Metabolic disturbance and dementia: A modifiable link

Dietary changes to correct hyperinsulinemia might slow cognitive decline

In addition to increasing patients’ risk for cardiovascular disease, stroke, and cancer, obesity and metabolic disturbance contribute to age-related cognitive decline and dementia. In particular, insulin resistance and hyperinsulinemia promote neurocognitive dysfunction and neurodegenerative changes during the extended, preclinical phase of Alzheimer’s disease (AD). However, with dietary modification it may be possible to resensitize insulin receptors, correct hyperinsulinemia, and improve memory function.

Metabolic disturbance and neurodegeneration

In the United States, 5.4 million people have AD, and there will be an estimated 16 million cases by 2050. Simultaneously we are experiencing an epidemic of metabolic disturbance and obesity. Approximately, 64% of adults in the United States are overweight (body mass index [BMI]: 25.0 to 29.9 kg/m²) and 34% are obese (BMI: ≥30 kg/m²). By 2030, 86% of adults will be overweight and 51% will be obese. This confluence of epidemics is not coincidental but instead reflects the fact that metabolic disturbance is a fundamental factor contributing to cognitive decline and neurodegeneration.

Ninety-six percent of AD cases are classified as late onset, sporadic AD, occurring after age 64. Mild cognitive impairment (MCI) is a clinical construct that entails greater than expected memory impairment for the patient’s age and identifies older adults who are at increased risk for dementia. MCI represents the first clinical manifestation of neurodegeneration for a subset of patients who will progress to AD. MCI is distinguished from age-associated memory...
Insulin resistance and dementia

Hyperinsulinemia is the precursor to T2DM. However, hyperinsulinemia is not well recognized in clinical contexts and generally is not a treatment target. Nonetheless, it contributes to several health problems, and insulin resistance in middle age is associated with age-related diseases such as hypertension, coronary artery disease, stroke, and cancer, while insulin sensitivity protects against such disorders.

Chronic insulin resistance may contribute more to dementia development than T2DM because of the extended period of hyperinsulinemia that precedes T2DM onset. In population studies, insulin resistance syndrome increases risk for developing AD independent of apolipoprotein E (APOE e4) allele status, and in a longitudinal study, the risk for AD solely attributable to peripheral hyperinsulinemia was up to 39%. Being overweight in midlife increases risk for dementia in late life, and APOE e4 allele status does not contribute additional risk after accounting for BMI.

Middle-aged individuals with hyperinsulinemia show memory decline, and obesity in middle age was associated with greater cognitive impairment after 6-year follow-up. Even in older adults who seem cognitively unimpaired, BMI and fasting insulin are positively correlated with atrophy in frontal, temporal, and subcortical brain regions, and obesity is an independent risk for atrophy in several brain regions, including the hippocampus.

Compared with healthy older adults, individuals with AD have lower ratios of cerebrospinal fluid to plasma insulin. This lower ratio reflects the peripheral-to-central gradient of insulin levels in AD

### Table

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<tr>
<th>Waist circumference and metabolic factors in 122 older adults with MCI&lt;sup&gt;a&lt;/sup&gt;</th>
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<tbody>
<tr>
<td>Metabolic indicator</td>
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<tr>
<td>Mean (SD) fasting glucose, mg/dL</td>
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<td>Mean (SD) fasting insulin, µIU/mL</td>
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<td>Mean (SD) waist, cm</td>
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<td>Waist-insulin correlation</td>
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<sup>a</sup>Older adult patients (age ≥68) with subjective memory complaints were recruited from the community and screened with instruments assessing everyday functioning and objective memory performance to establish the presence of MCI.

MCI: mild cognitive impairment; SD: standard deviation.
and suggests an etiological role for such metabolic disturbance. Insulin resistance has downstream effects that potentiate neurodegenerative factors, and central hypoinsulinemia can accelerate neurodegenerative processes and cognitive decline. Brain insulin plays a direct role in regulating proinflammatory cytokines and neurotrophic and neuropsychiatric factors essential for memory function. Insulin degrading enzyme, which varies with insulin levels, regulates the generation and clearance of amyloid β (Aβ) from the brain.

