Assessment of Endothelial Function in Alzheimer's Disease: Is Alzheimer's Disease a Vascular Disease?

Didem Sener Dede, MD, Bunyamin Yavuz, MD,† Burcu Balam Yavuz, MD,‡ Mustafa Cankurtaran, MD,‡ Meltem Halil, MD,‡ Zekeriya Ulger, MD,* Eylem Sahin Cankurtaran, MD,§ Kudret Aytemir, MD,† Giray Kabakci, MD,† and Servet Ariogul, MD†*

OBJECTIVES: To compare endothelial function of people with Alzheimer's disease (AD) with that of people without.

DESIGN: Case-control study.

SETTING: Geriatric medicine outpatient clinic of a university hospital.

PARTICIPANTS: Twenty-five patients with AD who were free of vascular risk factors and 24 healthy elderly controls were enrolled. Exclusion criteria were diabetes mellitus, hypertension, dyslipidemia, evident stroke, smoking, documented coronary artery disease, history of myocardial infarction, heart failure, acute or chronic infection, malignancy, peripheral artery disease, renal disease, rheumatologic diseases, alcohol abuse, and certain drugs that may affect endothelial function. Both groups underwent comprehensive geriatric assessment and neuropsychiatric assessment.

MEASUREMENTS: Endothelial function was evaluated according to flow-mediated dilation (FMD) from the brachial artery.

RESULTS: Mean age ± standard deviation was 78 ± 5.9 in the group with AD (11 female and 14 male) and 72.1 ± 5.8 in the control group (9 female and 11 male). Multiple linear regression analysis revealed that FMD was significantly lower in patients with AD (median 3.45, range 0–7) than controls (median 8.41, range 1–14) ($P<.001$), independent of age. It was also found that FMD values were inversely correlated with the stage of the disease as determined according to the Clinical Dementia Rating scale ($r=-0.603$, $P<.001$).

CONCLUSION: Endothelial function is impaired in patients with AD. Endothelial function was worse in patients with severe AD. These findings provide evidence that vascular factors have a role in the pathogenesis of AD. **J Am Geriatr Soc 55:1613–1617, 2007.**

Key words: Alzheimer's disease; endothelial function; flow-mediated dilation; pathogenesis; vascular pathology

Alzheimer's disease (AD) is a progressive neurodegenerative disorder and the most common type of dementia.[1] Risk of dementia increases with advanced age, and several mechanisms have been implicated in the pathogenesis.[2]

In AD, cerebral atrophy, enlargement of ventricles, hippocampal atrophy, amyloid beta deposition, abnormal tau protein hyperphosphorylation, granulovacuolar degeneration, and neurotransmitter deficiencies occur in the brain.[3–5] The exact mechanism that causes these changes in the brains of people with AD is not understood. The most accepted hypothesis is that amyloid beta deposition causes the cascade leading to neuronal degeneration.[5] In addition, recent studies have shown that vascular factors play a role in this process.[6,7] There is increasing evidence regarding vascular changes in AD. Cerebral capillary atrophy, focal constriction, structural changes in endothelial cells, and amyloid deposition in vessel walls are some of these microvascular changes.[8] By obtaining evidence showing that vascular risk factors also increase the risk of AD, the question "Is AD a vascular disease?" is being raised. It was put forward that the toxic effect of amyloid beta may also affect endothelial cells and cause endothelial-dependent vasoconstriction.[9,10] Based on these findings, the goal of this study was to test the hypothesis that endothelial dysfunction may occur in AD.

The endothelium is the monolayer of endothelial cells lining the lumen of the vascular beds and is mechanically and metabolically strategically located, separating the vascular wall from the circulation and the blood components.[11] Brachial artery flow-mediated dilation (FMD) serves as a measure of endothelial vasodilator function in humans. Endothelial dysfunction measured according to

From the *Department of Internal Medicine, †Department of Cardiology, and ‡Division of Geriatric Medicine, Department of Internal Medicine, Hacettepe University, Ankara, Turkey; and §Department of Psychiatry, Ankara Oncology Hospital, Ankara, Turkey.

