The impact of insulin resistance on cognitive impairment and CSF biomarkers in Alzheimer's disease

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Introduction Insulin resistance (defined as the reduced efficacy of insulin in promoting glucose uptake and utilization in a targeted tissue) represents a key factor in the pathogenesis of diabetes and has recently been proposed as a modifiable risk factor for cognitive impairment and Alzheimer's disease (AD). The Homeostatic Model Assessment for Insulin Resistance (HOMA), easily obtained through a simple blood test, serves as a reliable surrogate marker of insulin resistance in humans.
The aim of this study is to investigate the influence of insulin resistance, as measured by HOMA, on CSF biomarkers for AD and cognitive performance in a cohort of individuals evaluated for cognitive impairment in a Memory Clinic setting.

Materials & Methods: One hundred and fifty consecutive individuals (mean age was 67.9 ± 8.2 years; 57% female) undergoing diagnostic evaluations for memory loss and cognitive impairment were enrolled. Subjects were categorized into AD (n=103) or non-AD (NAD;n=47). Subjects with diabetes (10 AD, 4 NAD) were excluded from the analyses. All participants underwent a comprehensive clinical evaluation, extensive neuropsychological assessments, and CSF biomarkers (Aβ42/40 ratio, p-tau181, t-tau), and HOMA (derived from fasting insulin and glucose levels) quantification. Group comparisons, correlations, and multivariate regression were performed.

Results: No significant differences in HOMA, insulin, blood glucose, CSF glucose, or related ratios were observed between the AD and NAD groups. Furthermore, insulin resistance was not significantly associated with CSF biomarkers (Figure 1).
However, within the AD continuum, individuals with dementia exhibited significantly higher insulin resistance than those with MCI (p=0.02), suggesting a link between insulin resistance and disease severity.
HOMA was significantly inversely correlated with MMSE score (p=0.004) across the entire cohort and in the AD group.
Moreover, multiple linear regression analyses adjusted for age, sex, education, and biomarker levels confirmed that insulin resistance independently predicted cognitive performance across several neuropsychological measures in the AD group, suggesting a link between insulin resistance and cognitive function within the AD continuum, particularly in executive function and language-related tasks, independent of amyloid and tau pathology (Figure 2).

Discussion & Conclusions: Although insulin resistance was not associated with CSF AD biomarkers, it was significantly associated with cognitive performance and disease severity in individuals within the AD continuum. These findings support the hypothesis that insulin resistance contributes to cognitive decline through mechanisms largely independent of core AD pathophysiology. Nevertheless, addressing insulin resistance may represent a promising avenue for therapeutic intervention or risk reduction in cognitive disorders.

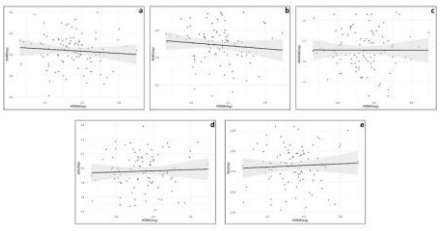

Figure 1. Correlations between HOMA and CSF biomarkers.
Correlations between HOMA and Aβ40 (a), Aβ42 (b), Aβ42/40 (c), p-tau (d) and t-tau (e) in the AD group. No significant associations were found.

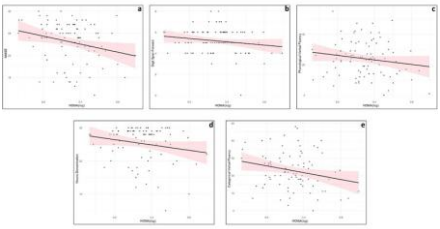

Figure 2. Associations between HOMA and neuropsychological assessments.
Significanct associations between HOMA and MMSE (a), Digit Span Forward (b), Phonological Verbal Fluency (c), Nouns Denomination (d), Categorical Verbal Fluency (e) in the AD group.

References

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