Oral Glucose Tolerance Test Predicts Episodic Memory Decline: A 10-Year Population-Based Follow-up Study

Sini Toppala,[1,2] Laura L. Ekblad,[1,3] Matti Viitanen,[3,4,5] Juha O. Rinne,[1] and Antti Jula[6]

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OBJECTIVE

To examine if the 2-h value of an oral glucose tolerance test (OGTT) can predict cognitive decline.

RESEARCH DESIGN AND METHODS

This study is based on a subpopulation of the Finnish population-based Health 2000 Survey and its follow-up, the Health 2011 study. Altogether, 961 individuals aged 45–74 (mean 55.6 years; 55.8% women) underwent OGTT in 2001–2002. Categorical verbal fluency, word-list learning, and word-list delayed recall were tested at baseline and at follow-up in 2011. Statistical analyses were performed with multivariable linear models adjusted for previously reported risk factors for cognitive decline.

RESULTS

A higher 2-h glucose value in the OGTT at baseline predicted worse performance (slope: −0.08; $P = 0.01$) and greater decline (slope: −0.07; $P = 0.007$) in the word-list delayed recall test after 10 years.

CONCLUSIONS

Our results indicate that higher 2-h glucose values in the OGTT predict a decline in episodic memory after 10 years.

Previous research indicates that not only diabetes, but also conditions associated with prediabetes, such as obesity, the metabolic syndrome, and insulin resistance, are associated with an increased risk for cognitive decline, dementia, and Alzheimer disease (1–3). We have previously shown that insulin resistance, measured with HOMA of insulin resistance (HOMA-IR), but not fasting glucose, predicts cognitive decline in the Finnish adult population after 11 years (2,3) and that midlife insulin resistance predicts cerebral amyloid accumulation (4), the early neuropathological hallmark of Alzheimer disease. However, measuring insulin resistance with HOMA-IR is not common practice in the clinical setting, and no cutoff values for HOMA-IR exist to classify patients as insulin-sensitive and insulin-resistant. Thus, the aim of the current study was to examine if the 2-h value of an oral glucose tolerance test (OGTT), a clinical measurement of glucose tolerance and an indirect measurement of insulin resistance, could be used as a predictor of cognitive decline.

[1]Turku PET Centre, University of Turku and Turku University Hospital, Turku, Finland
[2]Kuopio City Home Care, Rehabilitation and Medical Services for Elderly, Kuopio, Finland
[3]City of Turku, Welfare Division, Turku City Hospital, Turku, Finland
[4]Department of Geriatrics, Turku City Hospital, University of Turku, Turku, Finland
[5]Division of Clinical Geriatrics, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet, Stockholm, Sweden
[6]National Institute for Health and Welfare, Turku, Finland

Corresponding author: Laura L. Ekblad, llekbl@utu.fi

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RESEARCH DESIGN AND METHODS

This study is based on the Finnish population-based Health 2000 Examination Survey carried out in 2000–2001, its supplemental examinations on a subpopulation in 2001–2002, and its follow-up, the Health 2011 study, all conducted by the Finnish National Institute for Health and Welfare (5–7). In total, 961 individuals, who attended all the three surveys, were included in the current study. Details about the study population are presented in the Supplementary Material.

In the Health 2000 Survey, *APOE* genotyping was performed (those with one or two *ε4* alleles were considered *APOEε4* carriers), information about the participants' education and smoking was obtained, and depressive symptoms were assessed with the Beck depression inventory (BDI) (2).

In the supplemental examinations, blood samples were drawn after fasting for 10–12 h, and 2-h OGTT was performed (Supplementary Material). Type 2 diabetes was defined as use of oral diabetes medication or fasting glucose ≥7.0 mmol/L or 2-h OGTT value ≥11.1 mmol/L. Hypercholesterolemia was def-ined as serum total cholesterol >6.5 mmol/L or use of cholesterol-lowering medication. Hypertension was defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or use of antihypertensive treatment.

The participants were tested for verbal fluency and for encoding and retaining verbal material by selected tasks from the Finnish version of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) (8) test battery at baseline and at follow-up as previously reported (2).

Associations between the 2-h glucose value and the follow-up cognitive test scores as well as the change in cognitive test scores from baseline were assessed with multivariable linear models. Previously reported risk factors for cognitive impairment were included in the models. First, the analyses were adjusted for age, sex, and education in years. The fully adjusted analyses were further adjusted for *APOEε4* genotype, type 2 diabetes, hypertension, hypercholesterolemia, BMI, BDI score, and smoking. Additionally, the analyses for the change in cognitive tests over 11 years were adjusted for baseline cognitive test scores. Normality assumptions for the analyses were inspected from the residuals. Two-sided statistical significance was set at $P < 0.05$. The statistical analyses were performed with SAS JMP Pro 14 (SAS Institute, Cary, NC).

RESULTS

The mean age of the study participants was 55.6 years. There were 536 (56%) women, 86 (9%) smokers, and 304 (33%) *APOEε4* carriers. A total of 84 (8.7%) had type 2 diabetes, 518 (54%) hypertension, and 236 (26%) hypercholesterolemia. Characteristics of the study population are described in more detail in Supplementary Table 1.

