factors might have enhanced the atherogenicity in these three cases; however, a similar tendency of the clustering of CAD risk factors and the association of atherosclerotic cardiovascular diseases were also observed in younger patients with CD36-D.

We also investigated the morbidity and severity of atherosclerotic cardiovascular diseases in 40 patients with CD36-D who were identified by BMIPP scintigraphy and a screening study by FACS analysis. As shown in Table 2, we found extremely high morbidity of CAD (50%, 20 of 40 patients with CD36-D). Among 20 CD36-D patients with CAD, 13 (65%) were accompanied by unstable angina or acute myocardial infarction due to the stenosis and occlusion of coronary arteries; therefore, these data suggest that the morbidity and severity of CAD were significantly higher in patients with CD36-D than in CD36-positive control subjects. Furthermore, many patients with both CD36-D and CAD suffered from other atherosclerotic cardiovascular diseases involving the stenosis and occlusion of arteries in the upper and lower limbs.

Since 123I-BMIPP scintigraphy was performed in order to evaluate the myocardial damage of FFA metabolism in subjects with possible ischemic heart disease, the possibility could not be rejected that the 40 patients in the current study were extracted from a population with high morbidity of CAD. Watanabe et al. also reported patients with type I and type II CD36-D, many of whom were accompanied by CAD or cardiomyopathy, although these patients were found by 123I-BMIPP scintigraphy. Therefore, in the current study, we also examined the morbidity of CAD from a screening study. The morbidity of CAD was 50% in CD36-D patients identified by 123I-BMIPP scintigraphy, while 37.5% (3 CAD of 8 CD36-D patients) in the population in the screening study. Although these data further imply that the morbidity of CAD in patients with CD36-D is definitely high, the possibility of patient selection bias cannot be excluded.

To explore further the contribution of CD36-D to the development of CAD in the general population, we compared by FACS analysis the frequency of CD36-D between patients with CAD diagnosed by coronary angiography (n=322) and non-CAD subjects (n=1,239). As shown in Table 3, the frequency of CD36-D was significantly three times higher in patients with CAD than in non-CAD subjects; therefore, the risk for the development of CAD is significantly higher in CD36-D patients, although the uptake of oxidized LDL in vitro is reduced in monocyte-derived macrophages.

Since foam cell formation by the uptake of oxidized LDL was shown to be reduced in monocyte-derived macrophages of CD36-D patients, it may be necessary to explore novel mechanisms for the en-
hanced atherogenicity in a CD36-deficient condition. We will discuss these mechanisms in more detail as follows (Fig. 5):

1) Increased Lipoprotein Remnants and Postprandial Hyperlipidemia

In the postprandial state of CD36-D patients, we demonstrated that not only hypertriglyceridemia but also increased levels of apoB-48, chylomicron remnants, and small dense LDL were observed. In our previous papers, we demonstrated that CD36-null mice showed higher TG concentrations in plasma and intestinal lymph than wild-type mice even in a high fat loading state, suggesting that CD36-null mice may have intestinal overproduction of chylomicrons and may be a good mouse model of postprandial hyperlipidemia. Furthermore, patients with CD36-D were also associated with insulin resistance, as we reported. These profiles associated with impaired lipid and glucose metabolism proved to be independent coronary risk factors in the general CD36-positive population. Moreover, these profiles were linked; the increase in chylomicron remnants in the postprandial state was shown to be associated with insulin resistance; the production of small dense LDL was shown to be associated with the impaired postprandial clearance of TG-rich lipoproteins including remnants; the accumulation of TG-rich lipoproteins caused an increase in FFA levels; high levels of FFA may suppress lipoprotein lipase (LPL) activity and the clearance of TG-rich lipoproteins, resulting in increased remnants. Therefore, these lipoprotein phenotypes clustered in patients with CD36-D might have a synergistic influence and enhance the cardiovascular risk. Furthermore, as nicely reviewed by Fujioka et al., increased remnant lipoproteins (mainly chylomicron remnants) contribute to form atherosclerotic lesions through a variety of mechanisms. It was demonstrated that chylomicron remnants invade directly into the subendothelial spaces of arteries and are taken up by macrophages via several receptors, such as LDL receptor-related protein (LRP) or apoB-48 receptor, resulting in macrophage foam cell formation. We reported that increased serum chylomicron remnants are directly associated with enhanced carotid atherosclerosis in subjects with apparently normal TG levels. Chylomicron remnants induce the secretion of monocyte chemoattractant protein 1 (MCP-1), which stimulates the migration of monocytes through arterial endothelial layers and the production of plasminogen activator inhibitor-1 (PAI-1), which regulates thrombus formation on endothelial cells. Thus, abundant chylomicron remnants in the blood of CD36-D patients might enhance the foam cell formation of CD36-deficient macrophages, leading to the development of atherosclerotic cardiovascular diseases.

