

Increased Glucose Levels are Associated with Episodic Memory in Nondiabetic Women

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Running title: “Glucose and episodic memory in women”

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

ABSTRACT

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 data sets in Sweden. Firstly, the Betula study where a random sample from the population aged 35–85 years was investigated for cognitive function including episodic and semantic memory. Secondly, the Västerbotten Intervention Program, a health survey with subjects aged 40, 50 and 60 years. It includes measuring of fasting and 2-hour plasma glucose, along with other risk factors for diabetes and cardiovascular disease. We identified 411 (M/F 179/232, mean age 50.6 ± 8.0 years) nondiabetic subjects, free from dementia, who had participated in the two surveys within six 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 fPG and 2hPG were significantly negatively associated with episodic memory (fPG: B -0.198 , SE 0.068 , Beta -0.209 , $p = 0.004$ and 2hPG: B -0.061 , SE 0.031 , Beta -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.

ABBREVIATIONS. 2hPG, 2-hour plasma glucose; BMI, Body Mass Index; CES-D, the Center for Epidemiologic Studies Depression Scale; fPG, fasting plasma glucose; MMSE, Mini Mental State Examination; OGTT, Oral Glucose Tolerance Test; VIP, Västerbotten Intervention Program.

KEY WORDS. Cognition, episodic memory, fasting plasma glucose, gender..

The association between type 2 diabetes (T2D) 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 aetiopathogenic 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 (reviewed 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 (reviewed 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 cut-offs 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 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). In order 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 with more than 6 months between the surveys. We also excluded those with self-reported diabetes or glucose values in the oral glucose tolerance test (OGTT) indicating diabetes. Likewise, subjects with a Mini-Mental-State-Examination (MMSE) score below 24 were excluded, leaving 411 (M/W 179/232) subjects in the study.

In the Betula study the memory tests were: (i) episodic memory consisting

of two components: recall and recognition; and (ii) 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). 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 body mass index (BMI, kg/m^2) was calculated. Blood pressure was measured with subjects in a supine position after 5 minutes 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 (PG) on a Reflotron bench-top analyzer (Boeringer Mannheim GmbH, Mannheim, Germany) in a fasting state (fPG) and two hours after glucose administration (2hPG). 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 chi-square tests, respectively. Both fPG and 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, 2hPG and different potential confounders and effect modifiers. Collinearity between independent parameters was evaluated by estimation of variation 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, and for fluency but not for knowledge in semantic memory. Men had higher levels of fPG, 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 gender difference in the outcome variables, i.e. episodic and semantic memory, we stratified for gender.

Fasting PG was weakly correlated to 2hPG ($r=0.30$) in women but not in men ($r=0.15$). Episodic memory among women was negatively correlated to age, fPG, 2hPG, hypertension, 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, total cholesterol, and positively correlated to years in formal education. This was in contrast to men where 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 analysis (table 3a, 3b) 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 3a) 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 3b). 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, Beta -0.209, p=0.004 and 2hPG: B -0.061, SE 0.031, Beta -0.148, p=0.048, respectively) in women. When entered together there was no association between fPG and 2hPG and semantic memory either in women or in men (data not shown).

DISCUSSION

We found in our nondiabetic population 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 Study (ARICS) (14). The explanation why episodic memory is mainly affected can be the brain region where it is executed, i.e. the hippocampus. The hippocampus is the most susceptible brain region to metabolic changes (15). Studies in both humans (16) and rats (17) have shown effects of hyperglycemia on memory functional and abnormalities in 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 which 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 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 diabetes 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) maybe 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. Gender differences in memory are well-documented (22) but there is to date 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 e.g. hormonal replacement treatment or how many women were post menopausal. 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 since 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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TABLE 1. Characteristics of the study population by gender.

	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)
fP-Glucose (mmol/L)	5.2 (0.55)	5.3 (0.55)	0.03	5.2 (0.55)
2hP-glucose (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 P-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 n, % within group, and mean (SD). P-values are given for differences between genders. There were missing values in the following variables: 2hPG 30 (W/M 19/11), P-Cholesterol 4 (W/M 1/3), BMI 2 (W/M 2/0), smoking 5 (W/M 2/3), and depression 64 (W/M 38/26).

Table 2. Correlation between episodic and semantic memory and their components and age, fasting plasma glucose (fPG), 2-h plasma glucose (2hPG), systolic blood pressure (SBP), diastolic blood pressure (DBP), hypertension (HT), total cholesterol, body mass index (BMI), depression, smoking, cardiovascular disease (CVD), and years in formal education.

	Age	fPG	2hPG	SBP	DBP	HT	Cholesterol	BMI	Depression	Smoking	CVD	Education
Women												
<i>Episodic</i>	-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*
Recogn.	-0.15†	-0.25*	-0.17†	-0.06	-0.06	-0.14†	-0.11	-0.05	0.01	-0.01	-0.05	0.19†
<i>Semantic</i>	-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*
Knowl.	-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												
<i>Episodic</i>	-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*
Recogn.	-0.04	0.04	0.09	0.00	0.01	-0.01	-0.14	-0.12	-0.01	-0.11	0.13	0.25†
<i>Semantic</i>	-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*
Knowl.	-0.15†	0.08	-0.01	0.01	-0.03	-0.02	-0.05	-0.22†	-0.04	-0.16†	0.01	0.58*

† = <0.05, ‡ = <0.01, * = <0.001

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

	Univariate analysis				Model adjustment			
	B	SE	Beta	p	B	SE	Beta	p
<i>Women</i>								
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
<i>Men</i>								
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 P-cholesterol, BMI, educational level, depression, smoking and CVD were entered in the multivariate analysis together with fPG or 2hPG

TABLE 3B. Univariate and multivariate analysis of the effect of fPG, 2hPG and additional metabolic and environmental risk factors on semantic memory by gender.

	Univariate analysis				Model adjustment			
	B	SE	Beta	p	B	SE	Beta	p
<i>Women</i>								
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
<i>Men</i>								
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 P-cholesterol, BMI, educational level, depression, smoking and CVD were entered in the multivariate analysis together with fPG or 2hPG.