Address correspondence to Burcu Balam Yavuz, MD, Faculty of Medicine, Department of Internal Medicine, Division of Geriatric Medicine, Hacettepe University, Sihhiye, 06100 Ankara, Turkey.
E-mail: bbyavuz@hacettepe.edu.tr

DOI: 10.1111/j.1532-5415.2007.01378.x

© 2007, Copyright the Authors
Journal compilation © 2007, The American Geriatrics Society
0002-8614/07/$15.00

FMD is reported to be one of the early markers of atherosclerosis.[12] FMD is a noninvasive method of measuring the brachial artery diameter after reactive hyperemia. Reactive hyperemia is achieved by applying external pressure to the brachial artery[13,14] and results in increased blood flow and increased FMD in the artery. In the presence of endothelial dysfunction, dilatation is not sufficient, and decrease in FMD values occurs. This is a widely used, reproducible, inexpensive method of measuring endothelial function.[15]

The aim of this study was to investigate the relationship between AD and endothelial function, to examine the presence of endothelial dysfunction in AD, to try to find an answer to the question of whether AD is a vascular disease, and try to take a step toward understanding the pathogenesis of AD.

MATERIAL AND METHODS

Subjects

Forty-eight patients aged 65 and older admitted to an outpatient clinic were enrolled in this study. After exclusions according to the exclusion criteria and cognitive assessment, 25 geriatric subjects with AD and 24 controls were enrolled. Exclusion criteria were hypertension (blood pressure $>140/90$ mm Hg), hyperlipidemia (total cholesterol >200 mg/dL), coronary artery disease (stable or unstable angina pectoris, coronary intervention, myocardial infarction, positive result on treadmill test or thallium scanning, documented coronary artery disease according to coronary angiography), heart failure (based on history, clinical examination, and echocardiographic findings), infection, malignancy, peripheral artery disease (patients with claudication and absence of peripheral pulses), diabetes mellitus (patients with a history of diabetes mellitus, who were taking antidiabetic medication, or whose fasting plasma glucose was >126 mg/dL), chronic renal disease (creatinine >1.3 mg/dL for women, >1.5 mg/dL for men), collagen vascular disease, alcoholism (daily intake of ≥ 30 g alcohol), smokers (patients who were exsmokers for at least 10 years were not excluded), and medications that may alter endothelial function (antilipid drugs, angiotensin-converting enzyme inhibitors, angiotensin receptor antagonists, antioxidants, calcium channel blockers, beta-blockers, and corticosteroids). Transthoracic echocardiographic examination was performed on all subjects using a System Five cardiac ultrasound scanner (GE Vingmed Ultrasound, Horten, Norway) and 2.5 to 3.5 MHz transducers to exclude organic heart disease.

Comprehensive Geriatric Assessment and Cognitive Assessment

A medical history was taken and a physical and neurological examination, a comprehensive geriatric assessment (including activities of daily living (ADLs) (higher scores indicate less ability),[16] instrumental activities of daily living (IADLs) (lower scores indicate poorer ability),[17] Mini-Mental State Examination (MMSE),[18] clock drawing test,[19] and Yesavage Geriatric Depression Scale[20]), and a cognitive assessment were performed. AD diagnosis was made according to *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*,[21] and National Institute of Neurological and Communication Disorders and Stroke–Alzheimer's Disease and Related Disorders Association[22] criteria after cognitive assessment and neuroimaging performed using magnetic resonance imaging (MRI). The Clinical Dementia Rating (CDR) Scale was used to determine the severity of dementia.[23] A skilled team consisting of two geriatricians and a psychiatrist (BBY, MC, ESC) performed the cognitive assessment. This team made a diagnosis of AD after performing the cognitive tests and criteria explained above. All of the patients in the AD group underwent MRI to rule out intracranial pathologies and support the diagnosis.

The study protocol was consistent with the declaration of Helsinki and was approved by the local ethics committee. Informed consent was obtained before enrollment.

Laboratory Tests

Blood samples were obtained using venipuncture of the antecubital vein after an overnight fast and analyzed immediately. For both groups, complete blood count, liver and renal function tests, serum electrolytes, erythrocyte sedimentation rate, C-reactive protein (CRP), lipid profile, thyroid function tests, vitamin B_{12}, folic acid, ferritin, and homocysteine levels were measured. CRP levels were measured according to rate nephelometry (IMMAGE CRP Test, Beckman, CA). Turbidimetric immunoassay (IMMAGE FER Test, Beckman) was used to determine ferritin levels. Quantitative measurements of homocysteine levels were made using a fluorescence polarization immunoassay. Serum folic acid and vitamin B_{12} were measured using electrochemiluminescence immunoassay.

