Insulin Sensitivity and Lipid Metabolism in Human CD36 Deficiency

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OBJECTIVE — CD36 has been proposed as a fatty acid translocase and a receptor for HDL and oxidized LDL. The association between CD36 deficiency and insulin resistance remains controversial. We investigated glucose and lipid metabolism in human CD36 deficiency.

RESEARCH DESIGN AND METHODS — A total of 61 type I CD36-deficient patients and 25 control subjects were examined. Diabetes was defined as fasting glucose level ≥7 mmol/l or use of hypoglycemic agents. A homeostasis model assessment (HOMA) index was evaluated in patients without diabetes. Insulin resistance was defined as a HOMA index ≥1.73 (sensitivity 64.3%, specificity 78.9%; *J Japan Diab Soc*, 2000).

RESULTS — Diabetes was identified in 12 (20%) of the 61 CD36-deficient patients. Fasting glucose, HbA_{1c}, and total cholesterol levels in the diabetic CD36-deficient patients were significantly higher than in the control subjects and the nondiabetic CD36-deficient patients. Regardless of diabetes, HDL cholesterol concentrations in the CD36-deficient patients were significantly higher than in the control subjects. The nondiabetic CD36-deficient patients had higher triglyceride concentrations than the control subjects, and triglyceride concentrations were higher in the diabetic CD36-deficient patients than in the nondiabetic CD36-deficient patients. The prevalence of insulin resistance in the nondiabetic CD36-deficient patients was similar to that in the control subjects.

CONCLUSIONS — Human CD36 deficiency is not necessarily responsible for insulin resistance. Lipid abnormalities in CD36 deficiency may partly depend on the presence of diabetes, and increased levels of triglyceride and HDL cholesterol may be due to impaired binding of fatty acids and HDL to CD36 and subsequent clearance.

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CD36 is an 88-kDa glycoprotein expressed on various human cells, such as platelets, monocytes/macrophages, and capillary endothelial cells (1). CD36 has been proposed to be a platelet receptor for collagen (2) and thrombospondin (3), a scavenger receptor for oxidized LDL on macrophages (4), and a fatty acid translocase necessary for the transport of long-chain fatty acids (LCFAs) in adipose tissue, heart, and skeletal muscle (5,6). A recent study (7) has also shown that CD36 is a high-affinity receptor for HDL.

Human CD36 deficiency is present in ~3% of the Japanese population (8) and 0.34% of the U.S. population (9). The prevalence of type I CD36 deficiency, in which neither platelets nor monocytes express CD36, is only about one-seventh of that of type II CD36 deficiency, in which monocytes but not platelets express CD36 (10). Absent myocardial uptake of LCFAs by myocardial ^{123}I-labeled 15-(*p*-iodophenyl)-3-R,S-methyl-pentadecanoic acid ([^{123}I]BMIPP) scintigraphy was observed in type I CD36 deficiency (11,12). Tanaka et al. (13) showed a total defect of myocardial LCFAs uptake in 33 (0.47%) of 6,970 Japanese patients who underwent myocardial [^{123}I]BMIPP scintigraphy.

High levels of free fatty acids are a common feature of insulin-resistant states, and increasing the levels of fatty acids can induce acute insulin resistance (14). It has also been shown that muscle triglyceride contents are negatively related to insulin sensitivity (15). In CD36 deficiency, although fatty acids levels are known to be high at least in rodents (16), it is expected that muscle triglyceride contents are not increased but rather decreased because of impaired uptake of LCFAs via CD36 in skeletal muscles. In fact, CD36-deficient mice exhibit a decrease in uptake and use of LCFAs by oxidative skeletal muscles (16,17). These findings suggest that CD36 deficiency does not cause insulin resistance. In humans, however, a possible association between CD36 deficiency and insulin resistance has been suggested by the results of a study using a hyperinsulinemic glucose clamp in five CD36-deficient patients (18). Another report (19) has demonstrated that CD36 deficiency sometimes coexists with diabetes. Although a defective gene encoding for CD36 was proposed to be responsible for insulin resistance in spontaneously hypertensive rats (SHR) (20), no CD36 gene mutation was found in the original strains of SHR with insulin resistance, suggesting that a defect in CD36 is unlikely to be a major cause of insulin resistance in SHR (21). It was also reported that four young CD36-deficient individuals showed normal insulin response to an oral glucose tolerance test and normal blood concentrations of glucose and lipids (22). The relationship between human CD36 deficiency and insulin resistance has thus remained controversial because of the small cohort sizes. Therefore, we investigated insulin sensitivity and lipid metabolism in a

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Abbreviations: HOMA, homeostasis model assessment; LCFA, long-chain fatty acid; [^{123}I]BMIPP, ^{123}I-labeled 15-(*p*-iodophenyl)-3-R,S-methyl-pentadecanoic acid.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

larger number of human CD36-deficient patients.

