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Associations between apolipoprotein E phenotype, glucose metabolism and cognitive function in men. An explorative study in a population sample

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Abstract

Aims To investigate the associations of the apolipoprotein E phenotype (apoE) and disturbed glucose metabolism with cognitive function in a random population sample.

Methods A cross-sectional study was conducted, in which 528 men aged 54 or 60 years were recruited randomly from a larger population-based sample of 1516 men. A subject was defined as having abnormal glucose tolerance (AGT), if he had a clinical diagnosis of diabetes, with either dietary or oral antidiabetic treatment or showed impaired glucose tolerance in an oral glucose tolerance test. The subjects were divided into three groups according to apolipoprotein E phenotypes: (a) E2/4, E3/4 or E4/4 (apoE E4); (b) E 3/3 (apoE E3); and (c) E2/2 or E2/3 (apoE E2). Memory function was examined using a word-list learning with Buschke's selective reminding method and test. Executive functions were assessed with the Trail Making Test A and B.

Results Those subjects with apoE E2 and abnormal glucose metabolism demonstrated the worst cognitive executive control compared to other groups. Simple cognitive speed did not differ between the groups.

Conclusions The exploratory analyses revealed that subjects with apoE E2 allele and AGT had worse glycaemic control and cognitive executive control compared to other groups. Different apolipoprotein phenotypes together with impaired glucose tolerance may have different cumulative adverse effects on age-related cognitive performance. Some subgroups of subjects may be especially vulnerable to cognitive impairment.

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Keywords cognitive functions, glucose metabolism, apolipoprotein E phenotype

Abbreviations AGT, abnormal glucose tolerance; NGT, normal glucose tolerance; apoE, apolipoprotein E phenotype; OGTT, 2 h oral glucose tolerance test; IDDM, insulin-dependent diabetes mellitus; NIDDM, noninsulin-dependent diabetes mellitus; IGT, impaired glucose tolerance; TMT A, Trail Making Test A; TMT B, Trail Making Test B; KIHD, Kuopio Ischemic Heart Disease Risk Factor Study

Introduction

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The apolipoprotein E (apoE) E4 allele is an important risk factor for Alzheimer's disease [1,2]. The apoE E4 allele has

also been associated with decreased cognitive function in discordant twin pairs [3]. In that study, the authors suggest that E4 may represent a potential marker for accelerated cognitive ageing. Episodic memory decline [4] or cognitive decline [5] has been shown in older adults carrying the apoE E4 allele. The apoE E2 allele may play a protective role in normal ageing [6]. A cross-sectional study showed that the E2 allele is associated with better learning ability in nondemented elderly subjects [7]. A longitudinal population-based study showed that subjects with the apoE phenotypes E2/2 or 2/3 were able to maintain their verbal learning performance, while the learning ability of subjects with other apoE phenotypes deteriorated [8].

Patients with noninsulin-dependent diabetes mellitus (NIDDM) often show mild cognitive impairment [9,11,12]. It has been suggested that the presence of apoE phenotypes containing the E4 allele and cerebrovascular disease may have a synergistic effect on cognitive decline [13,14]. We investigated whether different apoE phenotypes and diabetes or impaired glucose tolerance had a cumulative adverse effect on cognitive performance in a population-based sample of middle-aged men in eastern Finland. In addition, we assessed the role of possible mediators of this relationship, such as control of glucose and lipid metabolism and cardiovascular diseases.

Subjects and methods

Subjects

The subjects were participants in the Kuopio Ischemic Heart Disease Risk Factor Study (KIHD). The recruitment of the subjects has been explained in detail previously [15]. The KIHD study was approved by the Research Ethics Committee of the University of Kuopio, Kuopio, Finland and all subjects gave written informed consent. The second cohort of the study population of the KIHD consisted of 1516 men aged 42, 48, 54 and 60 years (82.6% of those eligible) at the time of examination. A total of 1229 men underwent ultrasound examination of the right and left carotid arteries. The group was invited to participate in a follow-up study four years later. Cognitive examination was performed in the two oldest age groups of 555 men. Nine men did not participate in the cognitive examination. Due to missing data on glucose metabolism, 528 men were included in the final analyses. Of these men, none were receiving insulin treatment, 43 had NIDDM and 105 had IGT, according to the WHO criteria [16].

