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OXFORD

Brief report

Glycated Peptide Levels Are Associated With Cognitive Decline Among Nondiabetic Older Women

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Abstract

Background: The association between diabetes and dementia may be explained in part by elevated levels of glycated peptides; we sought to determine whether serum-glycated peptides predicted cognitive decline in nondiabetic older adults.

Methods: We prospectively studied 525 community-dwelling nondiabetic women, mean age of 82 years, and analyzed baseline glycated peptides (serum level of fructosamine and glycated albumin). Cognitive outcomes included 5-year decline on the short Mini-Mental State Examination (sMMSE), Trails B, and performance on a battery of five other cognitive tests at the follow-up visit. Generalized linear models were adjusted for education, age, race, physical activity, body mass index, and vascular disease.

Results: Women with higher level of fructosamine (upper two tertiles) had greater 5-year decline in Trails B performance compared with women in the lowest tertile (adjusted mean change = 67 vs 50 seconds, $p = .046$), but change in sMMSE was not different between groups. Higher fructosamine was also associated with worse cognitive function 5 years later: adjusted mean score for the California Verbal Learning Test-II Short Form was 22.7 versus 23.9 ($p = .010$) and for Category Fluency was 10.1 versus 11.1 ($p = .003$). Higher glycated albumin was also associated with worse performance on Category Fluency (10.1 vs 11.1, $p = .003$) but not on any other test.

Conclusions: Among older nondiabetic women, higher concentrations of glycated peptides may be associated with greater cognitive decline, especially in measures of executive function. These associations may present new opportunities for targeted prevention and therapeutic strategies in cognitive aging.

Keywords: Cognition, Diabetes, Glycation, Cognitive aging, Biomarkers.

Introduction

Potentially modifiable late-life metabolic risk factors are gaining attention as predictors of cognitive decline and dementia, making them attractive targets for prevention. Many studies have found that diabetes accelerates cognitive decline and increases the risk of progression of MCI to dementia (1). Examining potential mechanisms underlying this relationship may reveal preventative and therapeutic strategies for cognitive decline in older adults.

One mechanism linking hyperglycemia to cognitive aging is the presence of various glycated peptides which form at higher rates in the setting of hyperglycemia and high-oxidative stress (2). Increased glycated peptides contribute to pathological microvascular and

macrovascular processes by increasing inflammation and atherogenesis (2). However, the role of glycated peptides in cognitive aging remains largely unexplored. Preliminary cross-sectional investigations have found associations between elevated glycated albumin and worse cognitive performance (3), but longitudinal studies are lacking.

In a large prospective cohort study, we sought to determine whether older nondiabetic women with higher serum levels of glycated albumin and fructosamine would exhibit worse cognitive outcomes and greater 5-year decline on cognitive testing than those with lower levels.

Methods

The Study of Osteoporotic Fractures (SOF) is a multicenter prospective observational study of community-dwelling older women. During 1986–1988, 9,704 Caucasian women aged 65 years or older were recruited from community-based listings at the four study sites. Six hundred and sixty-two African-American women were enrolled during 1996–1998. Women were recruited irrespective of bone mineral density and fracture history; those unable to walk without assistance and those with bilateral hip replacements were excluded. All women provided written informed consent, and each site obtained institutional review board approval (4). Our analytic cohort is derived from an ancillary study on sleep, which included 2,732 women without dementia from the Minneapolis and Pittsburgh sites at visit 8 (approximately year 16 of SOF), the baseline for this study. Of these, 1,026 women provided baseline serum samples, and 587 completed a follow-up cognitive battery (average follow-up = 5.0 ± 0.6 years). Of the 434 women who did not complete the cognitive testing, 211 were deceased, 38 terminated the study, and 185 completed only a questionnaire. Sixty-two of the 587 women with follow-up testing reported having diabetes at baseline and were excluded from our analyses, leaving 525 women in our cohort. Thirty-one women developed diabetes over the course of the study period but were included in our analyses given our prospective cohort design; sensitivity analyses revealed no major differences in inferences.

Glycated peptides were assessed using serum samples that were collected at baseline and stored at −70°C. In June 2014, fructosamine assays were performed by Roche Diagnostics, Indianapolis, IN, and glycated albumin assays were performed by Asahi Kasei Pharma, Tokyo, Japan. Both labs used Roche Cobas 6000 chemistry analyzers.

