Insulin and Cognitive Function in an Elderly Population

The Rotterdam Study

RONALD P. STOLK, MD, PHD
MONIQUE M.B. BRETELER, MD, PHD
ALEWIJN OTT, MD
HUIBERT A.P. POLS, MD, PHD
STEVEN W.J. LAMBERTS, MD, PHD
DIEDERICK E. GROBBEE, MD, PHD
ALBERT HOFMAN, MD, PHD

OBJECTIVE — To examine the association between insulin and cognitive function in the population-based Rotterdam Study.

RESEARCH DESIGN AND METHODS — Serum insulin was measured 2 h after an oral glucose load, while global cognitive function was assessed by the Mini Mental State Examination in 5,510 subjects, aged 55 years and over.

RESULTS — An increase in postload insulin only in women was associated with a decrease in cognitive function (age-adjusted regression coefficient −0.10 per 50 mU/l insulin; 95% CI −0.16 to −0.04). The association between insulin resistance, assessed by the ratio of postload insulin over glucose, and cognitive function was not statistically significant. Further adjustment for the individual risk factors of serum glucose, BMI, HDL, systolic blood pressure, smoking, or use of estrogen did not change the results. The association was present in women with and without cardiovascular disease and present after excluding subjects with diabetes. Women with dementia, the extreme of cognitive dysfunction, had increased age-adjusted insulin levels (76.3 ± 4.9 vs. 66.8 ± 1.0 mU/l [means ± SE], $P = 0.06$).

CONCLUSIONS — The results of this study suggest that increased serum insulin may be associated with decreased cognitive function and dementia in women. These findings are more compatible with a direct effect of insulin on the brain than with an effect through an increase in cardiovascular risk factors.

Cognitive function decreases with age, but this decline is not uniformly distributed in the population. Several risk factors have been identified for accelerated cognitive decline and dementia.(1) Several studies have shown an increased risk of diabetes for decreased cognitive function and dementia (2–5). Glucose is the primary substrate for the brain. Because neurons are unable to synthesize or store glucose, it is likely that disorders in the glucose metabolism affect cognitive function. It has been suggested, both in animal and clinical studies, that changes in insulin levels can be related to, and in some studies directly regulate, changes in cognitive function (6–8).

Because the presence of cardiovascular disease has been shown to be associated with impaired cognitive function (9), the association between insulin and cognitive function may be the reflection of the "insulin resistance syndrome," a clustering of cardiovascular risk factors (10). However, results from animal studies indicate that insulin may have a direct effect on the brain and cognition (11). This would imply that elevated insulin levels, probably in response to raised insulin resistance, can also directly affect cognitive function.

As part of the population-based Rotterdam Study in elderly men and women, insulin and cognitive functions were assessed. This paper describes the associations of insulin level and insulin resistance with cognitive function in nondemented subjects. In addition, we analyzed differences in insulin among subjects with and without dementia.

RESEARCH DESIGN AND METHODS

Study population

The Rotterdam Study is a population-based cohort study of determinants of chronic disabling diseases in the elderly. The design of the study and its objectives have been published previously (12), as well as the procedure of the cognitive screening (13). Informed consent was obtained from all subjects, and the study was approved by the medical ethics committee of the Erasmus University Medical School. All inhabitants of a suburb of Rotterdam, aged 55 years and over, were invited to participate. Overall, 7,983 subjects participated (response rate 78%). The analyses presented here are restricted to the 5,510 subjects for whom the serum insulin level and a complete assessment of cognitive function were available.

