Increased Glucose Levels Are Associated With Episodic Memory in Nondiabetic Women

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OBJECTIVE—Patients with type 2 diabetes have an increased risk of a reduction in cognitive function. We investigated the hypothesis that plasma glucose is associated with a reduction in episodic and/or semantic memory already in nondiabetic subjects.

RESEARCH DESIGN AND METHODS—We linked two large population-based datasets in Sweden: the Betula study, in which a random sample from the population aged 35–85 years was investigated for cognitive function, including episodic and semantic memory; and the Västerbotten Intervention Program, a health survey with subjects aged 40, 50, and 60 years, that includes measuring of fasting and 2-h plasma glucose, along with other risk factors for diabetes and cardiovascular disease. We identified 411 (179 men and 232 women, mean age 50.6 ± 8.0 years) nondiabetic subjects, free from dementia, who had participated in the two surveys within 6 months.

RESULTS—Women had better episodic (score 7.37 ± 1.42) and semantic memory (score 16.05 ± 2.76) than men (score 6.59 ± 1.29 and 15.15 ± 2.92, respectively, $P < 0.001$ for both). In an adjusted multivariate model, fasting plasma glucose (fPG) and 2-h plasma glucose (2hPG) were significantly negatively associated with episodic memory (fPG: B −0.198, SE 0.068, β −0.209, $P = 0.004$; and 2hPG: B −0.061, SE 0.031, β −0.148, $P = 0.048$, respectively) in women but not in men. The association was not found in relation to semantic memory.

CONCLUSIONS—We conclude that an increase in plasma glucose is associated with impairment in episodic memory in women. This could be explained by a negative effect on the hippocampus caused by raised plasma glucose levels. ***Diabetes* 57:440–443, 2008**

The association between type 2 diabetes and different forms of cognitive impairment is well established (1). The mechanism behind the association is, however, still unrevealed. There are at least two alternative ethiopathogenic mechanisms linking diabetes to cognitive dysfunction. The first is the atherosclerotic mechanism (2), leading to an increased risk of vascular dementia and Alzheimer's disease. The second mechanism is the effect of metabolic disturbances per se on brain function. Experimental studies in animals (3) and humans (4) have shown that poor glucose regulation is associated with poorer performance in cognitive tests. Also, recent studies on subjects with impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) have reported a more profound cognitive decline than in subjects without IFG or IGT (5).

In contrast to previous studies that often used general cognitive processing as a dependent measure, we wanted to focus on a domain of cognition that is theoretically much developed, namely declarative memory as being composed of episodic and semantic memory (6). Episodic memory is more vulnerable to disturbances occurring in relation to diseases, including various metabolic conditions (rev. in 7). To propose a theoretically tenable explanation of the effect of a disease or some medical/biological condition, it is often necessary to demonstrate dissociation between memory systems that are based on different neural correlates. It has often been the case that episodic and semantic memories reveal such dissociations (rev. in 8). The basic reason for this variability in vulnerability is assumed to be the degree to which the hippocampus is involved in each task (9).

Thus, longstanding high glucose levels, defined as either IFG, IGT, or diabetes, have an impact on cognitive function. However, since the cutoffs for IFG, IGT, and diabetes are arbitrary, the aim was to use glucose level as a continuous variable in order to examine whether hyperglycemia in nondiabetic adults affects cognitive function when confounding factors are taken into account.

RESEARCH DESIGN AND METHODS

Our study population consisted of participants in two population-based surveys that complement each other in terms of cognitive tests and biochemical measurements. The first population was participants in the Betula Prospective Cohort Study ($n = 3,527$) (10). Subjects aged 35–85 years from the city of Umeå in the county of Västerbotten, Sweden, were selected randomly from the population registry in 1988–2000. The Betula database was linked to the database of participants in the Västerbotten Intervention Program (VIP; $n = 72,861$) (11). To limit the variation in metabolic parameters—most importantly, the variation in plasma glucose levels—between the different time points of the studies, we excluded subjects who had gone 6 months between taking each survey. We also excluded those with self-reported diabetes or glucose values in the diabetic range according to an oral glucose tolerance test (OGTT). Likewise, subjects with a Mini-Mental-State-Examination (MMSE) score below 24 were excluded, leaving 411 (232 women and 179 men) subjects in the study.

In the Betula study, the memory tests were *1*) episodic memory consisting of two components: recall and recognition; and *2*) semantic memory also with two components: knowledge and fluency (12). We transformed the results using the mean values and standard deviation from the youngest age group to compute a composite *z*-score (subjects' value minus mean score in the 40-year-old group divided by SD). The participants filled in a screening test for depression (the Center for Epidemiologic Studies Depression Scale [CES-D]).

