

The Metabolic Syndrome and Alzheimer Disease

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Background: The metabolic syndrome is a risk factor for cardiovascular diseases, which have been linked to Alzheimer disease. However, a link between Alzheimer disease and the metabolic syndrome has not yet been established.

Objective: To investigate the relationship between the metabolic syndrome and Alzheimer disease.

Design, Setting, and Participants: Case-control study of 50 consecutive patients diagnosed with probable Alzheimer disease from the Memory Disorders Clinics, Launceston, Australia, and Bristol, England, and 75 cognitively normal controls.

Main Outcome Measures: The odds ratio of the metabolic syndrome as defined by the National Cholesterol Education Program Adult Treatment Panel III.

Results: Compared with controls, patients with Alzheimer disease had a significantly larger mean waist circumference, higher mean plasma concentrations of triglycerides and glucose, and a lower mean plasma concentration of high-density lipoprotein cholesterol, but they had lower mean systolic blood pressure. The metabolic syndrome was associated with Alzheimer disease (odds ratio, 3.2; 95% confidence interval, 1.2-8.4; $P = .02$), and this association was strengthened when the hypertension component was excluded (odds ratio, 7.0; 95% confidence interval, 2.7-18.3; $P < .001$). All of the analyses were adjusted for age, sex, and location.

Conclusions: This study suggests that Alzheimer disease is associated with the metabolic syndrome. This could have implications for the prevention and treatment of Alzheimer disease.

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THE PREVALENCE OF THE metabolic syndrome, characterized by the clustering of abdominal obesity, hypertension, hyperglycemia, and dyslipidemia (high plasma concentration of triglycerides and low concentration of high-density lipoprotein [HDL] cholesterol), is now reaching epidemic proportions.¹ The syndrome is associated with an increased risk of type 2 diabetes mellitus and cardiovascular disease,² which have been linked to Alzheimer disease.^{3,4} However, a link between Alzheimer disease and the metabolic syndrome has not yet been established. We have therefore investigated the relationship between the metabolic syndrome and Alzheimer disease in a case-control study.

METHODS

Fifty consecutive patients with probable Alzheimer disease were selected from the Memory Disorders Clinics, Launceston, Australia, and

Bristol, England. Dementia was diagnosed according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, and the diagnosis of Alzheimer disease was made according to the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer Disease and Related Disorders Association. Seventy-five controls of a similar age range were recruited from patients' spouses and the local community through newspaper advertisements inviting them to participate in the study. They had no memory complaints and normal scores on the Mini-Mental State Examination. Patients and controls underwent a full medical examination and investigations including brain imaging. Exclusion criteria included treatment for cardiovascular disease or diabetes, which could influence blood pressure, plasma concentrations of glucose or lipoproteins, and lacunar infarct on brain imaging.

Data obtained included height and weight in indoor clothing without shoes (from which the body mass index was calculated as the weight in kilograms divided by the height in meters squared), waist circumference (the girth midway between 12th rib and the iliac crest

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Table 1. Participant Characteristics and Values for Each Component of the Metabolic Syndrome Using χ^2 Test and General Linear Model Analysis Adjusted for Age, Sex, and Location

Variable	Controls (n = 75)	Patients With Alzheimer Disease (n = 50)	P Value
Participant characteristics			
From Australia/England, No.	51/24	26/24	.07
M/F, No.	40/35	23/27	.42
Age, mean (range), y	72.4 (55-94)	75.0 (57-90)	.06
Mini-Mental State Examination score, mean (range)	29.5 (28-30)	16.2 (4-28)	<.001
Body mass index, mean (range)*	24.7 (19.7-33.5)	26.1 (15.1-36.1)	.08
Metabolic syndrome components, mean (SEM)			
Waist circumference, cm	85.3 (1.3)	91.1 (1.5)	.004
Triglyceride concentration, mmol/L†	1.2 (0.06)	1.6 (0.08)	<.001
HDL cholesterol concentration, mmol/L‡	1.4 (0.04)	1.2 (0.05)	.005
Systolic blood pressure, mm Hg	149.1 (2.4)	136.5 (2.8)	.001
Glucose concentration, mmol/L§	5.4 (0.17)	6.2 (0.21)	.005

Abbreviation: HDL, high-density lipoprotein.