Measurements

Global cognitive function was assessed with the Mini Mental State Examination (MMSE). This is a brief cognitive test that covers several cognitive functions and yields a maximum best score of 30 (14). Subjects who had an MMSE score of 25 or lower or a score greater than zero on the Geriatric Mental Schedule examination (organic level) were further evaluated by a physician. All subjects suspected of dementia were subsequently evaluated by a neurologist, and underwent extensive neuropsychological testing and neuroimaging. A diagnostic panel assessed, based on all available information, whether a dementia syndrome was

From the Department of Epidemiology and Biostatistics (R.P.S., M.M.B.B., A.O., H.A.P.P., D.E.G., A.H.) and the Department of Internal Medicine III (H.A.P.P., S.W.J.L.), the Erasmus University Medical School, Rotterdam; and the Julius Center for Patient-Oriented Research (R.P.S., D.E.G.), Utrecht University, Utrecht, The Netherlands.

Address correspondence and reprint requests to R.P. Stolk, MD, PhD, Department of Epidemiology and Biostatistics, Erasmus University Medical School, P.O. Box 1738, 3000 DR Rotterdam, The Netherlands. E-mail: stolk@epib.fgg.eur.nl.

Received for publication 19 April 1996 and accepted in revised form 2 December 1996.

MMSE, Mini Mental State Examination; sBP, systolic blood pressure.

Downloaded from http://diabetesjournals.org/care/article-pdf/20/5/792/584384/20-5-792.pdf by guest on 04 November 2024

Table 1—*Baseline characteristics*

	Men	Women	*P* value*
n	2,232	3,278	
Age (years)	67.9 ± 0.2	69.5 ± 0.2	—
BMI (kg/m²)	25.8 ± 0.1	26.7 ± 0.1	<0.001
Serum glucose (mmol/l)	6.9 ± 0.05	6.5 ± 0.04	<0.001
Postload serum insulin† (mU/l)	55.6 ± 1.0	67.2 ± 1.0	<0.001
Insulin resistance‡ (mU/mmol)	8.4 ± 0.1	9.3 ± 0.1	<0.001
MMSE	27.6 ± 0.05	27.3 ± 0.05	0.09
Dementia	2.7%	4.0%	0.79

Data are means ± SE or %. *Test for the difference between men and women, adjusted for age; †2 h after an oral glucose load of 75 g; ‡ratio of postload insulin over postload glucose.

present (15). On the basis of the clinical dementia rating scale (16), subjects with dementia were divided into minimal, mild, moderate, and severe cognitive impairment.

The participants came to the research center throughout the day. Blood was drawn by venipuncture, and subjects not using antidiabetes medication (tablets or insulin) received a glucose drink of 75 g of glucose. A second blood sample was obtained 2 h later. During this interval the other examinations were performed, including the cognitive assessment. Insulin was measured by radioimmunoassay (Medgenix Diagnostics, Brussels, Belgium) in the postload serum only. Because subjects using antidiabetes medication were not submitted to the glucose tolerance test, insulin was not measured in this group. Insulin resistance was assessed by the ratio of postload insulin over postload glucose. Diabetes was defined as the use of antidiabetes medication or a random or postload glucose level >11 mmol/l. Cardiovascular disease was defined as a history of myocardial infarction or stroke or as the presence of angina pectoris or intermittent claudication.

Data analysis

The changes of insulin and cognitive function with age were assessed by linear regression analyses. The associations between MMSE score and insulin level and insulin resistance were analyzed in subjects without dementia, using multiple linear regression. Besides age, a number of potential confounding variables were each separately included into the model; notably, glucose, lipids, blood pressure, smoking, and estrogen use. The analyses were also performed in subgroups by the presence of diabetes and age (younger and older than 75 years). Analysis of covariance was used to calculate age-adjusted mean values of MMSE score for categories of insulin. The same approach was used to calculate age-adjusted mean values of insulin for subjects with and without dementia and for severity of dementia. All analyses were performed for men and women separately.

RESULTS — The baseline characteristics of the study population are given in Table 1. In both men and women, insulin level and insulin resistance increased with age, whereas cognitive function significantly decreased with age (for all associations: $P < 0.01$).

