Dietary advanced glycation end products are associated with decline in memory in young elderly

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Evidence suggests that advanced glycation end products (AGEs) contribute to cognitive decline (Yaffe et al., 2011). AGEs encourage the formation and deposition of neurofibrillary tangles and amyloid plaques, the hallmarks of Alzheimer's Disease (AD). AGEs also appear to increase the levels and toxicity of beta-amyloid (Li et al., 2012; Li et al., 2013), higher levels of which are associated with accelerated memory decline in individuals with both normal cognition and mild cognitive impairment (Lim et al., 2014).

Numerous endogenous AGEs have been implicated in cognitive decline. AGE precursor methylglyoxal (MGO) has been found to be associated with poorer cognition and cerebral atrophy in older adults (Srikanth et al., 2012). As detailed below, Beeri et al. (2011) *reported a decline in performance on the Mini Mental State Exam (MMSE) with higher levels of serum methylglyoxal (sMG). Albumin, a protein abundant in serum and cerebrospinal fluid, is found in higher glycated levels in AD patients compared to controls* (Ramos-Fernández, et al., 2014). Higher levels of the AGE N^ε-(carboxymethyl)-lysine (CML) are associated with severity of cognitive impairment in people with cerebrovascular disease, suggesting a relationship between AGEs and vascular dementia (Southern, et al., 2007). Finally, individuals with high levels of urinary pentosidine demonstrated greater decline on the digit symbol substitution test in older adults with and without diabetes (Yaffe et al., 2011).

Exogenous dietary AGEs (dAGEs) are found in higher levels in animal-derived foods and high-and dry-heat processed foods (Uribarri, 2010) and are associated with elevated circulating AGE levels (Uribarri, 2010). *Clarifying the relationship between exogenous and endogenous AGEs and cognitive decline may provide promising directions for addressing and treating AD and vascular dementia.*

We reported higher levels of sMG to be associated with cognitive decline, as determined by the Mini Mental State Exam (MMSE), a screen for cognitive impairment (Beeri et al.,

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2011), in a sample of very elderly that were cognitively normal at baseline and followed over time. Here we examined the relationships of dAGE and sMG with cognitive domains in substantially younger elderly, also cognitively normal at baseline, assessed with a broad neuropsychological battery.

dAGEs were estimated by using a published database as described in Vlassara et al. (2009). Methods to measure sMG, sociodemographic and cardiovascular risk factors and statistical analyses were the same as described in Beeri et al. (2011). Forty nine subjects participating in a study on the relationships of AGEs with inflammatory/cardiovascular risk factors (R37 AG023188), who had baseline assessments for dAGE, sMG, sociodemographic (age, sex, education), and cardiovascular (diabetes status, blood pressure, BMI, APOE genotype), were assessed for cognitive outcomes.

Subjects averaged 71.0 (±8.1 S.D.) years of age, 15.9 (2.5) years of education, at baseline and had 35.9 (±13.5) months of follow-up. At baseline, their mean dAGE was 11.9 AGE Eq/d (±6.9), their mean sMG was 0.91 nmol/ml (±0.21 nmol/ml), BMI 25.5 (±4.3), and 76% of the sample were female. The average MMSE at baseline was 28.9 (±1.6) reflecting a cognitively normal sample. Compared to Beeri et al. (2011), subjects averaged 12 years younger, but years of education, length of follow-up, baseline sMG, and BMI were very similar.

Factor analysis summarized the neuropsychological measures into four domains by summing z-scores (reversed if necessary): attention (diamond and letter cancellation), executive (Trails A and B), memory (immediate and delayed recall, recognition), and language (animal fluency, similarities, Boston). Mixed regression model were used to assess the effect of baseline dAGE and sMG on the association between cognitive domain measures and time, controlling for sociodemographic and cardiovascular risk factors.

There was a significant interaction between dAGE and month of follow-up for memory scores—for each 1 unit increase in natural log of baseline dAGE, there was a decrease of .035 in the monthly rate of change of memory scores ($p = 0.012$). For descriptive purposes, Figure 1 presents the predicted memory scores over time for baseline dAGE levels of 1.6, 2.4, and 2.9 (the 10th, 50th, and 90th percentiles, respectively. Baseline dAGE was not a significant effect modifier of the associations between other neuropsychological measures and month of follow-up (Table 1). Interactions between sMG and month of follow-up were also significant for attention (p=.017). dAGE and sMG were highly correlated (r=.62; p<.001) but including each of them as covariates in the analysis of the other did not affect the results whatsoever.

To the best of our knowledge, this is the first report showing that high dAGE levels were associated with a faster rate of decline in memory over time in initially non-demented young elderly. Consistent with this result and with our previous report using a global measure of cognition, high sMG was associated with faster rate of decline in attention. dAGEs and sMG were not related to other cognitive factors in this small sample.

Higher levels of AGEs likely contribute to AD (Yaffe et al., 2011). Memory impairment, the primary symptom of AD, has been found to be linked to serum markers for AGEs (Srikanth

et al., 2013). *AGEs increase aggregation and cytotoxicity of amyloid-β* (Li et al., 2012; Li et al., 2013) *and are found in higher levels in individuals with AD* (Krautwald & Munch, 2010). dAGEs are strongly connected to elevated circulating AGEs (Uribarri, 2010), and thus it is plausible that through increases in circulating AGEs, they affect cognition deleteriously. However, including dAGE as a covariate in the sMG analysis and vice-versa did not alter the results, suggesting that dAGEs and circulating AGEs have unique contributions to cognitive decline.