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Received for publication 30 August 2007 and accepted in revised form 25 October 2007.

Published ahead of print at http://diabetes.diabetesjournals.org on 31 October 2007. DOI: 10.2337/db07-1215.

2hPG, 2-hour plasma glucose; CES-D, the Center for Epidemiologic Studies Depression Scale; fPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; MMSE, Mini Mental State Examination; OGTT, oral glucose tolerance test; VIF, variance inflation factor; VIP, Västerbotten Intervention Program.

TABLE 1
Characteristics of the study population by sex

	Women	Men	*P*	All
n	232	179	0.01	411
Difference between surveys (days)	11.4 ± 66.1	16.8 ± 70.9	NS	13.8 ± 68.2
Age (years)	50.7 ± 8.1	50.6 ± 8.0	NS	50.6 ± 8.0
40 years (*n*)	68	52	NS	120
50 years (*n*)	80	65	NS	145
60 years (*n*)	84	62	NS	146
Episodic memory (score)	7.37 ± 1.42	6.59 ± 1.29	<0.001	7.03 ± 1.42
Semantic memory (score)	16.05 ± 2.76	15.15 ± 2.92	0.001	15.6 ± 2.86
fPG (mmol/l)	5.2 ± 0.55	5.3 ± 0.55	0.03	5.2 ± 0.55
2hPG (mmol/l)	6.8 ± 1.19	6.3 ± 1.44	<0.001	6.6 ± 1.33
Hypertension (%)	33.6	41.9	NS	37.2
Total plasma cholesterol (mmol/l)	5.7 ± 1.24	5.9 ± 1.17	NS	5.8 ± 1.21
BMI	25 ± 4.1	26 ± 2.9	0.05	25 ± 3.6
Educational level (years)	12 ± 3.8	12 ± 3.8	NS	12 ± 3.8
Depression (CES-D scale)	7.8 ± 7.2	6.8 ± 6.1	NS	7.3 ± 6.7
Smoking (%)	45	57	0.01	51
Cardiovascular disease (%)	27	25	NS	26

Data are means ± SD unless otherwise indicated. *P* values are given for differences between sexes. There were missing values in the following variables: 2hPG 30 (n = 30; 19 women and 11 men), plasma cholesterol (4; 1 woman and 3 men), BMI (2; 2 women), smoking (5; 2 women and 3 men), and depression (64; 38 women and 26 men).

Subjects were asked about the number of years they had been in formal education, and they were interviewed about cardiovascular events.

In VIP, weight and height were measured and BMI (kg/m^2) was calculated. Blood pressure was measured with subjects in a supine position after 5 min of rest. Hypertension was defined as self-report of hypertension, the use of anti-hypertensive medication, or blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg. An OGTT was performed with a 75-g glucose load after fasting overnight. Glucose concentrations were measured on capillary plasma on a Reflotron bench-top analyzer (Boeringer Mannheim, Mannheim, Germany) in a fasting state and 2 h after glucose administration. Total cholesterol was measured on the Reflotron analyzer. Information on smoking was collected in a questionnaire. Smokers were defined as those reporting daily smoking, while ex-smokers or "occasional smokers" were classified as nonsmokers.

The participants gave their informed consent in both studies, and we obtained approval from the regional board of the ethics committee in Umeå, Sweden.

Statistical analysis. Data are presented as mean values (SD), numbers (*n*), and proportions (%). Statistical significance was tested for continuous and categorical variables by *t* tests and χ^2 tests, respectively. Both fasting plasma glucose (fPG) and 2-h plasma glucose (2hPG) were used as continuous variables in a bivariate analysis (Pearson's correlation coefficient [*r*]) and in the multivariate models. We performed univariate and multivariate linear analyses exploring the relationship between the dependent variables fPG and 2hPG and different potential confounders and effect modifiers. Collinearity between independent parameters was evaluated by estimation of variance inflation factor (VIF). A difference was regarded as statistically significant when $P < 0.05$.

RESULTS

The results revealed that women had higher levels of episodic memory, semantic memory, and 2hPG than men (Table 1). Regarding the subsystems of memory, the results showed a female superiority for both recall and recognition as the two components of episodic memory, as well as for fluency but not for knowledge in semantic memory. Men had higher levels of fPG and BMI than women and more men were smokers. Time difference between the two surveys was not associated with episodic or semantic memory (data not shown). Given the sex difference in the outcome variables, i.e., episodic and semantic memory, we stratified for sex.

fPG was weakly correlated to 2hPG ($r = 0.30$) in women

TABLE 2
Correlation between episodic and semantic memory and their components and age, fPG, 2hPG, systolic blood pressure (SBP), diastolic blood pressure (DBP), hypertension (HT), total cholesterol, BMI, depression, smoking, cardiovascular disease (CVD), and years in formal education

