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**Intranasal insulin and dulaglutide for cognition in metabolic syndrome MCI**

*This phase I clinical trial will evaluate the safety, tolerability and dose of the dual administration of insulin and another medication in individuals at risk for dementia.*

**Background**

Insulin is a hormone that helps the body maintain appropriate levels of blood sugar. Insulin can also be transported to the brain, where it helps maintain nerve cell energy levels and connections between nerve cells. Due to this important role in the brain, researchers believe insulin may also be associated with Alzheimer's disease progression. Past studies have shown that problems with how insulin sends signals in the brain, also known as "insulin resistance", could be associated with changes in brain cell networks and changes in memory and thinking observed in individuals with Alzheimer's. As a result, individuals with insulin resistance may be at greater risk for developing dementia.

Recent studies, including those led by Dr. Michal Schnaider Beeri and colleagues, have examined how a protein called glucagon-like peptide 1 (GLP-1) may promote the body's use of insulin and impact brain health. Using Alzheimer's-like mice and brain tissue from individuals who had Alzheimer's, the researchers found that compounds boosting GLP-1 activity (or GLP-1 "agonists") can reduce insulin resistance, promote the health of brain blood vessels, and improve brain function. Such compounds have also been shown to protect heart health and other factors that promote dementia.

**Research Plan**

Dr. Schnaider Beeri's team will now conduct a phase 1b/2a clinical trial with 80 older adults who have mild cognitive impairment (or MCI, a condition of subtle memory loss that may precede Alzheimer's) and metabolic syndrome (a general health condition that includes obesity, insulin resistance and high sugar levels in the blood). The study will have four groups: each individual will receive a combination therapy of both insulin and a GLP-1 agonist called

dulaglutide, or one of these medications, or none. This study will work to understand the feasibility, tolerability, and safety of combining the two treatments.

The primary outcome of this study is to evaluate the safety and tolerability of the combination of drugs. In secondary exploratory outcome measures, they will use cognitive tests and brain scans to assess how the combination treatment impacts memory, blood vessel function, and white matter in the brain (the primary wiring system of the brain that helps brain cells “talk” to one another). They will also take blood samples from the participants and examine how the therapy impacted levels of beta-amyloid and tau, both are hallmark brain changes seen in Alzheimer’s.

### **Impact**

Results from this study could inform larger clinical trials targeting insulin in the brain. It could also help shed new light on the complex role of insulin signaling in Alzheimer’s and other dementias.

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