Methods

Measurement of glucose tolerance

A 2 h oral glucose tolerance test (OGTT) was performed with a 75 g glucose load after at least 12 h of overnight fasting. Blood glucose was measured from fresh whole blood prior to, and two hours after, the glucose load using the glucose dehydrogenase method, after precipitation of proteins with tricloracetic acid.

Definition of NIDDM and IGT

A subject was considered to have noninsulin-diabetes (NIDDM) if he had a clinical diagnosis of diabetes and was undergoing either dietary or oral antidiabetic treatment or had a fasting venous blood glucose $\geqslant 6.7$ mmol/L or 2 h venous blood glucose $\geqslant 10.0$ mmol/L. IGT was defined as a fasting venous blood glucose < 6.7 mmol/L and 2 h venous blood glucose 6.7–10.0 mmol/L. A subject was defined as having an abnormal glucose tolerance (AGT) if he had either NIDDM or IGT.

Measurement of serum insulin

Fasting and 2 h serum insulin in OGTT was determined from frozen serum samples with radioimmunological methods (Pharmacia, Uppsala, Sweden). Serum glycated proteins were measured with an autoanalyser (Kone Specific, Espoo, Finland).

Resting blood pressure

This was measured between 8:00 and 9:00 a.m. using a random-zero mercury sphygmomanometer (Hawsley, United Kindom). After a supine rest of five minutes, three measurements were taken in the supine, one in the standing and two in the sitting position at five minutes intervals. The mean of these six measurements was used.

Waist-to-hip ratio

The waist-to-hip ratio was computed as the ratio of the circumference of the waist to the circumference of the hip.

Body mass index

This was calculated as weight divided by height squared (kg/m^2).

Medical history

This was recorded with a self-administered questionnaire, checked by a physician.

The apolipoprotein E phenotype

This was determined from plasma with isoelectric focusing and immunoblotting techniques [17]. The subjects were divided into three groups according to apolipoprotein E phenotypes. Subjects having one or two apolipoprotein ε4 alleles were included in the apoE E4 group. Subjects with the most common apolipoprotein E phenotype, E3/3, formed the apoE E3 group and subjects with apolipoprotein E2/2 or E2/3 made up the apoE E2 group.

Cognitive measurements

Memory function was examined using a word-list learning test using Buschke's selective reminding method (BSRT) [18]. The subjects were read 10 unrelated words and were asked for immediate recall of the entire list. On the second trial, the subjects were read only those words that they failed to recall on the first trial and were again asked to recall the entire list. The score was the sum of words recalled on six trials. Executive functions were examined by the Trail Making Test A (TMTA) and B (TMTB) [19]. In Trail Making Test B, the letters were replaced with the names of the months using the first three letters of each month. The time in seconds to complete each trial was recorded. A maximum time of 150 s for Trail Making Test A,

and 300 s for Trail Making Test B were allowed. If the test was not completed in the time allowed, the missing letters or numbers were scored as errors. The difference between times to complete the A and B parts was used as an indication of cognitive difficulty in changing between targets.

Statistical analysis

Statistical analyses were conducted with the SPSS for Windows Release 9.0. The differences between the groups were assessed uisng analysis of variance. The χ^2–test was used for dichotomous variables.

The association of apoE phenotype and AGT on cognitive impairment was analysed with analysis of variance adjusted for age group and education. We also adjusted the results for possible confounders: serum HDL cholesterol, BMI, cardiovascular diseases and medication. We furthermore adjusted the results for serum glycated proteins, fasting serum blood glucose, 2 h blood glucose, fasting serum insulin, or 2 h serum insulin.

