Association Between Raised Inflammatory Markers and Cognitive Decline in Elderly People With Type 2 Diabetes

The Edinburgh Type 2 Diabetes Study

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OBJECTIVE—To determine whether circulating levels of the inflammatory markers C-reactive protein (CRP), interleukin (IL)-6, and tumor necrosis factor (TNF)-α are associated with cognitive ability and estimated lifetime cognitive decline in an elderly population with type 2 diabetes.

RESEARCH DESIGN AND METHODS—A cross-sectional study of 1,066 men and women aged 60–75 years with type 2 diabetes and living in Lothian, Scotland (the Edinburgh Type 2 Diabetes Study), was performed. Seven cognitive tests were used to measure abilities in memory, nonverbal reasoning, information processing speed, executive function, and mental flexibility. The results were used to derive a general intelligence factor (*g*). A vocabulary–based test was administered as an estimate of peak prior cognitive ability. Results on the cognitive tests were assessed for statistical association with inflammatory markers measured in a venous blood sample at the time of cognitive testing.

RESULTS—Higher IL-6 and TNF-α levels were associated with poorer age- and sex-adjusted scores on the majority of the individual cognitive tests. They were also associated with *g* using standardized regression coefficients −0.074 to −0.173 ($P < 0.05$). After adjusting for vocabulary, education level, cardiovascular dysfunction, duration of diabetes, and glycemic control, IL-6 remained associated with three of the cognitive tests and with *g*.

CONCLUSIONS—In this representative population of people with type 2 diabetes, elevated circulating levels of inflammatory markers were associated with poorer cognitive ability. IL-6 levels were also associated with estimated lifetime cognitive decline.
***Diabetes* 59:710–713, 2010**

Type 2 diabetes is associated with an increased risk of cognitive impairment in older age, accelerated age-related cognitive decline, and a higher incidence of dementia (1). Identifying potentially modifiable risk factors for cognitive impairment in people with type 2 diabetes is therefore of major importance for future diabetes health care initiatives and the reduction of cognitive morbidity in the general population.

The cause of cognitive impairment in type 2 diabetes is unknown, but it is most likely multifactorial. Hyperglycemia, cerebral microvascular disease, severe hypoglycemia, and an increased prevalence of macrovascular disease have all been implicated but are unlikely to explain the entire effect (2). Systemic or cerebral inflammation may also be important, and evidence of chronic inflammation has been observed in the brains of people with dementia (3). Levels of circulating inflammatory markers are elevated in people with type 2 diabetes compared with an equivalent nondiabetic population (4). Inflammatory mediators may therefore have a role in the accelerated development of cognitive impairment in people with diabetes either by a direct effect on the brain or through an influence on the development of vascular disease.

The Edinburgh Type 2 Diabetes Study (ET2DS) tested the association between three markers of inflammation (C-reactive protein [CRP], interleukin [IL]-6, and tumor necrosis factor [TNF]-α) and cognitive impairment in a representative cohort of people with type 2 diabetes.

RESEARCH DESIGN AND METHODS

The ET2DS is a sample of men and women aged 60–75 years with type 2 diabetes. The subjects were randomly selected by sex and 5-year age bands from the comprehensive Lothian Diabetes Register (LDR) of people with type 2 diabetes living in Lothian, Scotland. A sample size of 1,000 was targeted to detect associations between baseline risk factors and both cognitive ability at baseline and cognitive change during subsequent follow-up. Exclusion criteria, applied at the time of physical examination, have been reported previously (5). All subjects provided written informed consent, and the study was approved by the Lothian Research Ethics Committee.