Assessment of Endothelial Function

The same examiner (BY), who was blind to the clinical characteristics of the subjects, performed all measurements. The brachial artery was imaged using a System Five cardiac ultrasound scanner and 7.5-mHz linear-array transducer. All subjects were evaluated after an overnight fast, and all measurements were performed in the morning at room temperature. Arterial flow was interrupted for 5 minutes using a cuff placed on the proximal forearm at whichever occlusion pressure would be higher than 250 mmHg. Using electrocardiographic triggering, end-diastolic measurements were taken at baseline and 2 minutes after cuff deflation. Baseline diameter was calculated as the average diameter from all baseline images measured. The 60-second diameter was calculated as the average of all images measured between 55 and 65 seconds after cuff deflation. FMD induced by reactive hyperemia was expressed as relative change from baseline (FMD% = 60-second diameter – baseline diameter/baseline diameter).

Statistical Analysis

Normal distributed continuous variables are demonstrated as means ± standard deviations and skew distributed continuous variables as medians (minimums–maximums). Categorical variables are given as percentages. To make comparisons between the groups, the Mann-Whitney U-test was used for skew-distributed continuous variables (laboratory results, ADL, and IADL scores), *t*-tests were used for normally distributed continuous variables (age, MMSE, and FMD), and the chi-square test was used for

categorical variables (sex, education status, and family history of AD). Correlation analyses to examine the correlation between MMSE, CDR, and FMD in the total sample were performed using Pearson and Spearman correlation tests. To determine the independent effect of AD on FMD, linear regression analysis was performed with the variables age, sex, and results of laboratory analysis. A *P*-value of .05 or less was considered to be statistically significant. Statistical package SPSS 11.0 for Windows was used (SPSS, Inc., Chicago, IL).

RESULTS

Demographic results and clinical properties of the study population are depicted in Table 1. Patients with AD were significantly older than controls ($P = .001$). Laboratory results, including serum electrolytes, renal and liver function tests, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, apolipoprotein A, apolipoprotein B, lipoprotein-a, homocysteine, vitamin B_{12}, folic acid, thyroid function, erythrocyte sedimentation rate, ferritin, and hemoglobin were similar between the groups. These laboratory results are summarized in Table 1. All of the patients with AD underwent MRI to exclude intracranial pathologies and support the diagnosis of AD. None of the patients in the study had intracranial pathologies, including tumor, demyelinization, hydrocephalus, infarct, and hemorrhage. Each patient in the AD group had global cerebral and temporal lobe atrophy and ventricular enlargement.

Significantly lower FMD was found in the AD group, which indicated endothelial dysfunction (mean FMD: AD group, $3.4 \pm 1.7\%$; control group, $8.4 \pm 3.3\%$; $P < .001$) (Table 1). The distribution of FMD values in the AD and control groups is depicted in Figure 1. When the correlation between CDR and MMSE scores and FMD values of the total sample ($N = 49$) was examined, it was found that FMD had a negative correlation with CDR score (correlation coefficient $(r) = -0.605$, $P < .001$) (Figure 2) and a positive correlation with MMSE score ($r = 0.560$, $P < .001$). Mean FMD values were 8.4 ± 3.6 for CDR = 0, 8.4 ± 2.7 for CDR = 0.5, 2.8 ± 1.6 for CDR = 1, 4.2 ± 1.9 for CDR = 2, and 3.0 ± 1.6 for CDR = 3 ($P < .001$; analysis of variance). A multiple linear regression analysis was performed by mak-

Table 1. Demographic Characteristics, Flow-Mediated Dilation (FMD), and Laboratory Results of the Study Population

