

UC Irvine

UC Irvine Previously Published Works

Title

In reply

Permalink

<https://escholarship.org/uc/item/2n78s1ht>

Journal

Journal of the American Geriatrics Society, 45(5)

ISSN

0002-8614

Authors

Nielson, KA
Sandman, CA
Mulnard, RA
[et al.](#)

Publication Date

1997-05-01

DOI

10.1111/j.1532-5415.1997.tb03109.x

Copyright Information

This work is made available under the terms of a Creative Commons Attribution License, available at <https://creativecommons.org/licenses/by/4.0/>

Peer reviewed

In reply: Non-insulin-dependent diabetes mellitus (NIDDM) and Alzheimer's disease (AD) are both devastating diseases of older adults. In response to suggestions that they may actually be dissociated, we investigated NIDDM and Apolipoprotein-E (Apo-E) genotype in our demented patients. We found a strong dissociation, such that NIDDM occurred in patients meeting criteria for vascular and mixed dementia, but not in those with "pure" AD.¹

The Apo-E data also suggested a dissociation between these disease processes. The E4 allele occurred frequently in AD (71%) as expected, but it occurred with only average frequency in NIDDM (39%). Importantly, in mixed dementia cases, E4 occurred frequently overall (55.6%) and in those with NIDDM (60%). Based on these results and the association of NIDDM with vascular dementia,² we hypothesized that those with NIDDM develop mixed dementia and, thus, are not diagnosed for AD.¹

Responses to our paper have stimulated other explanations as well.^{3,4} Halter³ suggests that the weight loss associated with AD may reduce insulin resistance and prevent

hyperglycemia. However, weight change is more common in the advanced stages of AD,⁵ and in our experience, it is associated with increased appetite, lack of satiety, and a preference for "sweets." These symptoms may reflect hypothalamic dysfunction occurring with progressive neurodegeneration. Halter also suggests the converse: perhaps hyperglycemia enhances accessibility to "brain fuel" and reduces the rate of degenerative lesion deposition. The latter is an intriguing possibility that needs further investigation, but the suggestion that chronic hyperglycemia may be beneficial is refuted by many reports of negative cognitive consequences in NIDDM.^{6,7}

We suggest that chronic hyperglycemia is a risk factor for developing vascular dementia with AD. This could arise by accelerated deposition of advanced glycation end-products (AGEPs) and oxidative damage.^{8,9} AGEPs accumulate in long-lived proteins through nonenzymatic reactions of glucose and other reducing sugars with free amino groups, particularly the ϵ -amino group lysine. These products are found in plaques, tangles, and vessels, and as they form, can cross-link adjacent peptides and proteins and thereby initiate the neural and vascular cell degeneration.¹⁰ Positive feedback mechanisms can drive these processes, including β -amyloid, which binds to the RAGE receptor, stimulating oxidative damage and inflammatory responses.¹¹ Thus, it is possible that common pathways exist for both vascular and neuronal damage, making those with NIDDM at high risk for mixed dementia.

Landi et al⁴ suggest that oral hypoglycemic agents (sulfonylureas) used for treating NIDDM can inhibit ATP-sensitive K^+ channels, much like tacrine does, thereby protecting NIDDM patients against AD. While this clearly merits further study, there is no evidence that tacrine slows degeneration in AD. Perhaps it is more important that oral hypoglycemic agents may mask or slow the onset of the clinical symptoms of AD, potentially leading to late or erroneous diagnosis.

Mixed dementias are relatively common (approximately 22% of our clinical population) and are often overlooked. The factors that drive this condition represent a critical area for further research, and the diabetes condition is one of the first leads into the problem.

*Kristy A. Nielson, PhD
Marquette University
Milwaukee, WI*

*Curt A. Sandman, PhD
Ruth A. Mulnard, DNSc
Carl W. Cotman, PhD
Institute for Brain
Aging and Dementia
University of California, Irvine
Irvine, CA*

REFERENCES

1. Nielson KA, Nolan JH, Berchtold NC et al. Apolipoprotein-E genotyping of diabetic dementia patients. Is diabetes rare in Alzheimer's disease? *J Am Geriatr Soc* 1996;44:897-904.
2. Skoog I. Risk factors for vascular dementia: A review. *Dementia* 1994;5:137-144.
3. Halter JB. Alzheimer's disease and non-insulin-dependent diabetes mellitus: Common features do not make common bedfellows. *J Am Geriatr Soc* 1996;44:992-993.

4. Landi F, Bernabei R, Gambassi G. Non-insulin-dependent diabetes mellitus and Alzheimer's disease. *J Am Geriatr Soc* 1996;45:654.
5. White H, Pieper C, Schmader K, Fillenbaum G. Weight changes in Alzheimer's disease. *J Am Geriatr Soc* 1996;44:265-272.
6. Meneilly GS, Cheung E, Tessier D et al. The effect of improved glycemic control on cognitive functions in the elderly patient with diabetes. *J Gerontol* 1993;48:M117-121.
7. Richardson JT. Cognitive function in diabetes mellitus. *Neurosci Biobehav Rev* 1990;14:385-358.
8. Smith MA, Taneda S, Richey PL et al. Advanced maillard reaction end products are associated with Alzheimer's disease pathology. *Proc Natl Acad Sci USA* 1994;91:5710-5714.
9. Smith MA, Sayre LM, Perry G. Diabetes mellitus and Alzheimer's disease: Glycation as a biochemical link (letter). *Diabetologia* 1996;39:247.
10. Cotman CW, Cribbs DH, Anderson AJ. The B-amyloid model of Alzheimer's disease. Conformation change, receptor cross-linking, and the initiation of apoptosis. In: Wasco W, Tanzi RE, eds. *Molecular Mechanisms of Dementia*. Totowa, NJ: Humana Press, 1996:73-90.
11. Yan SD, Chen X, Fu J et al. RAGE and amyloid-B peptide neurotoxicity in Alzheimer's disease. *Nature* 1996;382:685-691.