Because low MMSE scores primarily reflect the underlying cause of dementia in demented subjects, the analyses were restricted to subjects without dementia. Insulin level but not insulin resistance in women was inversely associated with cognitive function (Table 2). In men, insulin was not associated with cognitive function. Further adjustment for random serum glucose, BMI, HDL, systolic blood pressure (sBP), smoking, or use of estrogen did not change the association between insulin and cognitive function (Table 3). If all these variables were included into one model, the association between insulin and MMSE score would no longer be statistically significant: the regression coefficient was 0.04 per 50 mU/l insulin in men (95% CI −0.04 to 0.11) and −0.05 per 50 mU/l insulin (95% CI −0.11 to 0.01) in women. Figure 1 gives the age-adjusted MMSE score by categories of postload insulin, showing that in women the MMSE score steadily decreased over the whole range of insulin values.

The association between insulin and cognitive function was significant in women with and without cardiovascular disease. Excluding subjects with diabetes did not change the results either. In subjects younger than 75 years, the associations were weaker than in the total population and not statistically significant. In women older than 75 years, the regression coefficients of MMSE score were −0.21 per 50 mU/l insulin (95% CI −0.40 to −0.03) and −0.13 per 5 mU/mmol insulin resistance (95% CI −0.29 to 0.04).

Finally, subjects with dementia (132 women, 83.5 ± 7.1 years [means ± SD], and 60 men, 80.0 ± 7.9 years) were compared with nondemented subjects. The age-adjusted mean postload insulin level in women with and without dementia was 76.3 ± 4.9 and 66.8 ± 1.0 mU/l (means ± SE) ($P = 0.06$), whereas insulin resistance was 10.4 ± 0.6 and 9.3 ± 0.1 mU/mmol ($P = 0.04$), respectively. In men with dementia the mean insulin level was 62.3 ± 6.5 mU/l, which was 55.4 ± 1.0 mU/l in nondemented men. For insulin resistance, 9.4 ± 0.9 and 8.3 ± 0.1 mU/mmol was found (for both comparisons: $P > 0.20$). In neither men nor women was severity of dementia associated with insulin level or insulin resistance (data not shown).

CONCLUSIONS — The results of this cross-sectional population-based study among 5,510 elderly men and women indicate that increased postload insulin levels are associated with decreased cognitive function in women only. Adjustment for age, glucose, BMI, HDL, sBP, smoking, or use of estrogen did not change the results. The association was present in women with and without cardiovascular disease and present after excluding subjects with diabetes.

Table 2—*Associations between insulin and MMSE score in subjects without dementia (n = 5,318)*

	Men	Women
Postload insulin (per 50 mU/l)	0.03 (−0.04 to 0.10)	−0.10 (−0.16 to −0.04)
Insulin resistance† (per 5 mU/mmol)	0.03 (−0.02 to 0.08)	−0.03 (−0.09 to 0.02)

Data are age-adjusted coefficients of linear regression and 95% CI (range). †Ratio of postload insulin over postload glucose.

Downloaded from http://diabetesjournals.org/care/article-pdf/20/5/792/584384/20-5-792.pdf by guest on 04 November 2024

Table 3—*Associations between postload insulin (per 50 mU/l) and MMSE score in subjects without dementia* (n = *5,318*)

Adjustments	Men	Women
Age	0.03 (−0.04 to 0.10)	−0.10 (−0.16 to −0.04)
Age, serum glucose	0.03 (−0.04 to 0.10)	−0.08 (−0.14 to −0.02)
Age, BMI	0.02 (−0.05 to 0.09)	−0.07 (−0.13 to −0.01)
Age, HDL	0.04 (−0.04 to 0.11)	−0.08 (−0.14 to −0.02)
Age, sBP	0.03 (−0.04 to 0.10)	−0.08 (−0.14 to −0.02)
Age, smoking	0.02 (−0.05 to 0.09)	−0.10 (−0.16 to −0.04)
Age, estrogen use	—	−0.10 (−0.16 to −0.04)

Data are age-adjusted coefficients of linear regression and 95% CI (range).