Increased baseline sMG levels were found to be related to attentional decline. Since the attention tests were all timed, our results suggest that high sMG may negatively affect processing speed (McGuinness et al., 2010). Impairments in attention and processing speed have been linked to cerebrovascular disease (Wiederkehr et al., 2009) and its risk factors, such as metabolic syndrome (Segura et al., 2009), which are associated with dementia (Wiederkehr et al., 2009; Segura et al., 2009). AGEs accumulate in, and thicken and stiffen, vascular walls, increasing risk of hypertension (Goh & Cooper, 2008) potentially leading to cognitive impairment via cerebrovascular disease.

Since subjects were cognitively normal at baseline, our findings suggest that elevated dAGEs may negatively impact memory before clinical symptoms of cognitive decline are expressed. A low-AGE diet may reduce circulating AGEs (Cai et al., 2013; Vlassara et al., 2009; Uribarri et al, 2010), potentially providing a simple intervention by which risk for cognitive compromise may be reduced. Since individuals with diabetes have higher circulating AGEs (Uribarri et al., 2010), our results suggest an explanation for the higher rates of cognitive decline and AD in diabetes (Krautwald & Munch, 2010; McCrimmon, Ryan, & Frier, 2012).

The study is limited by the small number of subjects and by use of a convenience sample but is strengthened by its longitudinal design, a broad neuropsychological battery that permits assessment of several cognitive domains, and by numerous, directly measured, potential confounders that were accounted for.

Acknowledgments

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Highlights

- Advanced glycation end products are associated cognitive decline.

- High levels of dietary AGEs (dAGEs) are associated with faster decline in memory.

- High serum methylglyoxal levels are associated with faster decline in attention.

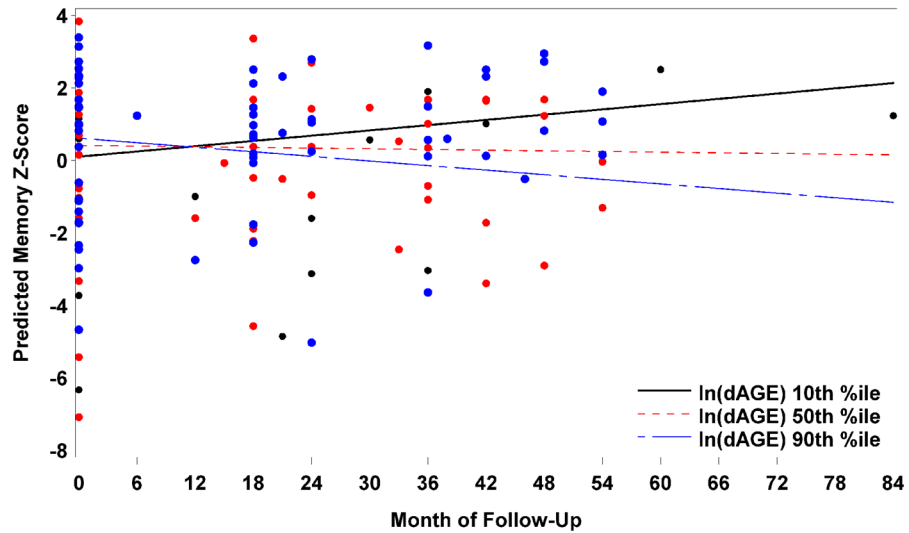- Modifying AGEs in the diet may be a strategy to diminish cognitive compromise.

Figure 1.
Predicted memory scores over time for 10th, 50th and 90th percentile of baseline dietary AGE (dAGE) – adjusted for sex, age, education, diabetes, systolic blood pressure, diastolic blood pressure, APOE4, and BMI. The points on the plot represent the observed memory scores.

Table 1

Mixed Regression Model Estimates for interaction of baseline dAGE and sMG with time for cognitive domains, adjusted for months of follow-up, baseline of the cognitive outcome, age, years of education, sex, diabetes, systolic and diastolic blood pressure, APOE4 genotype, and BMI.

Outcome		Estimate	SE	T-value	P-value
Memory	sMG	−0.04847	0.03380	−1.43	0.1560
	dAGE	−0.03465	0.01348	−2.57	0.0123[*]
Attention	sMG	0.04644	0.02059	2.26	0.0273[*]
	d AGE	0.008015	0.008716	0.92	0.3610
Language	sMG	−0.03894	0.03297	−1.18	0.2416
	dAGE	−0.00226	0.01403	−0.16	0.8725
Executive	sMG	−0.00791	0.03969	−0.20	0.8425
	dAGE	0.01439	0.01619	0.89	0.3771
MMSE	sMG	−0.05648	0.04626	−1.22	0.2281
	dAGE	−0.00625	0.01869	−0.33	0.7398

[*] indicates p<.05

Table 2

Participant characteristics

Characteristic	Mean	SD	Minimum	Maximum
Follow-up Months	35.94	13.50	15.00	84.00
dAGE	11.88	6.87	3.80	35.25
sMG	0.91	0.21	0.46	1.36
Age at baseline	70.99	8.06	60.00	89.69
Years of education	15.88	2.47	10.00	20.00
Systolic blood pressure	126.41	16.05	83.00	164.00
Diastolic blood pressure	69.16	8.94	49.25	90.00
BMI	25.47	4.33	16.00	34.50
Diabetes	3 (6%)			
Female	37 (76%)			
APOE4	9 (18%)			
Baseline MMSE	28.90	1.56	24.00	30.00
Baseline memory	0.11	2.49	−7.08	3.39
Baseline attention	0.06	1.81	−2.88	4.21
Baseline language	0.01	3.65	−13.95	4.18
Baseline executive	−0.17	1.97	−6.15	2.37