Results

Characteristics of ApoE and AGT groups

Percentages of subjects in the two age groups were similar in the different apoE groups. Education did not differ between the different apoE groups. The subjects with apoE E2 had higher fasting blood glucose, 2 h glucose, fasting insulin, and serum triglycerides than subjects with other phenotypes (Table 1). Education or age group distribution did not differ between the NGT and AGT groups (data not shown). AGT was related to higher BMI, waist-to-hip ratio, serum glycated proteins, fasting and 2 h blood glucose, fasting and 2 h serum insulin, diastolic blood pressure, and lower serum HDL cholesterol (data not shown).

Association between apoE phenotype and glycaemic control

Serum glycated proteins, fasting blood glucose, and 2 h blood glucose were higher in the apoE E2 group than in other groups (Table 1). The AGT subjects with an apoE E2 allele had highest levels of serum glycated proteins [$F_{2,527} = 7.19$, $P < 0.001$ for the interaction] (Fig. 1), fasting blood glucose [$F_{2,527} = 99.7$, $P < 0.003$ for the interaction] (data not shown) and 2 h blood glucose [$F_{2,527} = 6.45$, $P < 0.002$ for the interaction] (Fig. 2).

Association between apoE phenotype, AGT and cognitive function

Executive or memory functions did not differ in the different apoE groups or between the AGT and NGT groups (data not shown). However, the subjects with AGT and the apoE E2 allele performed worst on Trail Making Test B after adjustment for education and age group

(Table 2). The performance was, nevertheless, within normal range. Although the variance in Trail Making Test was greatest in subjects with the apoE E2 allele with AGT, the median of Trail Making Test was also lower in this group than in the other groups. Furthermore, the median was close to the mean in the apoE E2 group. Men with the apoE E2 allele and AGT also performed worst in Trail Making Test B–A (Table 2). The results of Trail Making Test A and word list learning did not differ between the groups. The analyses were also performed in the IGT, NIDDM, and NGT groups, but the results were essentially the same.

Analyses of possible confounding factors

When serum glycated proteins, fasting blood glucose, blood 2 h glucose, fasting insulin, 2 h insulin, serum HDL cholesterol, or BMI was used alone as a covariate, the results did not change (data not shown). When education and age group were added into model as covariates, together with serum glycated proteins, fasting blood glucose, 2 h blood glucose, or fasting insulin, the results did not change (Table 3). The regression coefficients and 95% confidence intervals of the relationship of abnormal glucose tolerance and apoE E2 phenotype compared to other apoE phenotypes and glucose tolerance groups to Trail Making Test B and Trail Making Test B-A are presented in Table 3. When age group without education was in the model with serum glycated proteins, fasting blood glucose, 2 h blood glucose, or fasting insulin, the significance disappeared. Potentially mediating factors such as cardiovascular diseases, i.e. cardiomyopathia, cardiac insufficiency, angina pectoris, claudication or hypertension, and medications, i.e. any drug for hypertension, diuretics, or any β-blocker, did not explain the results. The exclusion of stroke patients from the analyses did not change the results.

Discussion

In the present study, subjects with the apoE E2 allele had poorer glycaemic control than subjects with other apoE phenotypes. Subjects with AGT and apoE E2 allele also performed less well in their cognitive executive control compared to those with other apoE phenotypes or NGT. We did not find any independent association between cognitive function and AGT or between cognitive function and apoE phenotype.