Clinical assessment. Physical examinations were performed between August 2006 and August 2007 by trained researchers using standard operating procedures (5). Quality control measures included tests of inter- and intra-observer variability. A fasting venous blood sample was taken for measurement of inflammatory markers, total serum cholesterol, and plasma A1C. Following measurements of height and weight, a 12-lead electrocardiogram (ECG) was taken for subsequent Minnesota coding (http://www.epi.umn.edu/ecg/). After a 10-min rest in the supine position, systolic and diastolic blood pressure was measured in the right arm using a standard stethoscope and aneroid dial sphygmomanometer. Right and left brachial, posterior tibial, and dorsalis pedis systolic pressures were then taken using an aneroid sphygmo-

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Received 5 August 2009 and accepted 16 November 2009. Published ahead of print at http://diabetes.diabetesjournals.org on 3 December 2009. DOI: 10.2337/db09-1163.

manometer and a Doppler probe. A self-administered questionnaire included questions on education; history of myocardial infarction (MI), stroke or angina; year of diabetes diagnosis; smoking; current medications; and the World Health Organization (WHO) chest pain questionnaire (6). Data were collected from the Information and Services Division of the National Health Service (NHS) Health Services Scotland on all medical and surgical discharges from Scottish hospitals since 1981 (Scottish Morbidity Record [SMR01] scheme [7]), and any ICD-10 codes (or the equivalent ICD-9 codes) indicating cardiovascular or cerebrovascular disease were extracted.

Cognitive assessment. Cognitive assessment took place after a snack and confirmation that blood glucose was >4 mmol/l. Fluid cognitive ability was assessed using tests of: nonverbal memory and immediate and delayed verbal declarative memory (Faces and Family Pictures Subtest, Logical Memory subtest from the Wechsler Memory Scale III$^{U.K.}$ [8]); working memory, nonverbal reasoning, and processing speed (Letter Number Sequencing, Matrix Reasoning, Digit Symbol Test from the Wechsler Adult Intelligence Scale-III [WAIS III$^{U.K.}$] [9]); executive function (Verbal Fluency Test[10]); and mental flexibility (Trail Making Test–Part B [11]). Vocabulary (crystallized intelligence) was measured using the combined Junior and Senior Mill Hill Vocabulary Scale (MHVS) synonyms (12). As results on vocabulary-based tests vary little with ageing, they can be used to approximate peak prior cognitive ability (13). Late-life cognition adjusted for vocabulary also correlates highly with actual cognitive change (14). The Hospital Anxiety and Depression Scale (15) was also administered because mood can affect cognitive test results.

Measurement of inflammatory markers. Blood samples were processed at the research clinic, and plasma was stored at −40°C. Assays for plasma CRP, IL-6, and TNF-α were performed in the University Department of Medicine, Glasgow Royal Infirmary. CRP was assayed using a high-sensitivity immunonephelometric assay (16). TNF-α and IL-6 antigen levels were determined using high-sensitivity ELISA kits (R&D Systems, Oxon, U.K.).

Data analysis. Information on the questionnaire and recording forms was checked by clinic staff. Two clerks independently entered the data onto an Access database. Errors identified by comparing the double data entries were resolved by referring to the paper records. Anonymized data on demographic and clinical variables from the LDR were used to compare the characteristics of study responders and nonresponders.

Ankle brachial index, a measure of subclinical atherosclerosis (17), was calculated by dividing the lowest of the ankle pressures by the higher of the arm pressures. Smoking was categorized as current, ex, or never-smoked, with anyone stopping within the past 6 months recategorized as a current smoker. Duration of diabetes was calculated to the nearest year by subtracting the self-reported year of diagnosis from the date of attendance at the research clinic. The highest self-reported level of education was categorized as primary, secondary, professional qualification, or university/college degree. Scottish Index of Multiple Deprivation (deprivation) (18) was assigned to each subject according to their postcode of residence. The following criteria were used to define MI: *1*) subject recall of a doctor's diagnosis of MI, *2*) positive WHO chest pain questionnaire for MI, *3*) ECG evidence of ischemia (Minnesota codes 1.1–1.3, 4.1–4.2, 5.1–5.3 or 7.1), and *4*) prior hospital discharge code for MI (ICD-10 codes I21–I23, I252). MI was recorded if two of the first three criteria were met or if both the first and last criteria were met. Equivalent criteria for angina were: *1*) subject recall of a doctor's diagnosis of the condition or being on regular medication for angina, *2*) positive WHO chest pain questionnaire for angina, *3*) ECG evidence of ischemia, and *4*) prior hospital discharge code for ischemic heart disease (ICD-10 codes I20–I25). Angina was recorded if two of the first three criteria were met or if both the first and last criteria were met. Stroke was recorded if two of three of the following criteria were met: *1*) subject recall of a doctor's diagnosis of stroke, *2*) prior hospital discharge code consistent with stroke (ICD-10 codes I61, I63–I66, I679, I694), and *3*) confirmation by review of clinical notes that the event was not due to a transient ischemic attack.