A higher 2-h glucose value in the OGTT in 2001–2002 predicted worse performance in the word-list delayed recall test after 10 years (fully adjusted model slope −0.08; $P = 0.01$) and greater decline in the word-list delayed recall test from 2000–2001 to 2011 (fully adjusted model slope −0.07; $P = 0.007$). The associations remained significant even after adding fasting glucose into the fully adjusted model (data not shown). A higher 2-h glucose value also predicted worse performance (slope −0.14; $P = 0.0005$) and greater decline (slope −0.10; $P = 0.006$) in the word-list learning test, but only in the age, sex, and education adjusted model. No association was found between 2-h glucose value and verbal fluency (Table 1). Adjusted coefficients of determination (r^2_{adj}) of the models predicting cognitive performance in 2011 are shown in Supplementary Table 2. Interactions for type 2 diabetes, *APOEε4* genotype, age, and sex were tested. Only the interaction "2-h glucose × age" was significant for predicting change in word-list learning ($P = 0.04$). None of the interactions were significant after Bonferroni correction (Supplementary Material).

CONCLUSIONS

This study indicates that a higher 2-h glucose in the OGTT predicts a decline in episodic memory after 10 years. A higher 2-h glucose predicted poorer word-list delayed recall at follow-up and greater decline from the baseline.

To date, only few large longitudinal studies have been performed (9–12). Our results are in concordance with a study that showed persistent impaired glucose tolerance to increase the risk of cognitive decline after 3.5 years ($n = 586$; mean age 73 years) (9). In a cohort of 1,125 elderly men (follow-up 12 years), OGTT 2-h glucose value was associated with an increased risk of cognitive impairment and dementia (11). Another study ($n = 999$; aged 42–89 years; follow-up 4 years) showed that impaired glucose tolerance was associated with impaired verbal fluency, but only when the 25th percentile cutoff point for cognitive decline was used (10). Our study extends the previous results by providing a longer follow-up on a middle-aged population, including both men and women.

We found that a higher 2-h glucose value in the OGTT predicts weaker performance in the CERAD word-list delayed recall test, a test of episodic memory that is typically affected early in Alzheimer disease (13). Mid- and earlier life vascular and metabolic risk factors are crucial in the development of later cognitive impairment, whereas in late life, they may not reach to increase the risk of cognitive decline (14). The pathological process of cognitive decline and Alzheimer disease is known to be slow, and β-amyloid (15) as well as cerebrovascular changes are estimated to accumulate years prior to the onset of symptoms.

Our study has some limitations. First, more detailed neuropsychological tests than CERAD are more sensitive to detect early cognitive decline. However, an association between 2-h glucose and a simple measure of episodic memory from CERAD that is used for screening for Alzheimer disease suggests that the decline in episodic memory we detected might be clinically meaningful. Second, brain imaging (evaluation of β-amyloid accumulation and atrophy) could have given more information about the pathophysiological mechanisms of cognitive decline, but neuroimaging was not performed in the Health 2000 or 2011 studies. The strengths of this study in summary are the long follow-up time; a large, population-based study population; cognitive tests performed at baseline and at follow-up; and the possibility to adjust the results for known risk factors of cognitive decline.

In this study, we show that higher 2-h glucose values in the OGTT predict a

Table 1—The associations between 2-h glucose values of the OGTT at baseline and the cognitive test results at follow-up as well as the associations between 2-h glucose values at baseline and the change in cognitive tests from 2000 to 2011

	Verbal fluency	Word-list learning	Word-list delayed recall
Cognitive test score 2011			
2-h glucose[A]	−0.11 (−0.26 to 0.03)	−0.14 (−0.23 to −0.06)***	−0.08 (−0.12 to −0.04)***
2-h glucose[B]	0.02 (−0.19 to 0.23)	−0.07 (−0.19 to 0.05)	−0.08 (−0.14 to −0.02)*
Change in cognition 2000–2011			
2-h glucose[C]	−0.05 (−0.17 to 0.07)	−0.10 (−0.17 to −0.03)**	−0.07 (−0.11 to −0.04)***
2-h glucose[D]	0.03 (−0.14 to 0.20)	−0.05 (−0.16 to 0.05)	−0.07 (−0.13 to −0.02)**

Data are slope (95% CI). The change in the cognitive test scores at follow-up was calculated by the equation: cognitive test score at follow-up (year 2011) − cognitive test score at baseline (year 2000). A negative change indicates a decline in cognitive performance. [A]Adjusted for age, sex, and education. [B]Further adjusted for *APOEε4* genotype, type 2 diabetes, hypertension, hypercholesterolemia, BMI, BDI score, and smoking. [C]Adjusted for age, sex, education, and baseline cognitive test scores. [D]Further adjusted for *APOEε4* genotype, type 2 diabetes, hypertension, hypercholesterolemia, BMI, BDI score, and smoking. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

decline in episodic memory after 10 years in a middle-aged sample of the Finnish population. Our results suggest that 2-h OGTT could potentially be used as a predictor of future episodic memory decline. Considering that OGTT is easily available and already used in clinical practice, these results may be helpful in detecting individuals at risk for cognitive decline even in the prediabetic stage and in guiding treatment strategies to prevent cognitive decline and dementia.

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