The association of apoE phenotype and abnormalities of glucose regulation has been previously studied in patients with dementia. Hyperinsulinaemia was associated with an increased risk for Alzheimer's disease in nondiabetic subjects without the ApoE E4 allele [20]. Higher fasting plasma insulin levels and reduced cerebrospinal fluid-to-plasma insulin ratios, indication of insulin resistance, have

Table 1 Characteristics of subjects with different apolipoprotein E (apoE) phenotypes

	ApoE E2 (N = 43) Mean (SD) or %	ApoE E3 (N = 319) Mean (SD) or %	ApoE E4 (N = 166) Mean (SD) or %	P^1
54 year-old age group	5.1	30.6	16.1	Ns
60 year-old age group	3.0	29.7	15.3	Ns
Education, years	8.8 (3.0)	8.2 (3.0)	7.6 (2.9)	Ns
Body mass index (kg/m²)	28.4 (4.6)	27.4 (3.4)	27.8 (3.9)	Ns
Waist-to-hip ratio	1.02 (0.04)	1.00 (0.05)	1.01 (0.04)	Ns
Serum glycated proteins (Umol/L)	246.0 (41.1)	237.7 (26.7)	239.90 (34.7)	Ns
Fasting blood glucose (mmol/L)	5.6 (1.7)	5.0 (0.9)	5.2 (1.5)	0.007
2 h blood glucose (mmol/L)	6.8 (4.3)	5.8 (2.3)	6.5 (3.2)	0.016
Fasting serum insulin (mUL/L)	10.4 (8.0)	7.7 (4.5)	9.3 (7.4)	0.001
2 h serum insulin (mUL/L)	55.1 (47.9)	52.9 (41.7)	63.9 (67.2)	0.079
Serum triglycerides (mmol/L)	2.0 (1.1)	1.5 (0.7)	1.7 (1.0)	0.000
Serum HDL cholesterol (mmol/L)	1.1 (0.3)	1.1 (0.3)	1.0 (0.3)	0.083
Systolic blood pressure (mmHg)	144.0 (19.5)	138.8 (16.8)	138.6 (15.4)	Ns
Diastolic blood pressure (mmHg)	93.0 (9.6)	88.4 (10.3)	88.9 (9.5)	0.018
Stroke %	2.3	3.4	4.8	Ns
Cardiomyopathia %	0	0.9	1.2	Ns
Cardiac insufficiency %	11.6	9.7	11.4	Ns
Angina pectoris %	20.9	19.5	24.1	Ns
Claudication %	9.3	8.2	5.5	Ns
Hypertension %	48.8	33.0	42.2	Ns
Drug for hypertension %	46.5	32.3	44.0	Ns
Diuretics %	4.7	2.2	4.2	Ns
Any β-blocker %	11.6	14.1	19.3	Ns
Diabetes/IGT %	11.6/23.3	6.3/19.7	10.8/19.3	Ns
Diabetes four years earlier %	9.3	2.5	4.8	0.064

P^1 = Analysis of variance, main effect of apoE group.

been observed in patients with Alzheimer's disease who do not possess an apolipoprotein E e4 allele [21]. This finding suggests that there is a difference in insulin metabolism in E4 homozygotes compared with the non-E4 homozygotes with respect to Alzheimer's disease. In the present study, the highest fasting and 2 h blood glucose, and fasting serum insulin values were associated with apoE E2 allele in a normal population.

The mechanisms of cognitive impairment related to NIDDM are not fully understood. The chronic hyperglycaemia, typical of NIDDM, may link diabetes and cognitive function. Epidemiological studies have found poorer cognitive performance to be associated with NIDDM [22,23] and with impaired glucose tolerance [24,25]. Longitudinal studies have also shown an association between diabetes mellitus and Alzheimer's disease [26,27]. Some have demonstrated that poor glycaemic control as assessed by HbA_{1c} correlates with cognitive decrement [9,28,29] but others have not [30,31]. No correlation has been found between cognitive performance and fasting blood glucose [28,32]. In a small clinical sample, improved glycaemic control in the elderly patients with NIDDM led to better cognitive performance [33]. Impaired verbal memory has been most frequently found
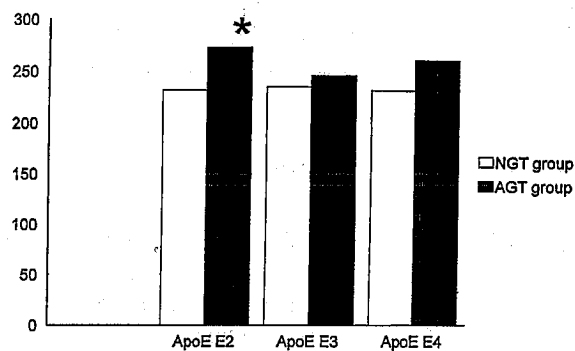
Analysis of variance, adjusted for age, * For interaction P<0.001

