

# The Primary Care Guide To Understanding The Role Of Diabetes As A Risk Factor For Cognitive Loss Or Dementia In Adults

## 1. Introduction

Glucose intolerance is common in older individuals and this metabolic symptom can progress to Type II diabetes in older individuals. Type II diabetes is an integral part of the metabolic syndrome in midlife that increases the risk of cognitive loss in later life. Glucose intolerance and diabetes in midlife produce a two-fold increased risk of cognitive loss in later life (8). Older diabetic individuals are more likely to have hypertension, cardiovascular disease, and atherosclerosis that produce diseases associated with dementia, including heart disease and renal failure.

Primary care physicians can encourage middle aged individuals to comply with weight loss, exercise, and dietary discretion by discussing the potential benefit for late life cognitive function, especially those individuals with strong family histories for Alzheimer's disease (8), (9).

## 2. The Molecular Function Of Insulin In The Brain

Studies show substantial numbers of insulin receptors in the cerebral cortex and hippocampus of the human brain (10). Insulin receptors are linked to second messenger systems within neurons that may control the production of neurofibrillary tangles through the regulation of phosphorylation of the microtubule-associated protein "tau".

Insulin serves many functions in the human brain, including: 1) the regulation of glucose metabolism, 2) mediation of a neurotrophic effect, 3) signal transduction, and 4) modulation of neuroendocrine function. The role of insulin far exceeds simple regulation of glucose that is available to the cerebral cortex via the blood supply.

Brain insulin receptors are diminished in the cerebral cortex during normal aging; however, their density appears greater in persons with Alzheimer's disease versus aged-matched controls. This finding may suggest a compensatory upregulation of insulin receptors to compensate for insulin resistance (19).

The activity of insulin degrading enzyme (IDE) is diminished in brain tissue from Alzheimer's patients as compared to controls. This enzyme also metabolizes intracellular and extracellular A $\beta$  amyloid. Individuals with APOE 4 genes have diminished mRNA expression for IDE in the human hippocampus. Rodent models for Alzheimer's disease demonstrate that elimination of the IDE gene through knockout models increases relative concentration of A $\beta$  in the brain. Hyperinsulinemia can provoke increased markers for inflammation and beta amyloid protein in older humans (18).

## 3. Clinical studies of diabetes and dementia

Multiple studies have examined the relationship between glucose intolerance or diabetes and cognitive loss or Alzheimer's disease. The majority of studies demonstrate a modest

relationship of impaired glucose tolerance to either diminished cognitive function or risk for Alzheimer's disease. Although a few studies have questioned this result, the majority support the observation that diabetes is a risk factor developing dementia in later life (See **Table 1**).

**Table 1. The Relationship of Glucose Dysregulation on Diabetes Mellitus to Cognitive Function**

Study	n	Duration	Outcome	Refs
1	1811	30	History and duration ↑ risk	1
2	915	CS	Only minor ↓ cognitive function	2
3	999	4 yrs	↓ Cognitive function in white women	3
4	10963	6 yrs	↓ Cognitive function	4
5	6330	CS	+ relationship (1.3 / 1.0 to 1.9)	5
6	5647	15yrs	Associated with selective poor cognitive function	6
7	1455	15yrs	↑ Risk for dementia	7
8	5510	CS	↑ Insulin = ↓ cognitive function	11
CS – cross-sectional				

2513.94. Metabolic Syndrome

A comparison of cerebral spinal fluid findings from individuals with Alzheimer's disease versus age-matched controlled individuals demonstrates that Alzheimer's patients have diminished CSF insulin in contrast to increased serum insulin, suggesting increased insulin resistance in the brain.

Overall, cross-sectional and longitudinal studies suggest a relative, two-fold increased risk for developing cognitive loss in persons with glucose intolerance or diabetes. Individuals with metabolic syndrome, or diminished physical activity in midlife experience increased risk for developing dementia in later life (8). **CLICK HERE FOR MORE INFORMATION ON THE METABOLIC SYNDROME 2513.91.**

#### 4. Brain Pathology in Persons with Diabetes

The brains of elders with diabetes demonstrate a range of pathological findings to include increased risks for cerebral infarcts and small vessel disease, especially in those individuals with hypertension. Postmortem brain specimens from aging individuals with diabetes do not have greater densities of senile plaques than non-diabetic elders but they demonstrate increased rates of micro and macro infarcts. Demented individuals with both diabetes and APOE 4 genotype have the highest densities of neurofibrillary tangles and senile plaques at autopsy (12), (13). Elevated glycated hemoglobin A1 (HbA1c) may be correlated to accelerated atrophy in elders as demonstrated by brain imaging (17).

#### 5. Conclusion About the Relationship of Cognition and Diabetes

Systemic insulin dysregulation may accelerate damage in the aging human brain through several mechanisms, including: 1) increased glucose utilization, 2) increased oxidative stress, 3) accelerated tau phosphorylation, and 4) reduced insulin degrading enzyme that increases amyloid load in the brain (20). Randomized controlled studies to examine the

relative benefit of glucose control versus untreated diabetes will not be performed for obvious ethical and legal reasons. The best available information suggests that reduction of health risk factors for glucose intolerance in midlife through weight control, exercise, and dietary discretion may reduce the risk for late life diabetes. Aggressive management of hyperglycemia in later life may further reduce risk factors for dementia associated with glucose intolerance. Severe episodes of hypoglycemia also correlate to diminished cognitive function (14), (15). Careful management of blood sugars may slightly improve cognition in some elders. (16).

Primary care physicians are justified in advising middle-aged individuals and older patients that risk reduction for diabetes is one of many steps that may reduce risk of late life cognitive loss. Compliance data suggest that about half of diabetic patients are compliant with hypoglycemic agents and the promise of the brain benefit can be added to other potential protections for organs such as heart, eye, kidney, and others. This advice may particularly impact individuals with family histories for Alzheimer's disease or other types of dementia. **FOR MORE INFORMATION, CLICK HERE 2514.11.**

#### **Recommendations to Primary Care Physician**

1. Weight control and regular exercise may reduce the risk for diabetes and dementia.
2. Inform patients that risk reduction of glucose intolerance is a component of dementia prevention.
3. Meticulous control of blood sugars in diabetic patients may enhance cognition.
4. Severe or sustained hypoglycemia may be a risk factor for dementia.

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