Small Dense Low-Density Lipoprotein and Carotid Atherosclerosis in Relation to Vascular Dementia

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Vascular dementia (VaD) and Alzheimer's disease (AD) are the most common causes of dementia in the elderly. The aim of this study was to investigate carotid atherosclerosis, serum lipid profiles, and atherogenic hormone levels in nondiabetic Japanese men with VaD or AD. Carotid artery intima-media thickness (IMT) and plaque, serum lipid and lipoprotein profiles, including low-density lipoprotein (LDL) particle size, as well as insulin-like growth factor-I (IGF-I, somatomedin C) and testosterone levels, were determined in 34 patients with AD, 37 patients with VaD, and 63 healthy male controls. Age, body mass index, systolic and diastolic blood pressure, and fasting plasma glucose, hemoglobin A_{1c} (HbA_{1c}), triglyceride, high-density lipoprotein (HDL)-cholesterol, and apolipoproteins (apo) A-I, B, and E levels did not differ significantly among the 3 groups. However, the mean value of carotid IMT, the frequency of atherosclerotic plaque deposition, the serum levels of LDL-cholesterol, lipoprotein(a), and lipid peroxides, and the incidence of small dense LDL (particle diameter ≤ 25.5 nm) were increased significantly in VaD patients compared with AD patients or controls. VaD patients had a close reverse correlation between carotid IMT and LDL particle diameter, which were statistically proven independent risk factors for VaD. In contrast, AD patients had significantly lower serum levels of IGF-I and testosterone than either VaD patients or contols. Our results indicate that VaD is associated with atherogenic dyslipidemia, in particular, small dense LDL and carotid atherosclerosis, whereas AD is associated with hyposomatomedinemia and hypogonadism rather than atherosclerosis.

DEMENTIA is an important cause of disability, particularly in the elderly. In Japan, vascular dementia (VaD) is responsible for at least half of all dementia cases, whereas in Western countries, Alzheimer's disease (AD) accounts for the majority of dementia cases.[1] There is no doubt that dementia might be related to atherosclerosis of the cerebral vessels. However, so far, few studies have investigated the association between dementia (VaD and dementia of Alzheimer's type) and arterial atherosclerosis.[2,3]

Traditional risk factors such as hypertension, smoking, and diabetes mellitus increase the risk of developing dementia, as well as cerebrovascular disease and coronary artery disease.[4-8] It is also well known that increased levels of low-density lipoprotein (LDL)-cholesterol and lipoprotein(a) and lowered levels of high-density lipoprotein (HDL)-cholesterol are independent risk factors of atherogenesis.[9] In recent years, small dense LDL that is more prone to oxidation than large buoyant LDL,[10,11] oxidatively modified LDL, and lipid peroxides have been linked to the development of atherosclerosis.[12,13] Insulin-like growth factor-I (IGF-I, somatomedin C) and testosterone are also involved in atherosclerotic plaque development.[14,15] However, the relation of these biochemical risk factors to dementia remains still unclear.

Carotid B-mode ultrasonography provides noninvasive evaluation of carotid-lumen diameter, intima-media thickness (IMT), and presence and extent of focal atherosclerosis (plaques). Measurement of carotid artery IMT is regarded as a valid index of the involvement of other arterial beds with atherosclerosis.[16] Several studies have shown that carotid IMT is strongly associated with the incidence of stroke and myocardial infarction in older adults.[16,17] In addition, carotid IMT of 1 mm or more has been reported to be associated with a 3- to 4-fold greater hazard rate of subsequent ischemic stroke.[18] However, in patients with dementia, reports on association between the carotid IMT and LDL particle size have not appeared to date.

The aim of the present study was to investigate biochemical risk factors such as LDL-cholesterol, small dense LDL particles, lipoprotein(a), lipid peroxides, IGF-I, and testosterone, and carotid atherosclerosis as assessed by increased carotid IMT and plaques on B-mode ultrasonography in nondiabetic Japanese men with VaD or AD.