Figure 1 Serum glycated proteins (umol/L) in different apoE groups with normal (NGT) and abnormal (AGT) glucose tolerance.

[28–30,34] but associations with impaired attention or concentration [29,35,36] have also been reported. The formation of advanced glycation end products contribute to the pathogenesis of diabetic complications, but could contribute to the characteristic protein deposits in Alzheimer's disease, including neurofibrillary tangles and beta-amyloid plaques [37,38]. However, the serum

glycated proteins did not differ between apoE groups in the present study.

Duration of diabetes has been related to cognitive decline [22,40]. Croxson et al. [41] reported that those with known diabetes were more likely than normal subjects to have a low Mini Mental Status Examination score, while newly diagnosed diabetic subjects did not. However, we do not know how long the glycaemic control has been poor in our subjects.

Insulin might also affect neuronal activity and cognition. An association between high postload insulin and glucose levels, and poor cognitive function has been reported [23]. Moreover, Craft et al. [42] recently showed that insulin administration improved memory performance in Alzheimer's disease subjects without an ε4 allele, whereas the memory performance of the Alzheimer's disease ε4 patients did not improve. This suggests that glycaemic control may be related to cognitive impairment in a subgroup of Alzheimer's disease patients only. This is partly supported by our observation that only subjects with an apoE E2 allele and AGT performed more poorly than those with AGT and other alleles.

Table 3 Regression coefficients (95% Confidence interval) of abnormal glucose tolerance and apoE E2 phenotype to Trail Making Test B and Trail Making Test B-A

	Trail Making Test B β-coefficient (95% CI)	Trail Making Test B-A β-coefficient (95% CI)
Model 1:	58.61 (11.85–105.37)	52.68 (13.47–91.88)
Model 2:	65.07 (21.52–108.62	57.36 (20.14–94.59)
Model 3:	56.21 (12.84–99.57)	50.01 (12.92–87.10)
Model 4.	55.16 (11.75–98.56)	48.89 (11.78–85.99)
Model 5:	55.13 (11.68–98.58)	48.72 (11.58–85.85)
Model 6:	56.39 (12.86–99.92)	49.44 (12.22–86.65)
Model 7:	56.47 (13.12–99.94)	50.32 (13.14–87.49)
Model 8:	56.15 (12.75–99.55)	49.98 (12.86–87.11)
Model 9:	57.25 (14.17–100.87)	50.99 (13.89–88.09)
Model 10:	56.19 (12.75–99.63)	49.90 (12.74–87.05)
Model 11:	58.75 (15.05–102.46)	51.44 (14.04–88.84)

