Differences in the Association of Peripheral Insulin with Cognitive Function in non-Diabetic AD Cases and Normal Controls

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Background

- Chronic hyperinsulinemia, a feature of T2DM and metabolic syndrome, increases the risk of cognitive impairment and AD.
- Increased insulin levels in the brain may improve AD symptoms.
- The role of peripheral insulin as a biomarker of increased AD risk and cognitive changes in AD needs further elucidation.

Objective

- To determine association between serum insulin and cognitive performance in AD cases and controls without type 2DM enrolled in the Texas Alzheimer's Research and Care Consortium (TARCC).

Methods

- **Participants:** 197 AD cases (25 with T2DM) and 198 normal controls (25 with T2DM) enrolled at 4 centers in Texas. After calculating descriptive statistics, we excluded the 50 T2DM cases from the analysis of insulinemia and cognitive function.
- **Measurements:** History of CVD and CVD risk factors, multiplexed serum (non-fasting) protein immunoassay, including insulin, lipid profile and HbA1c measurements performed by standard assays, APOE genotype.
- **Cognitive Domain/Tests:** MMSE, WMS Digit Span, Trails A and B, WMS Logical Memory I and II, Boston Naming and COWAT (FAS), WMS Visual Reproduction I and II, AMNART errors. Tests scored using MOANS norms.

Analysis:

- Linear regression was used to assess association of log transformed serum insulin and the performance in individual cognitive domains.
- Each model was adjusted for age, sex, years of education, and BMI.
- Cases and Controls were analyzed separately after interaction tests showed differences in association of insulin and cognitive outcomes on some tests. Participants with T2DM were excluded.
- Additional covariates were tested for impact on observed significant associations: history of CVD/CVD Equivalent (see definition in Table footnote), APOE genotype, HbA1c.

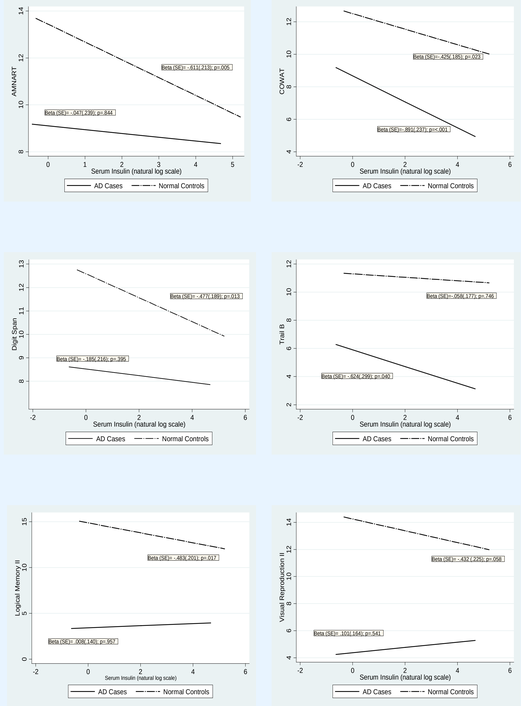
Results

- Higher insulin was associated with **worse** performance on AMNART, COWAT, Digit Span, LMI and LMII, and VRII in controls.
- Higher insulin was associated with **worse** performance on Trail B (only 97/172 cases tested) and COWAT in cases.
- MMSE, Boston Naming and Trails A were not affected by insulin levels in cases or controls.
- Adjustment for other covariates, or limiting the analysis to mild AD cases did not alter the findings.

Table 1. Characteristics of Cases and Controls

	AD Cases	Normal Controls	
	Mean (±SD) or Percent	Mean (±SD) or Percent	p
Covariates			
Age at Visit	77.41 (8.29)	70.42 (8.89)	<.001
Sex (% female)	34.52	32.82	.569
Education (yrs)	13.98	15.53	<.001
Hispanic (%)*	3.55	5.56	.340
ApoE 4 Genotype			
0 alleles	39.23	73.85	<.001
1 allele	45.86	23.59	
2 alleles	14.92	2.56	
Cardiovascular Risk Factors			
BMI (kilos/meters²)	25.70 (4.95)	27.48 (4.82)	<.001
Diabetes (%)	11.22	11.28	.681
CVD Equivalent**	48.22	46.46	.726
Total Cholesterol	210.12 (50.12)	209.36 (62.04)	.894
LDL Cholesterol	107.36 (40.17)	94.80 (39.28)	.002
HbA1c	5.74 (.65)	5.86 (.88)	.133
Serum Insulin (uIU/mL)	10.26 (13.87)	10.43 (17.84)	.913
Cognitive Scores			
MMSE	19.18 (6.22)	29.42 (.88)	<.001
AMNART Errors	8.77 (3.64)	12.11 (3.37)	<.001
COWAT	7.11 (3.13)	11.64 (2.74)	<.001
Boston Naming	6.33 (3.83)	11.92 (3.03)	
Digit Span	8.23 (2.97)	11.69 (2.78)	<.001
Trail A	6.08 (3.06)	10.34 (2.69)	<.001
Trail B	4.94 (3.31)	10.97 (2.54)	<.001
LM I	4.0 (2.42)	13.57 (2.75)	<.001
LM II	3.57 (1.84)	13.99 (2.63)	<.001
VR I	4.52 (2.74)	12.37 (3.20)	<.001
VR II	4.71 (2.14)	13.56 (3.13)	<.001

*<2 % of any other race in sample
**Calculated according to ATP III guidelines (history of MI, CHF, Diabetes, or any two of HTN, hyperlipidemia, or current smoking)



Conclusion

- The relationship between peripheral insulin and cognitive performance differs in AD cases compared to controls.
- Interventions to improve insulin sensitivity in AD cases may have different cognitive outcomes than in persons who have not developed AD.

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