Characteristics and Laboratory Results	Alzheimer's Disease ($n = 25$)	Control ($n = 24$)	*P*-Value
Age, mean ± SD	78.0 ± 5.9	72.1 ± 5.8	.001
Male/female, n	11/14	9/15	.75
Illiterate, n	16	8	.02
Family history of dementia, n	9	2	.02
MMSE score, mean ± SD	17.4 ± 6.0	28.2 ± 1.9	<.001
CDR, median (range)	2 (1–3)	0 (0–0)	<.001
ADLs, median (range)	0 (0–11)	0 (0–2)	.11
IADLs, median (range)	11 (1–16)	16 (7–17)	<.001
FMD, %, mean ± SD	3.4 ± 1.7	8.4 ± 3.3	<.001
Laboratory results, median (range)			
Sodium, mEq/L	142.5 (135–147)	141.0 (135–146)	.12
Potassium, mEq/L	4.2 (3.0–5.7)	4.5 (3.5–5.1)	.28
Creatinine, mg/dL	0.9 (0.6–1.9)	0.9 (0.6–1.4)	.20
Alanine aminotransferase, U/L	14 (8–112)	15 (6–40)	.61
Aspartate aminotransferase, U/L	22.5 (13–46)	22 (10–37)	.79
Total cholesterol, mg/dL	192 (143–205)	190 (151–205)	.71
Triglycerides, mg/dL	108.5 (68–255)	127 (74–185)	.53
Low-density lipoprotein cholesterol, mg/dL	121 (69–149)	113 (73–155)	.16
Lipoprotein-a, mg/dL	24.4 (1.9–114)	20.3 (2–173)	.55
Apolipoprotein A, mg/dL	136.5 (97–136)	135 (75–202)	.58
Apolipoprotein B, mg/dL	114 (70–165)	96.7 (84–151)	.28
Homocysteine, umol/L	14 (6.5–199)	14.7 (8.9–31.6)	.92
Folic acid, ng/mL	3.5 (0–7)	9 (1–14)	.42
Vitamin B_{12}, pg/mL	298 (90–2,000)	332 (128–625)	.95
Ferritin, ng/mL	76 (6.83–410)	87.1 (14.8–313)	.22
Thyroid-stimulating hormone, μIU/mL	1.1 (0–4.45)	1.2 (0.46–2.47)	.77
Hemoglobin, g/dL	13.2 (11.5–16.3)	14 (12.4–15.6)	.23
C-reactive protein, mg/dL	0.3 (0.03–3.8)	0.3 (0.1–1.8)	.17

Note: Normally distributed continuous variables (age, Mini-Mental State Examination (MMSE), and FMD) were compared using the *t*-test, skew-distributed continuous variables (activities of daily living (ADLs), instrumental activities of daily living (IADLs), and laboratory results) using the Mann-Whitney *U*-test, and categorical variables (sex, literacy, family history of dementia, and Clinical Dementia Rating (CDR)) using the chi-square test.
SD = standard deviation.

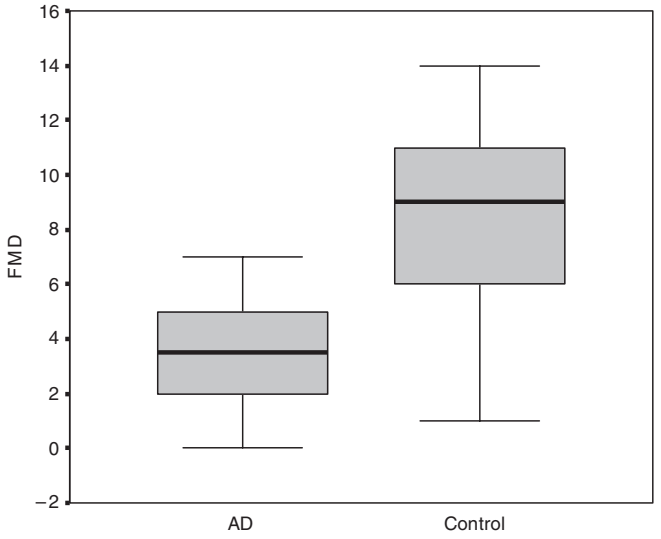

Figure 1. Distribution of flow-mediated dilation (FMD) values in the group with Alzheimer's disease (AD) and the control group. The box plot shows FMD values for AD and control groups. The black lines within the boxes indicate the median, the edges of the boxes are the 25th and 75th percentiles, and the lines extend to the maximum and minimum values. Mean value ± standard deviation of FMD: AD group, 3.4 ± 1.7%; control group, 8.4 ± 3.3; $P < .001$.

ing adjustment for age to determine the independent effect of AD on endothelial function. The results showed statistically significant correlation between FMD and AD independent of age (beta = 0.5, $t = 4.49$, 95% confidence interval = 1.99–5.25, $P < .001$).