Hyperinsulinemia typically is evident in increasing waist circumference and body weight. Waist circumference of ≥100 cm (39 inches) is a sensitive, specific, and independent predictor of hyperinsulinemia for men and women and a stronger predictor than BMI, waist-to-hip ratio, and other measures of body fat. Unpublished data derived from our clinical research with MCI subjects supports the association of metabolic disturbance with age-related cognitive decline. Our subjects are recruited from the community on the basis of mild memory decline and—other than excluding those with diabetes—weight and metabolic status are not considered in evaluating individuals for enrollment. The Table (page 18) contains data on waist circumference and metabolic function in 122 older adults (age ≥68) with MCI. On average, these individuals exhibited fasting insulin values in the hyperinsulinemia range and elevated fasting glucose levels that indicated borderline diabetes. Waist circumference also was high, indicating excessive visceral fat deposition. We also observed a relationship between waist circumference and insulin, a consistent observation in older adults with memory decline. These data would not be surprising in any sample of older adults because of the population base rates for these conditions. However, we also found that waist circumference was a significant predictor of memory performance in patients with MCI. Abdominal adiposity is highly correlated with intrahepatic fat. Given this and recent indications that Alzheimer’s-type neuropathologic factors are generated in the liver,

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Insulin resistance and dementia

Clinical Point

Reducing insulin by restricting calories or maintaining a ketogenic diet has been associated with improved memory function.

Dietary interventions

There is no cure for dementia, and it is not clear when effective therapy might be developed. Prevention and risk mitigation represent the best means of reducing the impact of this public health problem. Researchers have proposed that interventions initiated when individuals have predementia conditions such as AAMI and MCI might stall progression of cognitive decline, and MCI may be the last point when interventions might be effective because of the self-reinforcing neuropathologic cascades of AD. Because central hypoinsulinemia may promote central inflammation, Aβ generation, and reduced neuroplasticity, approaches aimed at improving metabolic function (and in particular correcting hyperinsulinemia) could influence fundamental neurodegenerative processes. Dietary approaches to preventing dementia are effective, low-risk, yet underutilized interventions. Reducing insulin by restricting calories or maintaining a ketogenic diet has been associated with improved memory function in middle-aged and older adults.

Carbohydrate consumption is the principal determinant of insulin secretion. Eliminating high-glycemic foods, including processed carbohydrates and sweets, would sensitize insulin receptors and correct hyperinsulinemia. In addition, replacing high glyemic foods with fruits and vegetables would increase polyphenol intake. Epidemiologic evidence supports the idea that greater consumption of polyphenol-containing vegetables and fruits mitigates risk for neurocognitive decline and dementia. Preclinical evidence suggests that such protection may be related to neuronal signaling effects and anti-inflammatory and antioxidant actions. In addition, certain polyphenol compounds, such as those found in berries, enhance metabolic function. In a 12-week pilot trial, older adults with early memory changes (N = 9, mean age 76) who drank supplemental blueberry juice showed enhanced memory and improved metabolic parameters.

Dietary changes that preserve insulin receptor sensitivity can help ensure general health with aging and substantially mitigate risk for neurodegeneration. The Western diet is particularly insulinogenic and dietary habits are difficult to change. However, the substantial benefits, absence of adverse effects, and low cost make dietary intervention the optimal means of protecting against neurodegeneration and other age-related diseases. Embarking on such a program early in life would be best, although late-life intervention can be effective.

Related Resources


Disclosure

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cognitive complaints show brain atrophy similar to that of amnestic MCI. Neurology. 2006;67(5):834-842.


**Bottom Line**

Insulin resistance and hyperinsulinemia drive neurodegeneration and increase risk for age-related cognitive decline and dementia. In the absence of effective pharmacotherapy, nutritional approaches that correct hyperinsulinemia offer the possibility of slowing or preventing progression of cognitive decline. Correcting hyperinsulinemia by eliminating high-glycemic carbohydrate foods may be the most robust intervention available to reduce dementia risk.