At baseline and follow-up, the Trails B (executive function) and the 26-point short Mini-Mental State Examination (sMMSE) (global cognition) were administered. Five additional tests were administered at follow-up: Teng 3MS measures global cognition, Category Fluency assesses semantic memory, Verbal Fluency assesses phonemic verbal production, California Verbal Learning Test-II Short Form (CVLT) measures verbal memory for immediate recall, and the Digit Span Backwards test assesses working memory (5).

Baseline questionnaires assessed age, race, education, medical history, alcohol use, and physical activity. Self-reported physician diagnoses included stroke, diabetes, hypertension, and coronary heart disease. During physical examination, height and weight were assessed and body mass index (BMI) calculated.

In the interest of presenting clinically applicable results and maintaining consistency with prior literature, we first analyzed glycated peptides by tertile and then grouped the upper two tertiles into a single category ("high") versus lowest tertile ("low"). We compared associations between tertiles of glycated protein and baseline characteristics using chi-square tests for categorical variables, analysis of variance for normally distributed continuous variables, and Kruskal–Wallis tests for skewed continuous variables. Using the least square means procedure, we examined the association between glycated peptide level and both change in cognitive scores over 5 years and cognitive outcomes at follow-up. Based on current biological and sociological models of cognitive decline and metabolism, statistical models were adjusted for education, age, race, physical activity, BMI, heart attack, hypertension, and stroke. The difference in means for cognitive outcomes by glycated peptide level was determined using Cohen's *d* as the standardized effect size (Fig 1). All analyses

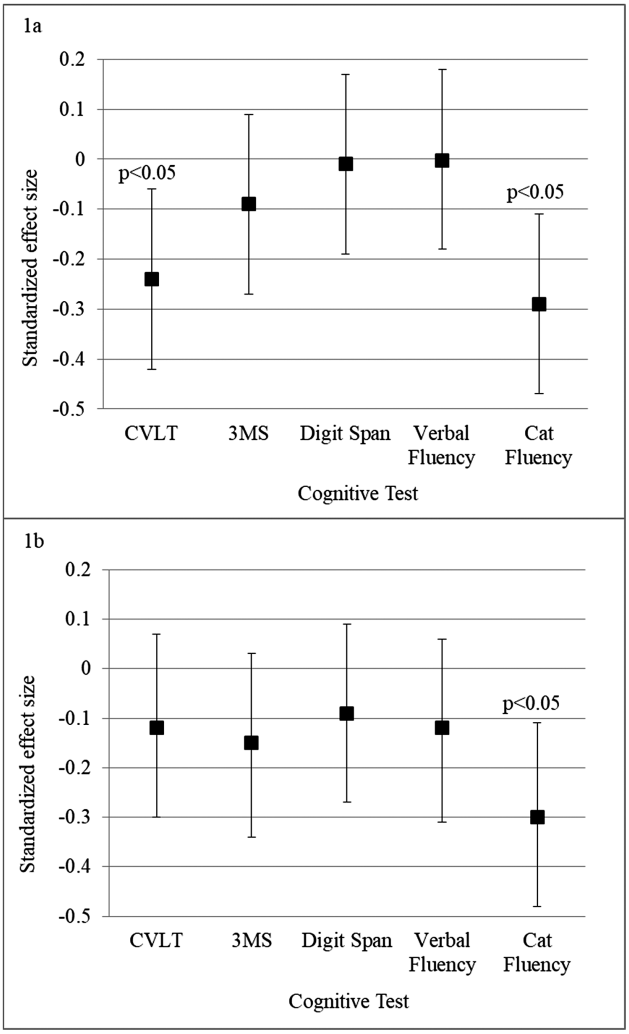

Figure 1. High versus low glycated peptides and 5-year cognitive outcomes in nondiabetic older women. High versus low fructosamine (**a**) and glycated albumin (**b**) versus adjusted standardized cognitive test score outcomes at 5 years, showing a difference in CVLT and Category Fluency. Standardized effect size (Cohen's *d*) is calculated as the difference in means between groups divided by the pooled standard deviation. High levels represent combined mid and high tertile-glycated peptides. Generalized linear models were adjusted for education, age, race, physical activity, body mass index (BMI), heart attack, hypertension, and stroke. Note. CVLT = California Verbal Learning Test-II Short Form; 3MS = Teng modified Mini-Mental State Examination; Cat Fluency = Category Fluency.

were conducted using SAS 9.4 statistical software (SAS Institute, Cary, NC) and were two-tailed with $p < .05$. We did not apply a correction for multiple comparisons given that our hypotheses were established a priori and were generally related as investigations of cognitive function.