RESEARCH DESIGN AND METHODS

Subjects

A total of 61 patients with type I CD36 deficiency (38 men and 23 women; 61 ± 14 years of age, mean ± SD) were identified as having a total defect in myocardial uptake of LCFAs by myocardial [^{123}I] BMIPP scintigraphy. In all of the patients, flow cytometry using an anti-human CD36 monoclonal antibody (OKM5; Ortho Diagnostic Systems, Raritan, NJ) showed a lack of CD36 molecule expression on both platelets and monocytes. A total of 25 age-, sex-, and BMI-matched control subjects (15 men and 10 women; 61 ± 9 years of age, mean ± SD) were also recruited for this study. This study was performed with the approval of the ethics committee of our institution, and informed consent was obtained from all of the subjects.

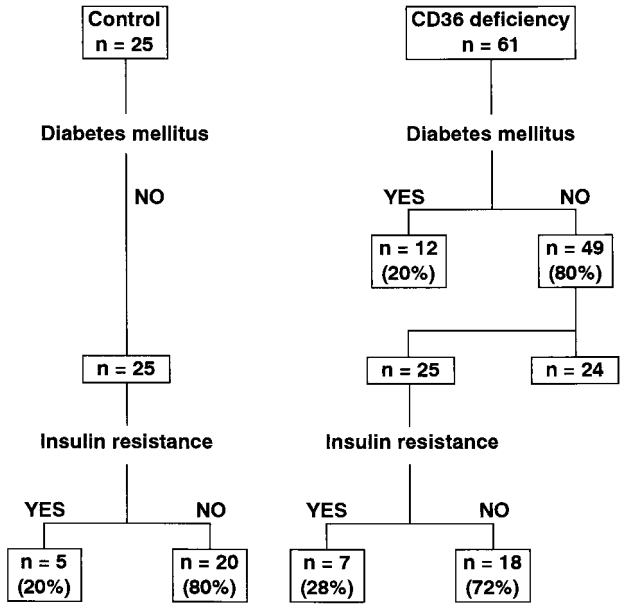

Figure 1—*A flow chart showing the studied number of control subjects and CD36-deficient patients. Subjects with diabetes were defined as those with fasting plasma glucose ≥7 mmol/l or those who were being treated with hypoglycemic agents. Insulin resistance was defined as HOMA index ≥1.73.*

Glucose and lipid profiles

After an overnight fast, plasma glucose, HbA_{1c}, and serum lipid profiles, including total cholesterol, HDL cholesterol, and triglycerides, were measured in all of the subjects.

Diabetes and insulin resistance

Subjects with diabetes were defined as those with fasting plasma glucose ≥7 mmol/l or those who were being treated with hypoglycemic agents. A 75-g oral glucose tolerance test was performed in subjects without diabetes. Based on the results of our previous study (23) using an euglycemic-hyperinsulinemic glucose clamp method in a Japanese population, we defined insulin resistance as follows: a homeostasis model assessment (HOMA) index (fasting plasma insulin [mU/l] × fasting plasma glucose [mmol/l]/22.5) of ≥1.73 (sensitivity 64.3%; specificity 78.9%). This criterion is simple and practical for evaluation of insulin resistance in daily practice, especially in the Japanese population.

Laboratory investigations

Plasma glucose level was measured by a glucose oxidase method. HbA_{1c} was determined by high-performance liquid chromatography. Serum lipids were estimated by enzymatic methods. Plasma insulin was measured by a radioimmunoassay technique (Insulin RIA bead; Dinabot, Tokyo, Japan).

Statistical analysis

Numeric variables are expressed as means ± SD. Group statistical comparisons were assessed by one-way ANOVA and χ^2 test. A P value <0.05 was considered statistically significant.

RESULTS — A total of 12 (20%) of the 61 CD36-deficient patients were found to have diabetes (Fig. 1). As shown in Table 1, there was no significant difference in gender or BMI among the control subjects, the nondiabetic CD36-deficient patients, and the diabetic CD36-deficient patients. The mean age of the diabetic CD36-deficient patients was higher, but not significantly, than that of the nondiabetic CD36-deficient patients. Fasting plasma glucose and HbA_{1c} levels in the diabetic CD36-deficient patients were significantly higher than in the control subjects and the nondiabetic CD36-deficient patients.