MATERIALS AND METHODS

Subjects

Since it has been reported that mean LDL size and sex hormones are significantly different between men and women, subjects were limited to men in this study.[15,19] Ninety consecutive newly diagnosed dementia patients (mean age, 74 ± 9 years; range, 53 to 94) hospitalized in Showa University Karasuyama Hospital were enrolled in the study. No patients were on lipid-lowering therapy or had diabetes mellitus, liver disease, or endocrine disease. According to the criteria in the International Classification of Disease, Tenth Edition (ICD-10),[20] the 71 patients with dementia were clinically divided into 2 groups: 34 patients had AD and the remaining 37 patients had VaD, excluding 19 patients with a combination of AD and VaD, so-called mixed dementia.[21] The control group consisted of 63 age-matched subjects (mean age, 72 ± 11 years; range, 54 to 90), who were generally healthy and had no evidence of dementia or cerebral ischemic events. The clinical characteristics of patients with AD or VaD and controls are shown in Table 1. Informed consent for the investigation was obtained from subjects or from their nearest relatives. The study was conducted according to the principles of the Helsinki declaration.

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Table 1. General Characteristics of Patients With AD or VaD and Controls

	AD (n = 34)	VaD (n = 37)	Controls (n = 63)
Age (yr)	76 ± 9	75 ± 8	72 ± 11
Body mass index (kg/m^2)	20 ± 3	21 ± 3	21 ± 3
Current alcohol consumption (%)	35	27	30
Current smoking (%)	18	22	24
Hyperlipidemia (%)	12	16	19
Hypertension (%)	35	46	37
Ischemic heart disease (%)	9	11	11
Systolic blood pressure (mm Hg)	131 ± 19	138 ± 20	132 ± 16
Diastolic blood pressure (mm Hg)	75 ± 13	78 ± 12	80 ± 16
HDS-R (points)	8 ± 6*	11 ± 6*	24 ± 2
MMSE (points)	10 ± 5*	13 ± 6*	26 ± 3
Plaque (%)	53†	76*,‡	24

*$P < .0001$, †$P < .005$ *v* the control group.
‡$P < .05$ *v* the AD group.

Dementia Diagnosis

Dementia was assessed by consensus at a conference of physicians and neuropsychologists based on medical history, physical examination, laboratory and neuropsychological tests, and brain computed tomography (CT). The diagnosis of dementia was made in accordance with the ICD-10 criteria.[20] The lipid measurements and carotid IMT were not available during the diagnostic process. On brain CT, all patients with VaD but not AD had significantly more vascular lesions, such as strokes, lacunes, and leukoaraiosis. All patients with VaD or AD classified by the ICD-10 criteria, respectively, fullfilled the probable criteria in the National Institute of Neurological Disorders and Stroke with support from the Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN),[22] or the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA).[23] Cognitive function and dementia severity were evaluated by the Mini-Mental State Examination (MMSE; normal score considered to be 25 to 30) and the Hasegawa Dementia Scale-Revised (HDS-R).[24] The HDS-R consists of 9 questions that test orientation, memory function, common knowledge, and calculation. The possible scores range from 0 to 30 points and the cutoff point for dementia is 20 or less.[24] In cases with values around cutoff points on the MMSE or HDS-R, the Wechsler Adult Intelligence Scale-Rivised (WAIS-R) was needed to distinguish whether their cognitive dysfunction might be related to dementia or aging.