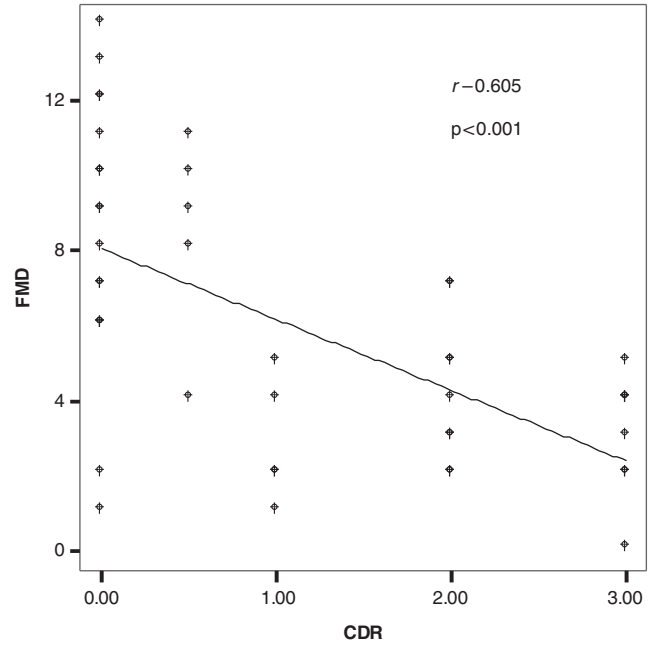

Figure 2. Correlation between Clinical Dementia Rating Scale (CDR) and flow-mediated dilation (FMD). r = correlation coefficient.

DISCUSSION

This study found a significant relationship between AD and FMD values, which provides evidence of endothelial dysfunction in AD. The study population consisted of subjects with AD and control subjects who were free of cardiovascular risk factors except advanced age. Because advanced age may influence endothelial function,[24–26] the results were adjusted for age, and it was found that AD was independently related to impaired endothelial function.

It has been proved that, in many diseases, including chronic renal failure, heart failure, hypertension, diabetes mellitus, and rheumatic diseases, endothelial function is impaired.[27–30] Some of these diseases that cause endothelial dysfunction are also risk factors for AD.[31–34] This finding also indicates that endothelial dysfunction may occur in AD, although studies on this are limited. One study evaluated endothelial function of 17 patients with AD using venous occlusion plethismography and found no difference from normal controls.[35] Serum soluble intercellular adhesion molecule-1, soluble E-selectin, and thrombomodulin were evaluated as potential markers for endothelial dysfunction in different studies, and significantly greater levels were detected in subjects with AD.[36,37] Another study detected endothelial alterations in patients with AD by measuring the response to acetylcholine iontophoresed into the skin using laser Doppler flowmetry.[38] In the current study, examining endothelial function using a noninvasive method of FMD, the AD group showed significantly impaired endothelial function. This result suggests that, in patients with AD, independent of any other cardiovascular risk factors, endothelial dysfunction occurs and that AD may be a consequence of a vascular pathology. Previous studies and the present study may indicate that AD has peripheral vasomotor effects.

Endothelial function was examined using FMD on peripheral arteries in this study. FMD is a noninvasive, commonly used, reproducible, and accurate method of evaluating endothelial function. Determining endothelial function from peripheral arteries can reflect vascular endothelium in the brain. This was proved in an experimental study showing that cerebral vessels respond like peripheral vessels to acetylcholine infusion.[35]

Endothelial dysfunction that was detected in patients with AD free of the diseases that may influence the integrity of vascular endothelium in this study may be a result of the beta-amyloid protein, which is known to be the most important pathological finding of AD. The theories trying to find a link between vascular hypothesis and beta-amyloid protein hypothesis in the pathogenesis of AD, which has been recently discussed in the literature, may explain the results.[26] It can be hypothesized that beta-amyloid protein may be causing neuronal cell loss directly or indirectly by leading to lipid peroxidation and reactive oxygen species, and impaired vascular endothelium may have a role in accelerating this phenomenon.

