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Advanced glycation end products, diabetes, and the brain

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Type 2 diabetes is associated with declines in cognition, including learning and memory, mental flexibility, and mental speed. The degree of decrement tends to be modest and evolves slowly as a person ages. However, some patients diagnosed with type 2 diabetes experience a different course, with increased risk of more severe cognitive deficits including Alzheimer disease (AD) or vascular dementia, suggesting different processes and possibly different risk factors and underlying mechanisms or intermediaries.¹

Among the possible intermediaries of brain injury in persons with diabetes are advanced glycation end products (AGEs), i.e., products resulting from chemical reactions occurring in long-lived tissue proteins after chronic exposure to hyperglycemia. AGEs damage organs, including the brain, by increasing oxidative stress and inflammation. Some suggest that AGEs contribute to the aging phenotype by accelerating multisystem decline.² AGEs may be linked to the current epidemic of diabetes and its comorbidities.^{3,4} AGEs may be an underlying mechanism for pathologic synergism of diabetes and both AD⁵ and vascular dementia.⁶

AGEs are a heterogeneous group of macromolecules formed when sugars react with proteins, lipids, and nucleic acids.² In vivo, these molecules form through a process known as glycation, the level of which depends on the duration of hyperglycemia and the half-life of the protein of interest. Most clinicians appreciate this process as the one responsible for “glycating” hemoglobin (hemoglobin A_{1C}). Because the half-life of hemoglobin is 60–90 days, glycated hemoglobin provides an objective marker of antecedent glycemic control for the previous 2–3 months. However, if turnover of tissue protein is very slow (for example, as occurs in proteins such as myelin in nerves), the glycation reaction continues to a later stage of complex crosslinks known as AGEs.⁷ Prominent AGEs include N-ε-carboxymethyl-lysine (CML), pentosidine, and glucodepane.²

Endogenous AGEs are formed continuously by the human body and accumulate in higher levels

among the elderly and in persons with diabetes or renal disease. Exogenous AGEs are ingested in foods prepared by deep frying and dry cooking methods that require high temperatures.³ AGEs are widely distributed in the body, tending to affect the vascular basement membrane and extracellular matrices. They localize in brain tissue and are found in neurofibrillary tangles and senile plaques of patients with AD. AGEs enter brain cells and activate the receptor RAGE, which upregulates inflammatory cytokines, adhesion molecules, and its own receptors leading to chronic inflammation, increased oxidative stress, and tissue damage.⁸

Persons with diabetes have a greater deposition of brain AGEs and RAGE, which may mediate a common proinflammatory pathway in neurodegenerative disorders.⁹ Immunohistochemical studies of human postmortem samples showed brains of patients with the combination of AD and diabetes had higher AGE levels, increased numbers of β-amyloid dense plaques, higher RAGE-positive and tau-positive cells, and major microglial activation compared to brains from patients with AD alone. These findings suggest that AGEs may promote an oxidative stress vicious cycle, which can explain the severe progression of patients with a combination of diabetes and AD.⁵

Also, CML staining was higher in postmortem cortical neurons and vessels and was associated with severity of cognitive impairment among older adults with a history of diabetes and cerebrovascular disease but minimal AD pathology, suggesting accumulation of AGEs may contribute to vascular dementia.⁶

In this issue of *Neurology*®, Yaffe et al.¹⁰ describe the relationship between levels of the AGE pentosidine, measured in urine, and cognitive aging in 920 elders without dementia (mean age 74) with and without diabetes. Pentosidine concentration, analyzed in tertiles, and cognitive performance were measured at baseline and repeatedly over 9 years. The authors found poorer Digit Symbol Substitution Test (DSST) scores but no differences in Modified

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Mini-Mental State Examination (3MS) scores at baseline among older adults in the higher pentosidine tertile. At 9-year follow-up, there were significant declines on the 3MS and DSST. After adjustment for demographic variables, hypertension, cardiovascular disease, estimated glomerular filtration rate, and diabetes, only 9-year declines on the 3MS remained significant. Similarly, unadjusted logistic regression models showed greater likelihood of 9-year decline on the 3MS and DSST for those in the mid and higher tertiles. After adjustment (as above), odds of decline on the DSST alone remained significant. Elders with diabetes exhibited greater decline in 9-year cognitive change scores than those without diabetes (figure in Yaffe et al.¹⁰), but the interactions between pentosidine tertile and diabetes status on cognition were not significant.

The study by Yaffe et al. presents novel findings for an association between urinary pentosidine and cognitive decline among a large, diverse elderly cohort without dementia. Urinary pentosidine, which is noninvasively and inexpensively sampled, would be an ideal biomarker of diabetes-related brain injury, compared to procedures typically used to assess the impact of vascular risk factors on the brain.

The study was not without weaknesses. The relationship between pentosidine level and cognition did not differ between persons with and without diabetes. This does not mitigate the importance of AGEs in cognitive decline, since they seem to be relevant to all elderly, with and without diabetes, but it does tend to weaken the argument for accumulation of AGEs in the brain as a possible mechanism uniquely linking diabetes to cognitive impairment. The authors suggest the lack of interaction may have been due to advanced age of the participants. An alternative explanation would be that the elders with diabetes who participated in the Health ABC study had relatively low AGE levels. Furthermore, the available cognitive measures limit the scope of findings. The 3MS is sensitive to global cognitive decline and the DSST is sensitive to attention, concentration, and psychomotor speed. Unfortunately, a sensitive measure of memory was not available.

Future studies should examine whether risk for cognitive decline varies by AGE levels among middle-aged adults with and without diabetes. Healthy middle-aged adults would not be expected to have accumulated the same level of AGEs as that demonstrated by the elderly participants in the present study.

The literature suggests a keen interest in AGEs, diabetes, and multisystem damage including the nervous system. Some hypothesize that the time is near for treatment of those at greatest risk for accumulation of AGEs, either with diet or pharmaceutical intervention, e.g., AGE breakers or AGE inhibitors. At present, large clinical trial data are lacking. Perhaps the convergence of AGEs, diabetes, and the brain would benefit from a translational approach.

AUTHOR CONTRIBUTIONS

Dr. Coker: drafting/revising the manuscript, analysis or interpretation of data. Dr. Wagenknecht: drafting/revising the manuscript.

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DISCLOSURE

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