	Age	fPG	2hPG	SBP	DBP	HT	Cholesterol	BMI	Depression	Smoking	CVD	Education
Women												
Episodic	−0.34*	−0.29*	−0.24*	−0.14†	−0.15†	−0.20‡	−0.24‡	−0.11	−0.03	0.05	−0.09	0.37*
Recall	−0.47*	−0.22‡	−0.24‡	−0.20‡	−0.20‡	−0.20‡	−0.32*	−0.16†	−0.08	0.11	−0.09	0.46*
Recognition	−0.15†	−0.25*	−0.17†	−0.06	−0.06	−0.14†	−0.11	−0.05	0.01	−0.01	−0.05	0.19‡
Semantic	−0.22‡	−0.10	−0.22‡	−0.15†	−0.20‡	−0.16†	−0.20‡	−0.12	0.01	0.09	−0.23*	0.52*
Fluency	−0.20‡	−0.09	−0.17†	−0.10	−0.15†	−0.13	−0.17†	−0.03	0.04	0.04	−0.10	0.35*
Knowledge	−0.18‡	−0.09	−0.20‡	−0.15†	−0.19‡	−0.14	−0.18‡	−0.15†	−0.01	0.09	−0.26*	0.51*
Men												
Episodic	−0.13	0.01	0.04	−0.09	−0.06	−0.10	−0.20‡	−0.16†	−0.07	−0.15†	0.02	0.43*
Recall	−0.31*	−0.03	−0.05	−0.19*	−0.13	−0.18†	−0.19†	−0.14	−0.12	−0.13	−0.15†	0.48*
Recognition	−0.04	0.04	0.09	0.00	0.01	−0.01	−0.14	−0.12	−0.01	−0.11	0.13	0.25‡
Semantic	−0.15†	0.08	0.03	−0.01	−0.05	−0.03	−0.05	−0.21†	−0.04	−0.15†	−0.01	0.58*
Fluency	−0.11	0.05	0.10	−0.05	−0.06	−0.11	−0.03	−0.13	−0.03	−0.09	−0.03	0.42*
Knowledge	−0.15†	0.08	−0.01	0.01	−0.03	−0.02	−0.05	−0.22‡	−0.04	−0.16†	0.01	0.58*

*$P < 0.001$; †$P < 0.05$; ‡$P < 0.01$.

TABLE 3
Univariate and multivariate analysis of the effect of fPG, 2hPG, and additional metabolic and environmental risk factors on episodic memory by sex

	Univariate analysis				Model adjustment			
	B	SE	β	*P*	B	SE	β	*P*
Women								
fPG (mmol/l)	–0.269	0.063	–0.271	<0.001	–0.215	0.066	–0.220	0.001
2hPG (mmol/l)	–0.110	0.030	–0.247	<0.001	–0.081	0.031	–0.196	0.009
Men								
fPG (mmol/l)	0.029	0.069	0.032	NS	0.029	0.073	0.032	NS
2hPG (mmol/l)	0.012	0.028	0.033	NS	0.024	0.029	0.070	NS

In the model adjustment, age, hypertension, total plasma cholesterol, BMI, educational level, depression, smoking and CVD were entered in the multivariate analysis together with fPG or 2hPG.

but not in men ($r = 0.15$). Episodic memory among women was negatively correlated to age, fPG, 2hPG, hypertension, and total cholesterol but positively correlated to years in formal education (Table 2). Recall followed the same pattern, whereas recognition was not correlated to blood pressure and total cholesterol. Semantic memory in women was negatively correlated to age, 2hPG, hypertension and total cholesterol and positively correlated to years in formal education. This was in contrast to men, for whom only BMI, total cholesterol, and smoking were negatively correlated and years in formal education positively correlated to episodic memory. Age, BMI, and smoking were negatively correlated to semantic memory in men, while years in formal education showed a positive correlation.

In a univariate and multivariate analyses (Tables 3 and 4), we entered the factors that were known to influence cognitive function, glucose metabolism, and CVD. Both increased fPG, and 2hPG levels were associated with a decrease in episodic memory in women, but not in men, in the univariate analysis and after the model adjustment (Table 3), with no collinearity between fPG and 2hPG (VIF = 1.04). Decrease in semantic memory was associated with increased levels of 2hPG among women but not in men (Table 4). However, after fPG and 2hPG were entered together in the adjusted model, both fPG and 2hPG remained negatively associated with episodic memory (fPG: B −0.198, SE 0.068, β −0.209, $P = 0.004$; and 2hPG: B −0.061, SE 0.031, β −0.148, $P = 0.048$, respectively) in women. When entered together, there was no association between fPG and 2hPG and semantic memory in either women or men (data not shown).