Results

Elevated levels of both glycated peptides were associated with several baseline characteristics (Table 1). Women with higher tertiles of fructosamine were older, had lower BMI, and were more likely to walk for exercise ($p < .05$ for all). Women with higher glycated albumin were less educated ($p < .05$) and consumed less alcohol ($p < .001$). There were no differences in cardiovascular disease or depressive symptoms by glycated peptide group.

Women with high fructosamine (those in the upper two tertiles) had a greater 5-year decline in Trails B performance compared with women with low fructosamine (the lowest tertile): in unadjusted models, mean change in seconds was 68.9 versus 47.1 ($p = .012$) (Table 2). This decline remained present after adjustment for education, age, race, physical activity, BMI, and comorbidities (67.3 vs 49.6 seconds, $p = .046$). Mean change in sMMSE was not different between fructosamine groups, and levels of glycated albumin were not associated with a change in Trails B time or sMMSE ($p > .05$ for all).

Participants with high fructosamine level had lower scores on cognitive testing 5 years later in unadjusted models for CVLT (22.5 vs 24.1, $p = .002$) and Category Fluency (10.1 vs 11.1, $p = .002$) and remained lower after adjustment (CVLT 22.7 vs 23.9, $p = .010$, Category Fluency 10.1 vs 11.1, $p = .003$) (Fig. 1a). Higher glycated albumin levels were similarly associated with worse performance on Category Fluency (unadjusted 10.1 vs 11.1, $p = .002$; adjusted 10.1 vs 11.1, $p = .003$), and 3MS (87.3 vs 89.4, $p = .026$) but not for the CVLT (22.8 vs 23.7, $p = .080$). After adjustment, the association for 3MS was no longer significant (88.5 vs 87.7, $p = .376$) There were no significant differences for the Digit Span or Verbal Fluency test for either glycated peptide ($p > .05$ for all) (Fig 1b).

Discussion

Among older community-dwelling women, those with higher levels of glycated peptides exhibited greater decline in executive function over 5 years and performed worse on several cognitive outcome measures, independent of demographic factors, and cardiovascular comorbidities. This study presents novel findings for an association between serum-glycated peptides and cognitive outcomes among older adults without diabetes.

This is the first study of serum fructosamine and cognitive outcomes. Two cross-sectional studies have found an association between elevated glycated albumin and cognitive impairment. In a study of hospitalized nondiabetic elders, Zhong and colleagues (6) found that elevated glycated albumin to hemoglobin A1c ratios (GA/HbA1c) were associated with lower MMSE scores. A similar study in Japan found that GA/HbA1c was an independent predictor of cognitive impairment (3).

Glycated peptides may also be potentially modifiable risk factors for major cardiovascular outcomes (7), and it is likely that the decline in executive function observed in our study is the result of vascular processes (8). With relatively short half-lives, fructosamine and glycated albumin are gaining attention for high-granularity monitoring of glycemic control (2), and increasing clinical use would facilitate a role in identifying individuals at higher risk of cognitive decline and

Table 1. Baseline Characteristics of the 525 Participants by Glycated Peptide Tertile[a]