In the Rotterdam Study, no fasting blood sample was obtained, and insulin levels were measured after a nonfasting oral glucose load. We reported previously that these insulin levels are comparable with the fasting postload levels (17). Insulin resistance was assessed by the ratio of postload insulin over glucose. In subjects without diabetes, this ratio is a good measure of insulin resistance (18). The presented results were based on those subjects who had completed all examinations at the research center, which may have introduced selective nonresponse toward less impaired cognitive function. Although the prevalence of dementia in this study population is lower than in the total population of the Rotterdam Study, we do not see how this could influence the associations between insulin and cognitive function.

The associations between insulin and cognitive function are assessed in those subjects without dementia and treated diabetes. As a result, the distributions of the MMSE score and the insulin levels are restricted, which leads, if anything, to a diminishing of the association. This implies that the "true" association might be even stronger than reported. In addition, the increased insulin level in women with dementia supports the inverse association between insulin level and cognitive function.

Men have higher glucose and insulin levels than women (Table 1). The associations between insulin and cognitive function were limited to women, which might in part be explained by a different insulin-androgen interaction in men and women (19). Moreover, it has been shown that hyperglycemia is associated with a worse prognosis after myocardial infarction (20). Therefore, it can be hypothesized that those men who survive until an older age are less sensitive to insulin than women of the same age.

Little data are available on the association between insulin and cognitive function in subjects without dementia. In a population-based study of elderly men in the Netherlands, lower MMSE scores were found in subjects with insulin levels in the upper quartile (21). Moreover, in a Finnish population-based study, hyperinsulinemia was associated with impaired cognitive function in subjects with hypertension (22).

Raised insulin resistance is associated with a number of other cardiovascular risk factors; notably, obesity, dyslipidemia, impaired glucose tolerance, and raised blood pressure (10). The sequence of occurrence of the components of this cluster of risk factors is still poorly understood, but it has been suggested that insulin resistance is the underlying defect (23). With this in mind, the increased insulin levels in cognitive dysfunction could reflect the adverse cardiovascular risk profile, as reported by several (9,24), but not all (25), authors. If that were the case, adjustment for other cardiovascular risk factors would reduce the association, which was not the case in our data (Table 3). This suggests that the cardiovascular risk of insulin cannot explain the decreased cognitive function. The absence of an association between insulin resistance, assessed by the ratio of postload insulin over glucose, and cognitive function further supports this notion (Table 2).

In animal studies, evidence of a direct effect of insulin on brain functions associated with cognition and on cognitive function itself has been found (6–8,11,26). It is not known if this effect is related to brain glucose utilization. Serum insulin is significantly associated with the insulin level in the cerebrospinal fluid (27). Therefore, serum insulin may be associated with the function of those areas of the brain with a dense distribution of insulin receptors, such as the hypothalamus, olfactory bulb, and hippocampus (28). As a result, the functions supported by these areas, such as memory, may be related to plasma insulin levels. The results of a recent study in patients with dementia indicate that insulin in particular may affect memory functions (8). The MMSE is a global cognitive screening test with only a small memory component (14). Therefore, it can be expected that the association with insulin will be more evident when specific memory tests are used.

