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] Halter[3] suggests that the weight loss associated with AD may reduce insulin resistance and prevent

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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 in 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 al[4] 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.

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