*Body mass index is calculated as the weight in kilograms divided by the height in meters squared.

†To convert triglycerides from millimoles per liter to milligrams per deciliter, divide millimoles per liter by 0.01129.

‡To convert HDL cholesterol from millimoles per liter to milligrams per deciliter, divide millimoles per liter by 0.02586.

§To convert glucose from millimoles per liter to milligrams per deciliter, divide millimoles per liter by 0.05551.

with the participant standing), and arterial blood pressure (systolic and diastolic) using an aneroid sphygmomanometer with the subject lying comfortably. Fasting venous blood was obtained from all of the participants and glucose and lipoprotein concentrations were measured using standard enzymatic techniques.

The metabolic syndrome has recently been defined by the National Cholesterol Education Program Adult Treatment Panel III as having 3 or more of the following: a waist circumference greater than 102 cm for men or 88 cm for women; a serum triglyceride concentration of at least 1.7 mmol/L (150.6 mg/dL); a serum HDL cholesterol concentration less than 1.04 mmol/L (40.22 mg/dL) for men or 1.29 mmol/L (49.88 mg/dL) for women; blood pressure of at least 130/85 mm Hg; and a fasting plasma glucose concentration of at least 6.1 mmol/L (109.9 mg/dL).⁵ These criteria were developed to identify subjects at an increased risk of developing cardiovascular disease.⁵ However, it has been argued that the criteria are less sensitive in predicting the risk of insulin resistance and diabetes.⁶

Statistical calculations were performed using Minitab Statistical Software, Release 13 for Windows 2000 (Minitab, Inc, State College, Pa). General linear model analysis was used for the comparison of groups, and χ^2 and logistic regression analyses were used to calculate the rates and odds ratios for each

component of the metabolic syndrome, as well as for the syndrome itself, adjusted for age, sex, and location.

The study was approved by the local ethics committees, and informed consent was provided by all of the participants or their guardians.

RESULTS

There were 50 patients with Alzheimer disease and 75 controls (9 [12%] recruited from patients' spouses and 66 [88%] from the local community). Most patients with Alzheimer disease had mild to moderate disease, with 37 (74%) having Mini-Mental State Examination scores of 12 or greater, and 47 (94%) were living in the community. **Table 1** presents participant characteristics and the adjusted mean values for each component of the metabolic syndrome. As compared with controls, patients with Alzheimer disease had a significantly larger mean waist circumference (larger by 5.8 cm [7% larger]), higher mean plasma concentrations of triglycerides (higher by 0.4 mmol/L [35.4 mg/dL] [33% higher]) and glucose (higher by 0.8 mmol/L [14.4 mg/dL] [15% higher]), and a lower mean HDL cholesterol concentration (lower by 0.2 mmol/L [7.7 mg/dL] [14% lower]), but they had a lower mean systolic blood pressure (lower by 12.6 mm Hg [8% lower]).

The rates and adjusted odds ratios for each component of the metabolic syndrome and the syndrome itself are presented in **Table 2**. Patients with Alzheimer disease had significantly higher rates of hyperglycemia and hypertriglyceridemia and lower HDL cholesterol concentrations, but they had lower rates of hypertension. Moreover, the metabolic syndrome was associated with more than a 3-fold increase in the risk of Alzheimer disease. As hypertension was protective of Alzheimer disease, the data were reanalyzed excluding blood pressure. This strengthened the association between the metabolic syndrome and Alzheimer disease to 7-fold.

COMMENT

This study demonstrates a link between Alzheimer disease and the metabolic syndrome, including its components of hyperglycemia, hypertriglyceridemia, and a low HDL cholesterol concentration. Hypertension, however, was associated with a decreased rather than increased risk of Alzheimer disease. This is consistent with cross-sectional studies showing an inverse association between blood pressure in later life and the risk of Alzheimer disease.⁷ However, longitudinal studies have described mixed results depending on age at data collection and duration of follow-up. Midlife longitudinal studies showed an association between high midlife blood pressure and the development of dementia and Alzheimer disease, whereas most later-life longitudinal studies found no association with high blood pressure or found an association with low blood pressure.⁷ The association between Alzheimer disease and low systolic blood pressure is interesting. It is unclear whether the low systolic blood pressure is the result of neurodegeneration leading to blood