Laboratory Measurements

Blood samples were drawn in the early morning after overnight fasting of more than 10 hours and the biochemical parameters as shown in Table 2 were determined immediately. Plasma glucose levels and serum total cholesterol and triglyceride levels were determined by enzymatic methods (Vitros Slides, Ortho-Clinical Diagnosis, Raritan, NJ),[25-27] and HDL-cholesterol levels were determined by a precipitation method (Vitros Slide)[28] in an autoanalyzer (Vitros 250 Chemical System, Ortho-Clinical Diagnosis). Hemoglobin A_{1c} (HbA_{1c}) and lipoprotein(a) levels were determined by the Latex agglutination test (Rapidia Auto HbA_{1c} and Lp(a) Latex, Daiichi Chemicals, Tokyo, Japan),[29,30] and lipid peroxides were quantified by the thiobarbituric acid reaction (Lipid Peroxides Test Wako, Wako Pure Chemical Industries, Osaka, Japan).[31] Serum levels of apolipoprotein (apo) A-I, B, and E were determined by turbidimetric immunoassay (Apo A-I, B, E Auto N, Daiichi Chemicals).[32] LDL-cholesterol was calculated using the Friedewald formula.[33] In the only 2 controls who had high levels of triglyceride (>400 mg/dL), LDL-cholesterol levels were measured by a precipitation method (BLF Eiken II, Eiken Chemical, Tokyo, Japan).[34] Mean LDL particle diameter was determined by electrophoresis on 2% to 16% polyacrylamide gels (Biocraft, Tokyo, Japan) as described previously.[35] The threshold mean LDL particle diameter of 25.5 nm or less defines the predominance in plasma of a subclass of LDL, the small dense LDL, a pattern also known as phenotype B.[35] Serum levels of testosterone and estradiol were determined by radioimmunoassay (DPC Total Testosterone kit and DPC Estradiol kit, Diagnostic Products Co, Los Angeles, CA),[36,37] and serum IGF-I levels were assayed with an immunoradiometric assay (IRMA) kit (IGF-I IRMA, Daiichi Radioisotope Laboratories, Chiba, Japan).[38]

Carotid Ultrasonography

Carotid atherosclerosis was evaluated by high resolution B-mode ultrasonography with a 7.5-MHz linear-array transducer (PLE-705S, Toshiba, Tokyo, Japan). The protocol involved scanning the right and the left common carotid arteries from 10 mm below the bifurcation, as well as the carotid bifurcation.[39] Two angles of incidence (anterolateral and posterolateral) were used and the beam was focused on the posterior (far) wall. The carotid IMT was measured as the difference between the first (intima-lumen) interface and the second (media-adventitia) interface on the far wall of the common carotid artery. Plaque was defined as a clearly identified focal increase in the thickness of the intima-media by 1 mm or more. The mean IMT was calculated for each subject as the average of eight measurements (excluding sites of plaque) in each segment. All measurements were determined by the same examiner, who was blinded to their clinical history or risk factor profile.

Smoking and Alcohol Intake

Information on cigarette smoking and alcohol intake was obtained from the patient or a surrogate regarding the age that the individual started smoking, total number of years spent smoking, amount of cigarettes consumed, and the usual weekly intake of alcoholic beverages over the previous several months. Alcohol intake was converted into a daily equivalent in terms of the number of go, a traditional Japanese unit of volume for sake (1 go = 180 mL and contains 22.7 g of ethanol). One go corresponds to one bottle (633 mL) of beer, 2 single shots (75 mL) of whisky, or 2 glasses (180 mL) of wine. In this study,

Table 2. Biochemical Parameters of Patients With AD or VaD and Controls

	AD (n = 34)	VD (n = 37)	Controls (n = 63)
Total cholesterol (mg/dL)	167 ± 29	179 ± 30	176 ± 36
LDL-cholesterol (mg/dL)	95 ± 25	110 ± 31*	94 ± 36
HDL-cholesterol (mg/dL)	50 ± 14	51 ± 10	50 ± 15
Triglyceride (mg/dL)	82 ± 58	93 ± 55	103 ± 65
ApoA-I (mg/dL)	124 ± 24	128 ± 20	133 ± 27
ApoB (mg/dL)	84 ± 21	97 ± 23	91 ± 26
ApoE (mg/dL)	4.0 ± 1.4	3.9 ± 0.9	4.1 ± 1.1
Lipoprotein(a) (mg/dL)	25 ± 22	45 ± 46†	14 ± 13
Lipid peroxides (nmol/mL)	2.4 ± 0.6	3.1 ± 0.7‡	2.6 ± 0.6
Fasting plasma glucose (mg/dL)	106 ± 27	104 ± 27	108 ± 24
HbA_{1c} (%)	5.3 ± 0.4	5.3 ± 0.8	5.5 ± 0.9
IGF-I (ng/mL)	112 ± 41†	143 ± 47	156 ± 51
Testosterone (ng/dL)	263 ± 73‡	300 ± 82	392 ± 105
Estradiol (pg/mL)	15 ± 8¶	14 ± 6¶	21 ± 8
Small dense LDL (%)	9	62§	13

*$P < .05$, †$P < .01$, ‡$P < .005$, §$P < .0001$ *v* other groups.
¶$P < .005$ *v* the control group.