Model 1: Unadjusted association of AGT × apoE E2
Model 2: Controlling for education
Model 3: Controlling for education and age group
Model 4: Controlling for education, age group, and serum glycated proteins
Model 5: Controlling for education, age group, and fasting blood glucose
Model 6: Controlling for education, age group, and 2 h blood glucose(mmol/L)
Model 7: Controlling for education, age group, and fasting serum insulin (mUL/L)
Model 8: Controlling for education, age group, and serum triglycerides (mmol/L)
Model 9: Controlling for education, age group, and diastolic blood pressure (mmHg)
Model 10: Controlling for education, age group, and body mass index (kg/m^2)
Model 11: Controlling for education, age group, serum glycated proteins, fasting blood glucose, 2 h blood glucose (mmol/L), fasting serum insulin (mUL/L), triglycerides (mmol/L), diastolic blood pressure (mmHg), and body mass index (kg/m^2).
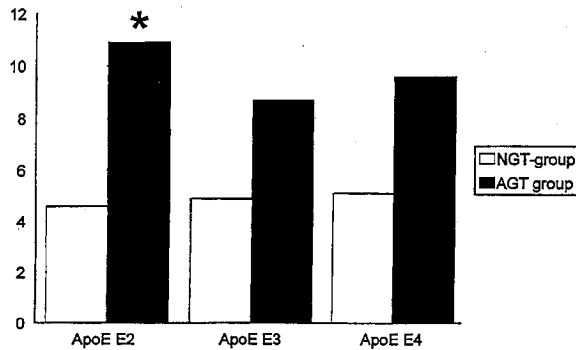
Analysis of variance, adjusted for age, *for interaction $P<0.002$

Figure 2 2 h blood glucose (mmol/L) in glucose tolerance test in different apoE groups with normal (NGT) and abnormal (AGT) glucose tolerance.

Table 2 Executive and memory function in men with abnormal glucose tolerance (AGT) and normal glucose tolerance (NGT) with different apolipoprotein E phenotypes (apoE)

	Abnormal glucose tolerance (AGT)			Normal glucose tolerance (NGT)					
	ApoE E2 (N = 15) Mean (SD)	ApoE E3 (N = 83) Mean (SD)	ApoE E4 (N = 50) Mean (SD)	ApoE E2 (N = 28) Mean (SD)	ApoE E3 (N = 235) Mean (SD)	ApoE E4 (N = 116) Mean (SD)	P^1	P^2	P^3
Trail Making A	51.7(15.0)	53.9(17.2)	48.7(15.5)	52.3(16.9)	52.3(20.0)	55.3(20.7)	Ns	0.000	0.061
Trail Making B	145.1(89.5)	131.0(64.5)	123.7(70.3)	102.0(48.0)	121.5(63.2)	139.3(68.1)	0.027	0.001	0.001
Trail Making B-A	93.2(81.2)	77.5(56.4)	75.0(59.6)	49.6(44.0)	69.2(50.0)	84.1(58.9)	0.029	0.001	0.001
List learning	34.1(7.9)	33.1(8.1)	34.6(7.9)	34.7(8.1)	34.7(8.7)	33.7(8.9)	Ns	0.001	0.015

Analysis of variance, adjusted for agegroup and education, P^1 Interaction between AGT and ApoE groups, P^2 Effect of education, P^3 Effect of age group. The values of cognitive tests are within normal range.

It is possible that other aspects related to the insulin resistance syndrome, such as accelerated atherosclerosis [14], could explain the association between the insulin resistance syndrome and cognitive impairment in elderly. It has been suggested that the presence of apolipoprotein E phenotypes containing the ε4 allele, cerebrovascular disease [14] and cardiovascular risk factors or subclinical cardiovascular disease [43] may act synergistically on cognitive decline.

The absolute postprandial triglyceridaemia was highest in subjects with apolipoprotein E2 allele [44]. They also had increased factor (VIIa) activity during postprandial triglyceridaemia. In the present study, the apoE E2 allele group had higher serum triglycerides and diastolic blood pressure. However, there was no difference in the prevalence of cardiovascular diseases between the groups.

These exploratory analyses revealed that subjects with an apoE E2 allele and AGT exhibited worse cognitive executive control than other subjects. They also had worse glycaemic control. Different apolipoprotein phenotypes, together with impaired glucose tolerance, may have different cumulative adverse effects on age-related cognitive performance. Some subgroups of subjects may be especially vulnerable to cognitive impairment. These findings require further study.

Acknowledgements

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