Serum total cholesterol concentrations in diabetic CD36-deficient patients were significantly higher than in the con-

Table 1—*Clinical characteristics of the study groups*

		CD36 deficiency	
	Control	Nondiabetic	Diabetic
n	25	49	12
Sex (men/women)	15/10	33/16	5/7
Age (years)	60.6 ± 9.4	59.4 ± 15.2	66.8 ± 9.5
BMI (kg/m^2)	23.6 ± 2.1	23.4 ± 3.7	23.7 ± 3.5
Fasting plasma glucose (mmol/l)	4.95 ± 0.41	5.14 ± 0.61	7.49 ± 2.06*
HbA_{1c} (%)	5.3 ± 0.5	5.4 ± 0.6	8.2 ± 1.6*
Serum total cholesterol (mmol/l)	4.86 ± 0.83	4.89 ± 0.98	5.79 ± 1.14*
Serum HDL cholesterol (mmol/l)	1.01 ± 0.23	1.26 ± 0.36†	1.33 ± 0.31†
Serum triglyceride (mmol/l)	1.08 ± 0.52	1.76 ± 0.8†	2.45 ± 1.12*

Data are *n* or means ± SD. *$P < 0.01$ versus the control and nondiabetic groups; †$P < 0.01$ versus the control group.

trol subjects and the nondiabetic CD36-deficient patients. Regardless of diabetes, serum HDL cholesterol concentrations in CD36-deficient patients were significantly higher than in the control subjects. The nondiabetic CD36-deficient patients had higher serum triglyceride concentrations than the control subjects, and triglyceride concentrations were higher in the diabetic CD36-deficient patients than in the nondiabetic CD36-deficient patients.

A total of 28% of the nondiabetic CD36-deficient patients had insulin resistance by HOMA index ≥1.73, whereas 20% of control subjects had insulin resistance (Fig. 1). There was no significant difference in prevalence of insulin resistance between the control subjects and the nondiabetic CD36-deficient patients.

CONCLUSIONS — Recent community-based studies have shown that the prevalence of diabetes is nearly 10% in the general Japanese population (24). Considering the selection bias of our CD36-deficient patients who had undergone cardiac scintigraphy for evaluation of suspected or known heart disease, the prevalence of diabetes in CD36-deficient patients in the present study (20%) does not seem to be high. Of greater importance is the fact that the prevalence of insulin resistance in the nondiabetic CD36-deficient patients was similar to that in the control subjects. The prevalence of insulin resistance in both groups (~20%) was comparable to that in normal Japanese subjects, as previously reported (25,26). Our findings suggest that human CD36 deficiency is not necessarily responsible for insulin resistance.

Manifestation of diabetes in CD36-deficient patients was not significantly associated with aging and BMI. Several kinds of CD36-related gene mutation were reported in CD36-deficient patients (13). Although little has been reported on phenotype-genotype correlation in CD36 deficiency, it is possible that a sort of CD36-related gene mutation is associated with the manifestation of diabetes in CD36-deficient patients. Further investigation of this association is necessary.

Metabolic phenotypes observed in CD36-null SHR (21), CD36-null mice (16), and CD36-deficient humans (18,22) were virtually inconsistent, which might be partly explained by the differences in the metabolic pathways among species and the genetic and environmental backgrounds between individuals. Our results showed that lipid abnormalities in CD36 deficiency might partly depend on the presence of diabetes, because total cholesterol and triglyceride levels in diabetic CD36-deficient patients were higher than in the control subjects and the nondiabetic CD36-deficient patients. The difference between data on glucose and lipid metabolism obtained in previous human studies (18,22) and those obtained in the present study seems to be due to the difference between prevalence of diabetes in the CD36-deficient patients enrolled.

Recent studies have shown that CD36 can bind to HDL as well as LCFAs (7) and have demonstrated that concentrations of HDL cholesterol and triglycerides are elevated in CD36-null mice (16). A possible mechanism accounting for the increase in HDL cholesterol and triglycerides in CD36-deficient patients may be absent from binding of HDL and LCFAs to CD36 molecules and subsequent clearance.

Some limitations must be considered. First, CD36-deficient patients in the present study were recruited from groups who underwent cardiac [^{123}I]BMIPP scintigraphy for evaluation of suspected or known heart disease, but not from normal volunteers. However, it is significant that the prevalence of insulin resistance in nondiabetic CD36-deficient patients was similar to that in the control subjects despite this selection bias. Second, this report is a cross-sectional study. Prospective studies are also needed to assess the relationship of human CD36 deficiency to insulin resistance or diabetes.

In conclusion, human CD36 deficiency is not necessarily responsible for insulin resistance. Lipid abnormalities in CD36 deficiency may partly depend on the presence of diabetes, and increased levels of triglycerides and HDL cholesterol may be due to impaired binding of LCFAs and HDL to CD36 molecules and subsequent clearance.

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