It has also been determined that higher FMD values, which indicate endothelial dysfunction, and the stage of AD are significantly correlated. This shows that endothelial function has a tendency to be more impaired when CDR scores are worse.

In this study, to evaluate the relationship between endothelial function and AD, biochemical parameters, lipid profile, serum iron, and ferritin were analyzed, in addition to FMD, but no relationship was found with any of these parameters, and FMD was significantly related with AD independent of these parameters and age.

CONCLUSION

AD is an important health problem of the geriatric population, because it increases health expenditures, its pathogenesis is not yet clearly identified, and no curative treatment is available. To demonstrate the factors that may play role in the pathogenesis of the disease is crucial in diagnosis, prevention, and treatment of the disease. Recent data indicate that endothelial dysfunction is of great importance in the pathogenesis and progression of AD. The results of this study support this hypothesis, although more studies and proofs are needed to verify the results.

ACKNOWLEDGMENTS

Financial Disclosure: None of the coauthors has any direct or indirect conflicts of interest, financial or otherwise, relating to the subject of our report.

Author Contributions: Didem Sener Dede designed the study, supervised the data collection, enrolled the subjects, carried out the statistical analysis, and wrote the manuscript. Bunyamin Yavuz designed the study, performed FMD measurements, and assisted with writing the manuscript. Burcu Balam Yavuz designed the study, collected data, and wrote the manuscript. Mustafa Cankurtaran and Meltem Halil collected the data and assisted with writing the manuscript. Zekeriya Ulger collected the data. Eylem Sahin Cankurtaran assisted with writing the manuscript. Kudret Aytemir designed the study and supervised FMD measurements. Giray Kabakci designed the study. Servet Ariogul designed the study, supervised the data collection, and assisted with writing the manuscript.

Sponsor's Role: No sponsor.