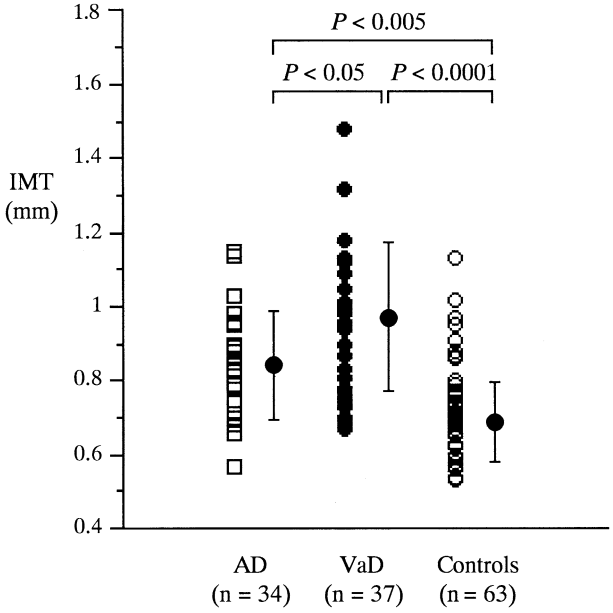

Fig 1. Carotid IMT in patients with AD or VaD and controls. The mean IMT was significantly greater in VaD patients than in AD patients and controls (0.94 ± 0.20 mm *v* 0.85 ± 0.14 mm and 0.68 ± 0.11 mm).

men who reported consuming 0.3 go or more per week were regarded as drinkers,[40] and a smoker was defined by current smoking 10 cigarettes or more per day for more than 1 year.[41]

Statistical Analysis

All data are expressed as mean ± SD for continuous variables and as frequencies for categorical variables. Differences among study groups were analyzed by 1-way analysis of variance (ANOVA) followed by Scheffé test, and the nonparametric Mann-Whitney *U* test, where appropriate. The chi-square test was used for categorical data. The correlation coefficients between serum levels of lipids or LDL particle diameter and carotid IMT were determined by Pearson's simple linear regression analysis. Multiple logistic regression analysis was performed to identify independent risk factors for VaD. Associations were calculated as odds ratios with 95% confidence intervals (CI). A value of $P < .05$ was considered to indicate statistical significance.

RESULTS

General characteristics of patients with AD or VaD and controls are shown in Table 1. The mean age and body mass index, the incidence of current alcohol consumption and smoking, and the prevalence of hyperlipidemia, hypertension (>140/90 mm Hg), and ischemic heart disease did not differ significantly among the 3 groups. Neither the average values of systolic nor diastolic blood pressure differed significantly among the 3 groups. The average scores of HDS-R and MMSE were significantly lower in patients with AD and VaD than in controls ($P < .0001$). The frequency of carotid atherosclerotic plaque (>1) was the greatest in VaD patients among the 3 groups. As shown in Fig 1, the mean IMT was increased significantly in VaD patients compared with AD patients and controls ($P < .05$ and $P < .0001$, respectively).

Biochemical parameters of the 3 study groups are shown in Table 2. Serum levels of total and HDL cholesterols, triglyceride, apoA-I, apoB, apoE, fasting plasma glucose, and HbA_{1c} did not differ significantly among the 3 groups. Serum levels of LDL cholesterol, lipoprotein(a), and lipid peroxides were significantly higher in VaD patients than in AD patients and controls ($P < .05$, $P < .01$, and $P < .005$, respectively). The prevalence of small dense LDL was significantly greater in VaD patients than in AD patients and controls ($P < .0001$). As shown in Fig 2, LDL particle diameter was significantly smaller in VaD patients than in AD patients and controls ($P < .0001$). As shown in Table 2, serum levels of IGF-I and testosterone were significantly lower in AD patients than in VaD patients and controls ($P < .01$ and $P < .005$, respectively). Serum estradiol levels were significantly lower in patients with AD and VaD than in controls ($P < .005$), but there were no significant differences between AD patients and VaD patients.