Continuous variables were normally distributed apart from Trail Making Test scores, CRP, IL-6, and TNF-α levels, which were transformed using natural logarithms. The inflammatory markers were trimmed for points exceeding 3.5 SDs from the mean prior to analysis. Scores from the fluid cognitive tests were used to obtain a general cognitive ability factor (*g*) via principal components analysis.

Age- and sex-adjusted linear regression assessed the association between cognitive scores and inflammatory markers. Further adjustments were made for vocabulary (MHVS) and then for additional covariates to adjust for mood (Hospital Anxiety and Depression Scale depression score), duration of diabetes, glycemic control (plasma A1C), cardiovascular risk factors (total cholesterol, BMI, diastolic blood pressure, smoking), cardiovascular disease (MI, angina, stroke, ankle brachial index), and level of education. The analyses had over 90% power for a two-sided significance test ($\alpha = 0.05$) to detect a standardized β coefficient of 0.10. Analyses were performed using R version 2.7.0 (19).

TABLE 1
Characteristics and clinical features of the ET2DS population and nonresponders

	ET2DS population	Nonresponders
n	1,066	4,386*
Age (years)	67.9 ± 4.20	67.9 ± 4.35
Male sex	547 (51.3)	1,839 (41.9)§
Duration of diabetes		
Up to 5 years	516 (48.4)	2,135 (48.7)
≥5 years	550 (51.6)	2,251 (51.3)
A1C (%)	7.4 (1.12)	7.4 (1.36)
Insulin treatment	185 (17.4)	704 (16.1)
Systolic BP (mmHg)	133.3 ± 16.44	137.2 ± 18.15§
Total cholesterol (mmol/l)	4.3 (0.90)	4.2 (0.96)‡
Quintile for SIMD		
Missing	0 ± 0	16 ± 0.4§
1	127 ± 11.9	736 ± 16.8
2	208 ± 19.5	1,134 ± 25.9
3	188 ± 17.6	820 ± 18.7
4	194 ± 18.2	782 ± 17.8
5	349 ± 32.7	897 ± 20.5

Data are means ± SD or *n* (%). *Two subjects on the LDR had no data and were discarded from the analyses (i.e., total number of nonresponders was 4,388); ‡$P < 0.01$; §$P < 0.001$ (χ^2 test for independence or *t* test for differences between groups). BP, blood pressure; SIMD, Scottish Index of Multiple Deprivation.

RESULTS

From 5,454 invitations sent out, 1,252 people initially agreed to participate in the study and 1,066 (85%) were recruited. Crude response rates varied between sex and 5-year age bands, from 13.6% in the oldest women aged 70–74 years, to 27.5% in men aged 65–69 years. Study participants were found to be similar to the 4,388 nonresponders (Table 1). Despite some statistically significant differences in demographic and clinical characteristics, the actual differences were small and of questionable clinical significance. Similarities persisted when comparison was made by sex and 5-year age band and when adjustment was made for error rates in LDR data recording (data not shown). A summary of the study participants is presented in Table 2.

Age- and sex-adjusted associations between inflammatory marker levels and cognitive test scores are shown in Table 3. Associations for CRP were weakly significant or nonsignificant. The associations for IL-6 and TNF-α were larger and statistically significant for the majority of the tests with standardized coefficients ranging from −0.074 to −0.173 (all $P < 0.05$).

All inflammatory measures associated with age- and sex-adjusted MHVS scores with standardized coefficients were: CRP −0.075 ($P < 0.05$), IL-6 −0.091 ($P < 0.01$), and TNF-α −0.087 ($P < 0.05$).