2) Reduced Serum HDL-C Levels

In CD36-D patients, we demonstrated a reduction of serum HDL-C, although there is a report showing an increase of serum HDL-C. More recently, Love-Gregory et al. reported a homozygote of SNP32 who was CD36-D accompanied by hypertriglyceridemia and reduction of serum HDL-C, although heterozygotes showed an opposite profile. The reduced serum HDL-C in our CD36-D patients could be one of the causes of enhanced atherogenicity.

3) Increased Free Fatty Acids Levels Caused by Deficiency of LCFA Transporter

CD36 is distributed in the heart, skeletal muscles and adipose tissues where it functions as one of the transporters of LCFA. CD36 may be a major transporter of LCFA in the heart, since the uptake of 123I-BMIPP, an analogue of LCFA, in cardiac scintigraphy is markedly deficient in CD36-D patients, which causes increased serum FFA and the 2-fold-enhanced influx of LCFA into the liver. Increased FFA flux into the liver may cause overproduction of VLDL and hypertriglyceridemia as well as insulin resistance.

4) Insulin Resistance and Impaired Glucose Metabolism

CD36-D was shown to be accompanied by insulin resistance; however, this is controversial. CD36 knockout mice developed marked glucose intolerance, hyperinsulinemia and decreased muscle glucose uptake on a fructose-rich diet, but not on a high-starch, low-fat diet. Goudriaan et al. demonstrated that CD36-D increases insulin sensitivity in muscle, but induces insulin resistance in the liver. Insulin resistance may lead to the down-regulation of lipoprotein lipase and finally to hypertriglyceridemia.

5) Hypertension

The average systolic and diastolic blood pressure in our CD36-D patients was significantly high compared with CD36-positive subjects, similar to the reported case of MetS and vasospastic angina. The mechanism for increased blood pressure is unknown; however, it may accelerate the development of atherosclerosis.

6) Increased PAI-1 Levels

Low plasma fibrinolytic activity in association with increased PAI-1 levels has been demonstrated to
be linked with an increased risk of atherosclerotic cardiovascular diseases in obesity, insulin resistance and diabetes mellitus. The increase of PAI-1 was partly attributed to the accumulation of abdominal visceral fat. Yanai et al. reported elevated PAI-1 levels in patients with CD36-D, although the mechanism was speculated to be linked to abnormal fatty acid metabolism.

Taken together, as illustrated in Fig. 5, despite the anti-atherosclerotic aspects of monocyte-derived macrophages from CD36-D patients due to the reduced uptake of oxidized LDL and decreased secretion of proinflammatory cytokines in vitro, the pro-atherogenic profiles in vivo may exceed the anti-atherosclerotic properties, thus enhancing the development of atherosclerosis. These pro-atherogenic profiles of CD36-D patients include: 1) increased lipoprotein remnants and postprandial hyperlipidemia, 2) reduced serum HDL-C levels, 3) increased FFA levels because of deficiency of LFCA transporter, 4) insulin resistance and impaired glucose metabolism, 5) hypertension, and 6) increased levels of PAI-1. These risk parameters may cluster and interact, finally leading to the marked enhancement of atherosclerosis; therefore, early screening and detection of CD36-D patients and assessment of atherosclerotic cardiovascular diseases are essential, especially in a population such as the Japanese in which their frequency is extremely high. Fur-
ther investigations into the molecular and vascular biological mechanisms of the progression of atherosclerosis in patients with CD36-D may be necessary in future studies.

Conclusions

Patients with CD36-D are associated with severe and enhanced atherosclerotic diseases. The morbidity of CAD is significantly higher in patients with CD36-D than in healthy subjects, and the frequency of CD36-D is significantly higher in patients with CAD than in healthy subjects. The clustering of atherogenic metabolic profiles such as dyslipidemia, including the accumulation of FFA and remnants, hypertension and insulin resistance, may enhance atherogenicity in patients with CD36-D.

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Conflicts of Interest

S. Yamashita has received consultancy fees from Otsuka Pharmaceutical Company and Skylight Biotech Co. The other co-authors have nothing to disclose.

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