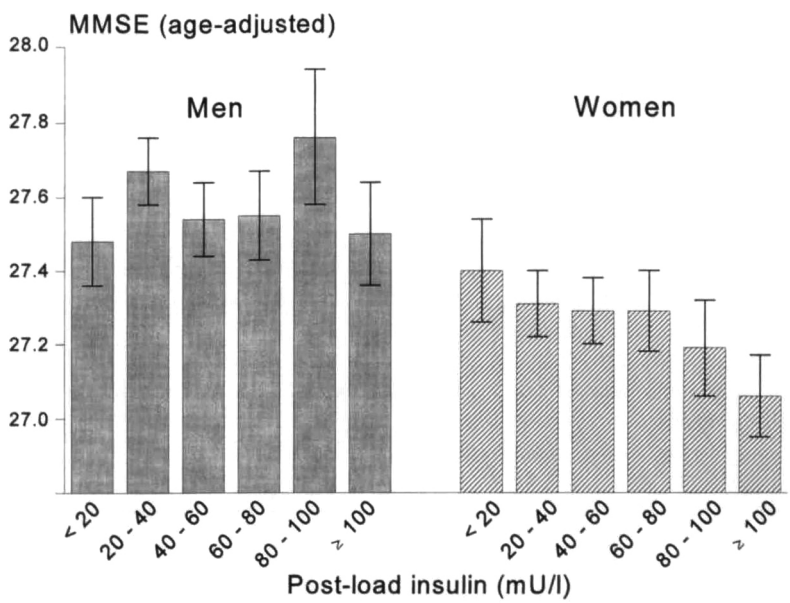

Figure 1—*Age-adjusted MMSE score by level of postload serum insulin. Data are means ± SE.*

Downloaded from http://diabetesjournals.org/care/article-pdf/20/5/792/584384/20-5-792.pdf by guest on 04 November 2024

In conclusion, the results of this study suggest that increased serum insulin level may be associated with decreased cognitive function and dementia in women. The analyses presented here are based on cross-sectional data, which means that no direct causal relationship can be established. However, these findings are more comparable with a direct effect of insulin on the brain than with an effect through an increase in cardiovascular risk factors. Follow-up studies are needed to study the associations among insulin, other cardiovascular risk factors, and cognitive function in the elderly.

Acknowledgments — We are indebted to the participants of the Rotterdam Study, to the research assistants of the research center, and to the workers in the laboratories of Internal Medicine III and Epidemiology.

This work was funded by the Netherlands Diabetes Fund and supported by the NESTOR program for geriatric research in the Netherlands (Ministry of Health and Ministry of Education).