We assessed the correlations of carotid IMT with serum levels of LDL cholesterol, lipoprotein(a), or lipid peroxides and with LDL particle size in patients with AD or VaD and controls. No significant correlations of carotid IMT with serum levels of LDL cholesterol ($r = 0.158$, $P = 0.1045$), lipoprotein(a) ($r = 0.168$, $P = .0857$), or lipid peroxides ($r = 0.082$, $P = .4018$) were observed in all subjects. However, carotid IMT showed a significant reverse correlation with LDL particle diameter in all subjects ($r = -0.279$, $P < .005$; Fig 3). Compared with AD patients and controls, VaD patients showed a stronger reverse correlation between carotid IMT and LDL particle diameter ($r = -0.487$, $P < .01$; Fig 4).

Finally, we performed a multiple logistic regression analysis to assess the risk factors for VaD in all subjects (Table 3). Increased carotid IMT (≥0.9 mm: the 75% percentile of mean IMT) and the presence of carotid plaque (≥1) and small dense LDL (≤25.5 nm) had significantly independent associations

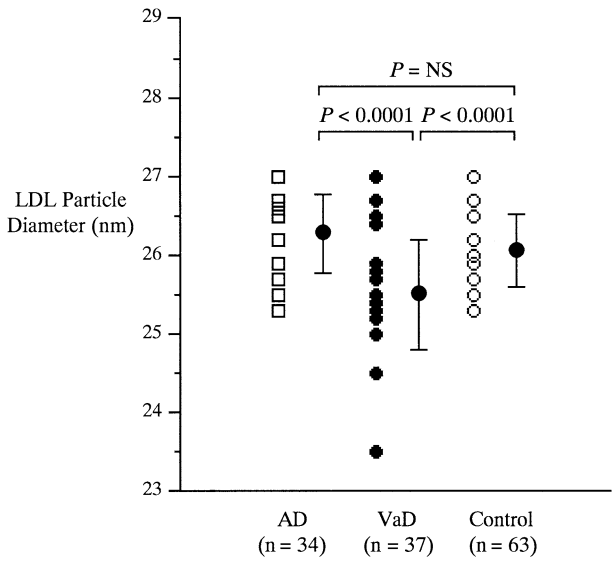

Fig 2. LDL particle size in patients with AD or VaD and controls. LDL particle diameter was significantly smaller in VaD patients than in AD patients and controls (25.6 ± 0.7 nm *v* 26.3 ± 0.5 nm and 26.1 ± 0.4 nm).

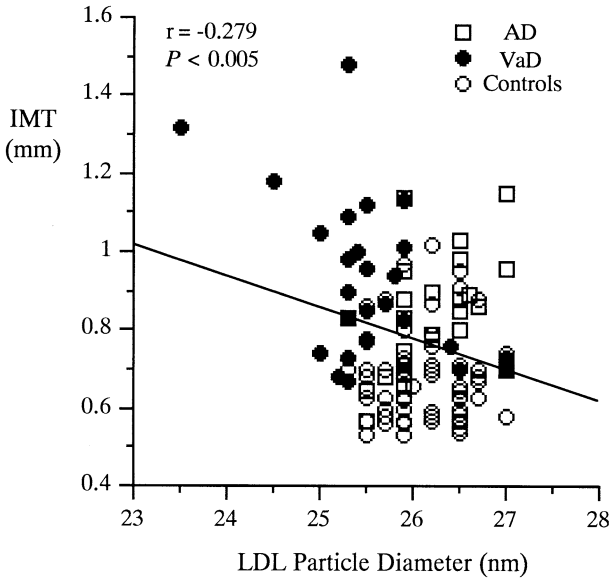

Fig 3. The relation between carotid IMT and LDL particle diameter in patients with AD or VaD and controls. There was a significant correlation between both parameters in all subjects (n = 134, $r = -0.279$, $P < .005$). The line on scattergram represents a regression line (Y = −0.087X + 3.05).

with VaD but serum levels of LDL-cholesterol, lipoprotein(a), and lipid peroxides did not.