REFERENCES

1. Knopman DS, Dekosky ST, Cummings JL et al. Practice parameter: Diagnosis of dementia (an evidence based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2001;56:1143–1153.
2. Vicioso BA. Dementia: When is it not Alzheimer's disease? Am J Med Sci 2002;324:84–95.
3. Yavuz BB, Ariogul S, Cankurtaran M et al. Hippocampal atrophy correlates with the severity of cognitive decline. Int Psychogeriatr 2006;28:1–11 [Epub ahead of print].
4. Petrella JR, Coleman RE, Doraiswamy PM. Neuroimaging and early diagnosis of Alzheimer disease: A look to the future. Radiology 2003;226:315–336.
5. Cummings JL. Alzheimer's disease. N Engl J Med 2004;351:56–67.
6. Launer L. Demonstrating the case that Alzheimer disease is a vascular disease: Epidemiologic evidence. Aging Res Rev 2002;1:61–67.
7. Pansari K, Gupta A, Thomas P. Alzheimer's disease and vascular factors. Facts and theories. Int J Clin Psychiatry 2002;56:197–203.
8. Buee L, Hof PR, Delacourte A. Brain microvascular changes in Alzheimer's disease and other dementias. Ann N Y Acad Sci 1997;826:7–24.
9. Klunk WE, Engler H, Nordberg A et al. Imaging brain amyloid in Alzheimer's disease with Pittsburgh Compound-B. Ann Neurol 2004;55:306–319.
10. Crawford F, Suo Z, Fang C et al. Characteristics of the in vitro vasoactivity of beta-amyloid peptides. Exp Neurol 1998;150:159–168.
11. Bonetti PO, Lerman LO, Lerman A. Endothelial dysfunction: A marker of atherosclerotic risk. Arterioscler Thromb Vasc Biol 2003;23:168–175.
12. Corretti MC, Anderson TJ, Benjamin EJ et al. Guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery: A report of the International Brachial Artery Reactivity Task Force. J Am Coll Cardiol 2002;39:257–265.
13. Zawar SD, Vyawahare MA, Nerkar M et al. Non-invasive detection of endothelial dysfunction in sickle cell disease by Doppler ultrasonography. J Assoc Physicians India 2005;53:677–680.
14. Sorensen KE, Celermajer DS, Spiegelhalter DJ et al. Non-invasive measurement of human endothelium dependent arterial responses: Accuracy and reproducibility. Br Heart J 1995;74:247–253.
15. Naka KK, Tweddel AC. Flow-mediated changes in pulse wave velocity: A new clinical measure of endothelial function. Eur Heart J 2006;27:302–309.
16. Mahoney FI, Barthel DW. Functional evaluation: The Barthel index. MD State Med J 1965;14:61–65.
17. Lawton MP, Broody EM. Assessment of older people: Self-maintaining and instrumental activities of daily living. Gerontologist 1969;9:179–186.
18. Folstein MF, Folstein JE, McHugh PR. "Mini Mental State". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–198.
19. Stahelin HB, Monsch AU, Spiegel R. Early diagnosis of dementia via a two-step screening and diagnostic procedure. Int Psychogeriatr 1997;9: 123–130.
20. Yesavage JA, Brink TL, Rose TL et al. Development and validation of a geriatric depression screening scale. A preliminary report. J Psychiatr Res 1983;17:37–49.
21. Diagnostic and Statistical Manual of Mental Disorders, 4th Ed. Washington, DC: American Psychiatric Association, 1994.
22. McKhann G, Drachman D, Folstein M et al. Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 1984;34:939–944.
23. Hughes CP, Berg L, Danziger WL et al. A new clinical scale for the staging of dementia. Br J Psychiatry 1982;140:566–572.
24. Yavuz B, Dede DS, Yavuz BB et al. Aging Progressively Impairs Endothelial Function. XIV.International Symposium on Atherosclerosis, Rome, Italy, 2006.
25. Andrawis N, Jones DS, Abernethy DR. Aging is associated with endothelial dysfunction in the human forearm vasculature. J Am Geriatr Soc 2000;48:193–198.
26. Roy S, Rauk A. Alzheimer's disease and the 'ABSENT' hypothesis: Mechanism for amyloid beta endothelial and neuronal toxicity. Med Hypotheses 2005;65:123–137.
27. Johnstone MT, Creager SJ, Scales KM et al. Impaired endothelium dependent vasodilation in patients with insulin dependent diabetes mellitus. Circulation 1993;88:2510–2516.
28. Panza JA, Quyyumi AA, Brush JE et al. Abnormal endothelium dependent vascular relaxation in patients with essential hypertension. N Engl J Med 1990;323:22–27.
29. Karadag O, Calguneri M, Atalar E et al. Novel cardiovascular risk factors and cardiac event predictors in female inactive systemic lupus erythematosus patients. Clin Rheumatol 2007;26:695–699.
30. Akdogan A, Calguneri M, Yavuz B et al. Are familial mediterranean fever (FMF) patients at increased risk for atherosclerosis? Impaired endothelial function and increased intima media thickness are found in FMF. J Am Coll Cardiol 2006;48:2351–2353.
31. Reitz C, Tang MX, Luchsinger J et al. Relation between plasma lipids to Alzheimer's disease and vascular dementia. Arch Neurol 2004;61:705–714.
32. Lanuner LJ, Ross GW, Petrovich J et al. Midlife blood pressure and dementia. Honolulu Aging Study. Neurobiol Aging 2000;21:49–55.
33. de la Torre JC. Vascular basis of Alzheimer's pathogenesis. Ann N Y Acad Sci 2002;977:196–215.
34. Ott A, Stolk RP, Hofman A et al. Association of diabetes mellitus and dementia: The Rotterdam Study. Diabetologia 1996;39:1392–1397.
35. McGleenon BM, Passmore AP, McAuley DF et al. No evidence of endothelial dysfunction in patients with Alzheimer's disease. Dement Geriatr Cogn Disord 2000;11:197–201.
36. Borroni B, Volpi R, Martini G et al. Peripheral blood abnormalities in Alzheimer disease: Evidence for early endothelial dysfunction. Alzheimer Dis Assoc Disord 2002;16:150–155.
37. Rentzos M, Michalopoulou M, Nikolaou C et al. Serum levels of soluble intercellular adhesion molecule-1 and soluble endothelial leukocyte adhesion molecule-1 in Alzheimer's disease. J Geriatr Psychiatry Neurol 2004;17:225–231.
38. Khalil Z, Logiudice D, Khodr B et al. Impaired peripheral endothelial microvascular responsiveness in Alzheimer's disease. J Alzheimers Dis 2007;11: 25–32.