DISCUSSION

In our nondiabetic population, we found that increased fPG and 2hPG levels were independently associated with impairment of episodic memory in women. There was also a weak association between 2hPG and semantic memory in women. However, this association disappeared when both fPG and 2hPG were entered together in the multivariate analysis, indicating that the 2hPG association with semantic memory was not independent of other factors in the model. The analyses of subcomponents of episodic memory revealed, as expected, stronger associations with recall than with recognition.

Our observation that glucose levels have an effect on cognitive function is in line with many previous cross-sectional (13) and longitudinal studies (5). However, in contrast to previous studies, we included nondiabetic subjects, and our outcome was cognitive function evaluated by elaborate and standardized memory testing and not clinically defined dementia (5). Also, our study population was younger than many other study populations.

We observed that increased glucose levels affected episodic memory more than semantic memory, as in the Atherosclerosis Risk in Communities (ARIC) Study (14). The explanation for why episodic memory is mainly affected may be the brain region where it is executed, i.e., the hippocampus. The hippocampus is the brain region most susceptible to metabolic changes (15). Studies in both humans (16) and rats (17) have shown effects of hyperglycemia on memory functional and abnormalities in the hippocampus.

Both fPG and 2hPG were associated with impairment in episodic memory. Whether glucose alone could exert this effect is debated. Glucose increases the risk of atherosclerosis, thereby increasing the risk of vascular dementia (18). Hyperglycemia is often coupled to other metabolic abnormalities that could be linked to cognitive impairment (2). However, we estimate that the influence of vascular dysfunction in our study was small, since the mean age was low and we were able to control for history of CVD

TABLE 4
Univariate and multivariate analysis of the effect of fPG, 2hPG, and additional metabolic and environmental risk factors on semantic memory by sex

	Univariate analysis				Model adjustment			
	B	SE	β	*P*	B	SE	β	*P*
Women								
fPG (mmol/l)	–0.145	0.104	–0.092	NS	–0.107	0.105	–0.066	NS
2hPG (mmol/l)	–0.152	0.049	–0.209	0.002	–0.098	0.050	–0.139	0.052
Men								
fPG (mmol/l)	0.121	0.125	0.073	NS	0.114	0.122	0.066	NS
2hPG (mmol/l)	0.019	0.050	0.030	NS	0.013	0.049	0.020	NS

In the model adjustment, age, hypertension, total plasma cholesterol, BMI, educational level, depression, smoking and CVD were entered in the multivariate analysis together with fPG or 2hPG.

and many of the components in the metabolic syndrome. There are studies supporting the hypothesis that glucose can be a major culprit. Awad et al. (4) gave students a 75-g glucose load, which resulted in poorer performance on memory tests. Improving metabolic control in diabetic patients has been reported to improve cognitive function (19). Alternative mechanisms could be considered. Insulin may act in a negative manner on cognitive function in humans (20), possibly through the function of the insulin-degrading enzyme (IDE), which is negatively affected by high levels of insulin, resulting in impaired degradation of amyloid-β (21).

Our observation of a relation between glucose levels and episodic memory was only found in women. Sex differences in memory are well documented (22) but to date there is no established explanation for the phenomenon. In our study, women aged 50 or 60 had lower semantic and episodic memory than 40-year-old women. The same difference was not seen in men. This could indicate a postmenopausal decline in memory among women. We are not able to draw any far-reaching conclusions concerning possible mechanisms from our study since it had a cross-sectional design. Also, we do not have information concerning, for example, hormonal replacement treatment or how many women were postmenopausal. In a metaanalysis by the *Cochrane Database of Systematic Reviews*, it was concluded that there was little evidence that estrogen replacement therapy (estrogen only) or hormone replacement therapy (estrogens combined with progestagen) had any overall effect on cognitive function in postmenopausal women (23).

The strength of our study was that our observation was a combination of two elaborate population-based studies. We were able to study in depth different aspects of cognition and measurements of metabolic parameters and could control for many of the confounding factors influencing both glucose metabolism and cognition. It should be recognized that our study had a cross-sectional design and there was a time gap between VIP and the Betula study. However, our observed mean time difference between the surveys was less than 2 weeks. This implies that it is unlikely that fPG and 2hPG levels changed dramatically during that period of time because blood glucose levels are generally tightly controlled in nondiabetic subjects (24).

In conclusion, we report an independent association between elevated levels of glucose and a decline in episodic memory in women. This could imply that chronically raised glucose levels exert a harmful effect on the hippocampus, which is the brain region where episodic memory is mainly executed. Our observation needs to be confirmed in a longitudinal study and the proposed mechanism should be evaluated with proper experimental methods.

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