Age, sex, and vocabulary adjustment weakened the magnitude and statistical significance of the associations (Table 3). However, the strongest IL-6 and TNF-α associations were retained after adjustments for both vocabulary and the other covariates. This was particularly evident for IL-6 with standardized coefficients for the full models in the ranges −0.074 to −0.113.

TABLE 2
Characteristics and clinical features of the ET2DS population

n	1,066
Age (years)	67.9 ± 4.20
Male sex	547 (51.3)
Duration of diabetes (years)	8.1 ± 6.46
Duration of diabetes	
Up to 5 years	516 (48.4)
≥5 years	550 (51.6)
A1C (%)	7.4 ± 1.12
Insulin treatment	185 (17.4)
Systolic BP (mmHg)	133.3 ± 16.44
Diastolic BP (mmHg)	69.1 ± 9.02
Total cholesterol (mmol/l)	4.3 ± 0.90
BMI (kg/m^2)	31.4 ± 5.69
Smoker	
Current	153 (14.4)
Ex-smoker	499 (46.8)
Never smoked	414 (38.8)
CHD (yes)	330 (31.0)
Stroke (yes)	62 (5.8)
Ankle-brachial index	0.98 ± 0.21
Education*	
Primary school	7 (0.7)
Secondary school	581 (54.5)
Professional qualification	307 (28.8)
University/college	171 (16.0)
HADS depression score	3 (1–6)
CRP (mg/l)	1.86 (0.87–4.37)
IL-6 (pg/ml)	2.87 (1.97–4.46)
TNF-α (pg/ml)	1.07 (0.69–1.62)
MR	12.8 ± 5.28
LNS	9.7 ± 2.75
VFT	36.9 ± 12.83
DST	49.2 ± 14.77
TMT	104 (81–138)
FACES	65.8 ± 7.88
LM	25.2 ± 8.17
g	0.00 ± 1.00
MHVS	30.9 ± 5.23

Data are means ± SD, median (quartile range), or *n* (%). *Self-reported highest education level attained. BP, blood pressure; CHD, coronary heart disease (MI or angina); DST, digit symbol test; FACES, Faces and Family Pictures Subtest; HADS, Hospital Anxiety and Depression Scale; LM, logical memory; LNS, letter-number sequencing; MR, matrix reasoning; TMT, Trail Making Test-Part B; VFT, Verbal Fluency Test.

DISCUSSION

In this representative population of people with type 2 diabetes, elevated levels of plasma CRP, IL-6, and TNF-α were significantly associated with poorer age- and sex-adjusted general cognitive abilities. The maximum effect size for the age- and sex-adjusted *g* associations was with IL-6, which corresponded to a 0.173 decrease in *g* for every twofold increase in IL-6 levels.

Adjustments for cardiovascular disease/risk factors, glycemic control, duration of diabetes, and education resulted in reductions to the effect sizes. However, this does not indicate whether these factors are confounders or whether they could be mediators in the same pathway leading to cognitive decline. The association between IL-6 and *g*, although weakened, remained statistically significant after full multivariate adjustment, suggesting a possible role for IL-6 in cognitive decline. Analyses were repeated to exclude potential dementia cases (Mini Mental State Examination score <24, $n = 33$), but this did not affect the results.

TABLE 3
Multivariate associations between biomarkers and late-life cognition, and estimated cognitive change