References

1. Breteler MMB, Claus JJ, van Duijn CM, Launer LJ, Hofman A: Epidemiology of Alzheimer's disease. *Epidemiol Rev* 14:59–82, 1992
2. Reaven GM, Thompson LW, Nahum D, Haskins E: Relationship between hyperglycemia and cognitive function in older NIDDM patients. *Diabetes Care* 13:16–21, 1990
3. Richardson JTE: Cognitive function in diabetes mellitus. *Neurosci Biobehav Rev* 14:385–388, 1990
4. Robertson-Tchabo EA, Arenberg D, Tobin JD, Plotz JB: A longitudinal study of cognitive performance in noninsulin dependent (type II) diabetic men. *Exp Gerontol* 21:459–467, 1986
5. Biessels GJ, Kappelle AC, Bravenboer B, Erkelens DW, Gispen WH: Cerebral function in diabetes mellitus. *Diabetologia* 37:643–650, 1994
6. Craft S, Dagogo-Jack SE, Wiethop BV, Murphy C, Nevins RT, Fleischman S, Rice V, Newcomer JW, Cryer PE: Effects of hyperglycemia on memory and hormone levels in dementia of the Alzheimer type: a longitudinal study. *Behav Neurosci* 107:926–940, 1993
7. Palovcik RA, Phillips MI, Kappy MS, Raizada MK: Insulin inhibits pyramidal neurons in hippocampal slices. *Brain Res* 309:187–191, 1984
8. Craft S, Newcomer J, Kanne S, Dagogo-Jack S, Cryer P, Sheline Y, Luby J, Dagogo-Jack A, Alderson A: Memory improvement following induced hyperinsulinemia in Alzheimer's disease. *Neurobiol Aging* 17:123–130, 1996
9. Breteler MMB, Claus JJ, Grobbee DE, Hofman A: Cardiovascular disease and distribution of cognitive function in elderly people: The Rotterdam Study. *BMJ* 308:1604–1608, 1994
10. DeFronzo RA, Ferrannini E: Insulin resistance: a multifaceted syndrome responsible for NIDDM, hypertension dyslipidemia, and atherosclerotic cardiovascular disease. *Diabetes Care* 14:173–194, 1991
11. Sipols AJ, Baskin DG, Schwartz MW: Effect of intracerebroventricular insulin infusion on diabetic hyperphagia and hypothalamic neuropeptide gene expression. *Diabetes* 44:147–151, 1995
12. Hofman A, Grobbee DE, de Jong PTVM, van de Ouweland FA: Determinants of disease and disability in the elderly: The Rotterdam Elderly Study. *Eur J Epidemiol* 7:403–422, 1991
13. Breteler MMB, van de Ouweland FA, Grobbee DE, Hofman A: A community-based study of dementia: The Rotterdam Elderly Study. *Neuroepidemiol* 11 (Suppl. 1):23–28, 1992
14. Folstein MF, Folstein SE, McHugh PR: Mini-mental State: a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 12:189–198, 1975
15. Ott A, Breteler MMB, van Harskamp F, Claus JJ, van der Cammen TJM, Grobbee DE, Hofman A: Prevalence of Alzheimer's disease and vascular dementia: association with education: The Rotterdam Study. *BMJ* 310:970–973, 1995
16. Hughes CP, Berg L, Danziger WL, Coben LA, Martin RL: A new clinical scale for the staging of dementia. *Br J Psychiatry* 140:566–572, 1982
17. Stolk RP, Orchard TJ, Grobbee DE: Why use the oral glucose tolerance test? *Diabetes Care* 18:1045–1049, 1995
18. Laakso M: How good a marker is insulin level for insulin resistance? *Am J Epidemiol* 137:959–965, 1993
19. Barrett-Connor EL, Cohn BA, Wingard DL, Edelstein SL: Why is diabetes mellitus a stronger risk factor for fatal ischemic heart disease in women than in men? *JAMA* 265:627–631, 1991
20. O'Sullivan JJ, Conroy RM, Robinson K, Hickey N, Mulcahy R: In-hospital prognosis of patients with fasting hyperglycemia after first myocardial infarction. *Diabetes Care* 14:758–760, 1991
21. Kalmijn S, Feskens EJM, Launer LJ, Stijnen T, Kromhout D: Glucose intolerance, hyperinsulinaemia and cognitive function in a general population of elderly men. *Diabetologia* 38:1096–1102, 1995
22. Kuusisto J, Koivisto K, Mykkänen L, Helkala EL, Vanhanen M, Hänninen T, Pyörälä K, Riekkinen P, Laakso M: Essential hypertension and cognitive function: the role of hyperinsulinemia. *Hypertension* 22:771–779, 1993
23. Ferrannini E, Haffner SM, Mitchell BD, Stern MP: Hyperinsulinaemia: the key feature of a cardiovascular and metabolic syndrome. *Diabetologia* 34:416–422, 1991
24. Desmond DW, Tatemichi TK, Paik M, Stern Y: Risk factors for cerebrovascular disease as correlates of cognitive function in a stroke-free cohort. *Arch Neurol* 50:162–166, 1993
25. Kilander L, Boberg M, Lithell H: Peripheral glucose metabolism and insulin sensitivity in Alzheimer's disease. *Acta Neurol Scand* 87:294–298, 1993
26. Marfaing P, Penicaud L, Broer Y, Mraovitch S, Calando Y, Picon L: Effects of hyperinsulinemia on local cerebral insulin binding and glucose utilization in normoglycemic awake rats. *Neurosci Lett* 115:279–285, 1990
27. Fujisawa Y, Sasaki K, Akiyama K: Increased insulin levels after OGTT load in peripheral blood and cerebrospinal fluid of patients with dementia of Alzheimer type. *Biol Psychiatry* 30:1219–1228, 1991
28. Unger J, McNeill TH, Moxley RT, White M, Moss A, Livingston JN: Distribution of insulin receptor-like immunoreactivity in the rat forebrain. *Neuroscience* 31:143–157, 1989

Downloaded from http://diabetesjournals.org/care/article-pdf/20/5/792/584384/20-5-792.pdf by guest on 04 November 2024