Demographic Variable	Overall ($n = 525$)	Fructosamine Tertile 1 ($n = 184$), T1 < 233 µmol/L	Fructosamine Tertile 2 ($n = 186$), 233 ≤ T2 < 253 µmol/L	Fructosamine Tertile 3 ($n = 155$), T3 ≥ 253 µmol/L	p Value[b]	Glycated Albumin Tertile 1 ($n = 169$), T1 < 0.45 g/dL	Glycated Albumin Tertile 2 ($n = 185$), 0.45 ≤ T2 < 0.53 g/dL	Glycated Albumin Tertile 3 ($n = 171$), T3 ≥ 0.53 g/dL	p Value[b]
Age, y	82.6 (3.2)	82.1 (2.6)	82.7 (3.5)	83 (3.2)	.01	82 (2.8)	83 (3.1)	83 (3.5)	.13
White race	488 (93.0)	172 (93.5)	174 (93.6)	142 (91.6)	.74	159 (94.1)	176 (95.1)	153 (89.5)	.09
Education, y	13.0 (2.7)	13.1 (2.9)	12.9 (2.6)	13.1 (2.5)	.71	13.3 (2.8)	13.1 (2.6)	12.7 (2.6)	.08
Alcohol, drinks/wk	1.3 (3.0)	1.6 (3.4)	1.4 (3.0)	1.0 (2.2)	.73	1.8 (3.4)	1.5 (3.3)	0.64 (1.9)	<.001
Current smoker	7 (1.3)	3 (1.6)	1 (0.5)	3 (1.9)	.48	2 (1.2)	3 (1.6)	2 (1.2)	.91
Walk for exercise	222 (42.4)	63 (34.2)	83 (44.6)	76 (49.4)	.01	67 (39.6)	90 (48.7)	65 (38.2)	.10
BMI, kg/m^2	27.3 (4.7)	28.6 (4.7)	26.7 (4.5)	26.4 (4.5)	<.001	27.7 (4.7)	27.1 (4.6)	27.1 (4.7)	.33
Hypertension	304 (57.9)	105 (57.1)	111 (59.7)	88 (56.8)	.83	105 (62.1)	99 (53.5)	100 (58.5)	.26
Depressive symptoms	38 (7.2)	15 (8.2)	12 (6.5)	11 (7.1)	.82	14 (8.3)	8 (4.3)	16 (9.4)	.15
History of stroke	45 (8.6)	17 (9.2)	17 (9.1)	11 (7.1)	.74	14 (8.3)	12 (6.5)	19 (11.1)	.29
History of heart attack	54 (10.3)	24 (13.0)	17 (9.1)	13 (8.4)	.30	18 (10.7)	18 (9.7)	18 (10.5)	.95
Baseline sMMSE	25 (1.35)	25 (1.1)	25 (1.5)	25 (1.4)	.86	25 (1.0)	25 (1.4)	25 (1.5)	.13
Baseline Trails B, s	129 (62.5)	129 (60.4)	128 (60.5)	132 (67.4)	.98	121 (53.5)	136 (66.9)	131 (65.2)	.08

Note. BMI = Body mass index, sMMSE = short modified Mini-Mental State Examination; Trails B = Trailmaking test, Part B.

[a]Values are mean (standard deviation) or N (%).[b]p value by chi-squared test for dichotomous variables, analysis of variance for normally distributed continuous variables, and Kruskal–Wallis tests for skewed continuous variables.

Table 2. Five-Year Change in Trails B and sMMSE by Glycated Peptide Level[a,b]

Mean 5-y Change								
	sMMSE				Trails B (s)			
	Crude	*p* Value	Adjusted[c]	*p* Value	Crude	*p* Value	Adjusted[b]	*p* Value
Fructosamine								
Low	−1.6 (3.3)	.424	−1.6 (3.4)	.587	47.1 (95.0)	.012	49.6 (95.7)	.046
High	−1.8 (3.3)		−1.8 (3.3)		68.9 (94.2)		67.3 (94.1)	
Glycated albumin								
Low	−1.5 (3.3)	.200	−1.5 (3.3)	.367	51.7 (94.0)	.103	53.0 (93.5)	.174
High	−1.8 (3.3)		−1.8 (3.3)		66.1 (95.2)		65.0 (94.0)	

Note: sMMSE = short modified Mini-Mental State Examination; Trails B = Trailmaking test, Part B.

[a]Values are mean (standard deviation). [b]Upper two tertiles set as "high" with lowest tertile as "low." [c]Multivariate model adjusted for education, age, race, physical activity, BMI, heart attack, hypertension, and stroke.

implementing prevention strategies. A few novel therapies targeting the formation of glycated albumin have shown promise in animal models, reducing not only the target molecule but the downstream expression of inflammatory markers (9).

Despite the advantages of examining this association in a large prospective study, we had several limitations. The SOF cohort primarily consists of Caucasian women, which limits the generalizability of our findings. Additionally, we did not have fasting blood glucose or hemoglobin A1c measures to account for cases of undiagnosed diabetes, though we would expect the prevalence of such cases to be relatively low among SOF participants, who are generally well connected to health care

Our findings suggest that higher glycated peptides are associated with poorer cognitive outcomes in older women. Future studies are needed to assess the clinical value of specific glycated peptides in identifying at-risk individuals and developing targeted interventions.

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Conflict of Interest

The authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements) or nonfinancial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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