DISCUSSION

The relation between serum lipids and lipoproteins and carotid atherosclerosis in VaD is not as clear cut as in coronary

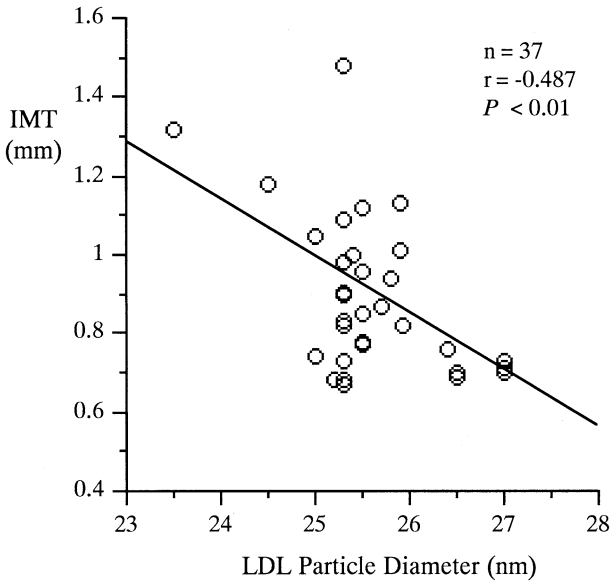

Fig 4. The relation between carotid IMT and LDL particle diameter in patients with VaD. Compared with all subjects as shown in Fig 3, the closer correlation between both parameters was observed in VaD patients (n = 37, $r = -0.487$, $P < .01$). The line on scattergram represents a regression line (Y = −0.145X + 4.62).

Table 3. Multiple Logistic Regression Analysis of Risk Factors for VaD

	Odds Ratio	95% CI	*P* Value
IMT ≥ 0.9 mm	3.2	1.1-9.4	.0351
Plaque ≥ 1	3.0	1.0-8.8	.0389
Small dense LDL ≤ 25.5 nm	8.6	3.1-23.1	<.0001
LDL cholesterol (mg/dL)	1.0	0.98-1.02	.8374
Lipoprotein(a) (mg/dL)	1.0	0.99-1.03	.0793
Lipid peroxides (nmol/mL)	1.23	0.56-2.66	.5989

artery disease. This study shows that the serum levels of LDL-cholesterol, lipoprotein(a), and lipid peroxides and the prevalence of small dense LDL are significantly higher, and increased carotid IMT and plaques are observed significantly frequently in VaD patients compared with AD patients and age-matched controls. To the best of our knowledge, the present case-control study is the first showing that high prevalence of small dense LDL and carotid atherosclerosis are independent risk factors for VaD and could be considered as clinical hallmarks predicting VaD in older Japanese men. Further, VaD patients showed a significantly stronger correlation between LDL particle size and carotid IMT than did AD patients and controls.