Table 2. Rates and Odds Ratios for the Metabolic Syndrome and Its Individual Components Using χ^2 Test and Logistic Regression Analysis Adjusted for Age, Sex, and Location

Variable	Controls, No. (%) (n = 75)	Patients With Alzheimer Disease, No. (%) (n = 50)	P Value for Patients vs Controls	OR (95% CI)	P Value for OR
Abdominal obesity	15 (20)	14 (28)	.30	1.8 (0.7-4.5)	.20
Hypertriglyceridemia	11 (15)	18 (36)	.006	4.8 (1.8-12.6)	.002
Low HDL cholesterol concentration	15 (20)	24 (48)	.001	3.3 (1.4-7.7)	.006
Hypertension	63 (84)	34 (68)	.008	0.2 (0.1-0.5)	.002
Hyperglycemia	5 (7)	12 (24)	.006	4.8 (1.4-16.3)	.01
Metabolic syndrome (≥ 3 of the above)	9 (12)	15 (30)	.01	3.2 (1.2-8.4)	.02
Metabolic syndrome (≥ 2 of the above, excluding hypertension)	9 (12)	22 (44)	<.001	7.0 (2.7-18.3)	<.001

Abbreviations: CI, confidence interval; HDL, high-density lipoprotein; OR, odds ratio.

pressure dysregulation or whether it preceded the development of the disease and contributed to its etiology through cerebral hypoperfusion.⁸

To our knowledge, our study is the first to investigate the relationship between Alzheimer disease and the metabolic syndrome using standard criteria. This is supported by a recent study⁹ that found that the metabolic syndrome contributes to cognitive impairment in elderly persons. Moreover, the Honolulu-Asia aging study by Kalmijn et al¹⁰ found an association between the metabolic syndrome and vascular dementia but not with Alzheimer disease; however, they did not use standard criteria in their definition of the metabolic syndrome.

The mechanisms through which the metabolic syndrome and its components may be associated with Alzheimer disease are not yet fully understood. Our finding of an association between Alzheimer disease and hyperglycemia, a marker for insulin resistance, is supported by previous studies¹¹ showing an association between Alzheimer disease, hyperinsulinemia, and insulin resistance. One possible reason for the association may be the direct effect of insulin resistance on the brain. Insulin may modulate levels of β -amyloid protein aggregation, the primary constituent of senile plaques, which are one of the neuropathological hallmarks of Alzheimer disease. Moreover, insulin inhibits the activity of glycogen synthase kinase-3 enzyme, preventing the phosphorylation of tau protein and therefore inhibiting the formation of neurofibrillary tangles, the other neuropathological hallmark of Alzheimer disease.¹²

Little is known about changes in concentrations of plasma triglycerides and HDL cholesterol in Alzheimer disease. This is relevant because HDL cholesterol is the main transporter of cholesterol in the brain, and a reduction in the HDL cholesterol concentration could lead to the impairment of cholesterol release to neurons, resulting in the formation of neurofibrillary tangles and senile plaques.¹³ In addition, a high plasma triglyceride concentration and a low plasma HDL concentration are recognized risk factors for atherosclerosis and could at least partly explain the vascular changes in the brains of patients with Alzheimer disease.

This case-control study has some limitations. It is not possible to distinguish between those factors that pre-

ceded the development of Alzheimer disease and may have a causal role and those factors that may have been altered as a consequence of the disease. There is also a selection bias in that patients with Alzheimer disease were selected from memory clinics; therefore, there may be a spurious identification of risk factors associated with clinic attendance rather than the disease itself. The method of selection of controls may also be criticized as not being random, although the inclusion of patients' spouses would possibly strengthen the study by controlling for lifestyle factors such as diet and exercise.

In conclusion, our study suggests that Alzheimer disease is associated with the metabolic syndrome. The increasing prevalence of the metabolic syndrome, coupled with the growing number of elderly people, will have serious implications for health care. Dietary modification and increased physical activity, which have been shown to reduce the risk of the metabolic syndrome, could have a role in the prevention and treatment of Alzheimer disease. Additional studies are now needed to explore this further.

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