	Standardized β coefficients (SE)							
	MR	LNS	VFT	DST	−ln(TMT)	FACES	LM	*g*
ln(C-reactive protein)								
+ age and sex	−0.063 (0.031)*	−0.008 (0.032)	−0.020 (0.032)	−0.047 (0.031)	−0.052 (0.031)	−0.020 (0.031)	0.027 (0.032)	−0.053 (0.031)
+ MHVS	−0.036 (0.028)	0.017 (0.029)	0.008 (0.029)	−0.023 (0.028)	−0.035 (0.029)	−0.002 (0.030)	0.050 (0.029)	−0.014 (0.025)
+ MHVS and adjustment variables	−0.002 (0.030)	0.030 (0.032)	0.019 (0.031)	0.015 (0.030)	−0.016 (0.031)	−0.010 (0.033)	0.053 (0.032)	−0.013 (0.027)
ln(IL-6)								
+ age and sex	−0.113 (0.030)‡	−0.075 (0.031)*	−0.077 (0.031)*	−0.152 (0.030)‡	−0.173 (0.030)‡	−0.084 (0.030)†	−0.018 (0.031)	−0.161 (0.030)‡
+ MHVS	−0.084 (0.027)†	−0.043 (0.028)	−0.045 (0.028)	−0.130 (0.027)‡	−0.147 (0.028)‡	−0.063 (0.029)*	0.009 (0.029)	−0.115 (0.024)‡
+ MHVS and adjustment variables	−0.074 (0.029)*	−0.028 (0.031)	−0.033 (0.030)	−0.076 (0.030)*	−0.113 (0.030)‡	−0.050 (0.032)	−0.004 (0.032)	−0.086 (0.026)†
ln(TNF-α)								
+ age and sex	−0.120 (0.030)‡	−0.055 (0.031)	−0.057 (0.031)	−0.029 (0.030)	−0.091 (0.030)†	−0.074 (0.030)*	−0.041 (0.031)	−0.106 (0.031)‡
+ MHVS	−0.087 (0.027)†	−0.017 (0.028)	−0.013 (0.028)	0.006 (0.028)	−0.064 (0.028)*	−0.051 (0.029)	−0.010 (0.029)	−0.052 (0.025)†
+ MHVS and adjustment variables	−0.084 (0.028)†	−0.009 (0.030)	−0.013 (0.029)	0.040 (0.028)	−0.049 (0.029)	−0.035 (0.031)	−0.018 (0.030)	−0.035 (0.025)

Adjustment variables are Hospital Anxiety and Depression Scale depression score, duration of diabetes, A1C, total cholesterol, BMI, diastolic blood pressure, smoking, coronary heart disease (MI or angina), stroke, ankle-brachial index, and level of education. *$P < 0.05$; †$P < 0.01$; ‡$P < 0.001$. DST, Digit Symbol Test; FACES, Faces and Family Pictures Subtest; LM, logical memory; LNS, letter-number sequencing; MR, matrix reasoning; TMT, Trail Making Test-Part B; VFT, Verbal Fluency Test.

A limited number of high-quality studies have investigated the relationship between inflammatory biomarkers and cognition in nondiabetic populations. These studies have found associations of a modest but similar order to those reported in the present study (20–24). As all our study participants had diabetes, we were not able to formally test for a differential effect size in diabetes.

The strengths of the present study include the application of a cognitive test battery covering major cognitive domains and extensive phenotyping for potential confounding or mediating factors. The use of a general cognitive factor (*g*) helped avoid potential problems caused by multiple testing. The study population had a verified clinical diagnosis of type 2 diabetes and was shown to be representative of the target population of elderly, community-dwelling men and women with the full spectrum of severity of type 2 diabetes (from diet-controlled to insulin-treated).

Although cross-sectional, the present results provide the best epidemiological evidence to date for an inflammation-cognition relationship in people with type 2 diabetes. As markers of inflammation are sensitive to acute illness and alter with age, it is questionable whether a single, late-life measurement accurately reflects the lifetime risk of exposure to inflammation (25). This will be addressed in follow-up phases of the ET2DS, when inflammatory markers and cognition will be remeasured and genetic predictors of inflammatory markers will be studied.

In conclusion, raised circulating inflammatory marker levels are associated with poorer late-life cognitive ability in people with type 2 diabetes, even after adjustment for a vocabulary-based estimate of peak prior cognitive ability. These findings were particularly notable for IL-6. Future longitudinal studies are required to confirm the direction of the association and whether there is evidence for causality.

ACKNOWLEDGMENTS

This study was supported by a grant from the U.K. Medical Research Council.

No potential conflicts of interest relevant to this article were reported.

We thank staff and participants of the ET2DS and staff at the Wellcome Trust Clinical Research Facility in Edinburgh where the clinical examinations were performed.

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