AD is a progressive neurodegenerative disorder characterized by accumulation of neurofibrillary tangles and neuritic plaques, and neuronal loss, affecting both the cerebral cortex and hypothalamus.[42] Recent research has revealed that DNA fragmentation occurs in cells within these brain areas of AD patients, suggesting that apoptosis may be the main mechanism involved in the selective neuronal cell death seen within the AD brain.[42] Apoptotic mechanisms may be triggered within the AD brain by neurotoxic properties associated with amyloid-β (Aβ) protein deposition.[42] Previous autopsy study showed that AD was little associated with cerebrovascular atherosclerosis.[43] However, Kalaria has recently shown that at least one third of AD cases may exhibit significant cerebrovascular pathology, which contributes to distinct small vessel disease.[44] Cerebral amyloid angiopathy, microvascular degeneration affecting the cerebral endothelium and smooth muscle cells, basal lamina alterations, hyalinosis, and fibrosis are often evident in AD.[44] Findings from the Rotterdam study suggest that the interaction between atherosclerosis and apoE genotypes may be involved in the etiology of AD.[3] In the Rotterdam study and our study, carotid atherosclerosis as assessed by increased IMT and plaques on ultrasonography was exactly observed in AD patients compared with controls. Further, compared with AD patients, the frequency and severity of atherosclerosis of the carotid arteries were still greater in VaD patients. Yanagihara has reported that VaD is related to atherosclerosis of the cervical and cerebral arteries.[45] Prior studies have shown that high levels of LDL-cholesterol, lipoprotein(a), and homocysteine and low levels of HDL are risk factors for VaD,[46-49] which in turn may lead to cognitive decline through cerebral embolism or hypoperfusion.[50] However, the relationships of small dense LDL and lipid peroxidation products with VaD have not been clarified.

Small dense LDL particles penetrate into the extracellular

space more easily and have a low binding affinity to the LDL receptor, resulting in prolongation of its residence time in the subendothelial space, a prooxidative environment.[51] Small dense LDL particles are more prone to oxidation than large buoyant LDL particles.[10] Additively, increased susceptibility of LDL to oxidation in vitro is related to the presence of small dense LDL.[51] These processes promote LDL modification in the arterial wall and initiate the development of atherosclerosis. Several other studies and our study show that small dense LDL is an independent risk factor of coronary artery disease,[11,52] carotid atherosclerosis,[53] and VaD. The prevalence of small dense LDL is reported to be closely associated with high plasma levels of triglyceride and low plasma levels of HDL cholesterol.[35,54] In this study, most patients with VaD essentially had normal triglyceride levels. The high prevalence of small dense LDL in these patients may have been due to postprandial lipemia with normal fasting triglyceride levels.[55]

Cholesterol oxidation in the brain is also believed to be particularly relevant to the pathogenesis of VaD.[56] According to expectation, VaD patients in this study exactly had the highest levels of lipid peroxides among the study groups. In contrast, recent studies have demonstrated that oxidative damage is one of the salient features of AD. Hypercholesterolemic diets may lead to microglial activation and Aβ plaque deposition. Lipid peroxides, capable of production of reactive oxygen species, have been shown to be elevated in AD brain tissue,[57] and may play a role in the neuronal death that underlies cognitive deficits in AD.[58] However, in this study, the serum levels of lipid peroxides were not increased in AD patients. The 2 main reasons why this discrepancy between our study and others occurred were thought to be as follows: (1) AD patients in our study were in the early stage of the disease as indicated by the short time since its diagnosis, and (2) it is possible that because our subjects including AD patients had a slightly decreased appetite with aging, they might be unable to have a balanced meal.

Serum estradiol levels were decreased significantly in the demented (VaD and AD) patients compared with the age-matched controls in this study. A recent study has shown that low estradiol levels of less than 15 pg/mL are the risk of developing dementia in elderly men,[59] which is compatible with our results (Table 2). IGF-I and testosterone levels are known to decline with decreasing cognitive function as well as aging.[60,61] In this study, serum levels of IGF-I and testosterone were decreased in both demented patient groups, especially in the AD group. Several studies have shown that serum levels of IGF-I and testosterone are reduced in AD patients.[62,63] Both IGF-I and its type I receptor, which are present in the brain, are involved in brain development,[64] and IGF-I has a neuroprotective role in the damaged brain.[42] IGF-I has also been shown to enhance neuronal survival and inhibit apoptosis via the activation of the phosphatidylinositol 3-kinase–dependent Akt kinase pathway.[65,66] The recent demonstration that IGF-I can protect hippocampal neurons against A$\beta_{25\text{-}35}$– and A$\beta_{1\text{-}42}$–induced toxicity may provide a basis for the intraventricular use of IGF-I in AD patients.[62] In addition to apoEϵ4 alleles and homocysteine, the potent risk factors for AD, which may be related to induce neurodegeneration,[48,67] an IGF-I deficit may contribute to neural cell loss later in life.

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