

Relationship Of HbA1c With Biomarkers Of Alzheimer’s Disease

Sierra Alban¹, Maya Jayaram¹, Paul T. Kang², Marwan Noel Sabbagh, MD³.

¹Creighton University School of Medicine, Phoenix, AZ, USA, ²Department of Clinical Research and Public Health, Creighton University School of Medicine, Phoenix, AZ, USA, ³Neurology, Barrow Neurological Institute, Phoenix, AZ, USA.



BACKGROUND

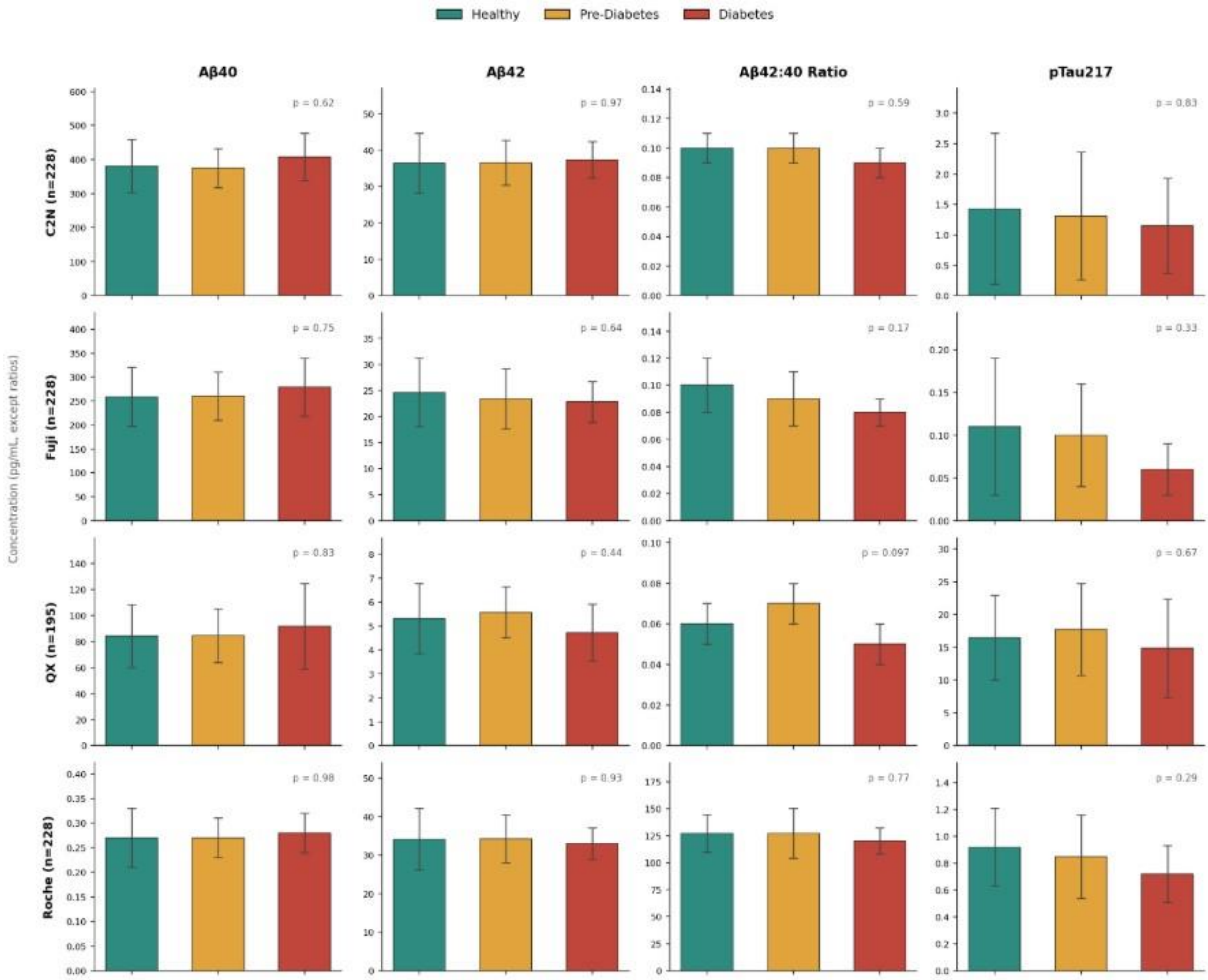
- Increased risk of Alzheimer’s disease (AD) has been linked to metabolic comorbidities, including type 2 diabetes (T2DM).
- This relationship is primarily mediated by metabolic or vascular factors, rather than neuropathological changes. T
- The relationship between hemoglobin A1c (HbA1c) as a marker for T2DM and biomarkers of AD is not well understood.
- We hypothesize that subjects with higher HbA1c will have increased amyloid-β and tau burden and increased white matter hyperintensities (WMH) as a marker for cerebrovascular disease.

METHODS

- Data were obtained from ADNI.
- Observational cohort of 1,266 participants.
- Subjects included in this study included cognitively unimpaired, mild cognitive impairment, and Alzheimer’s dementia,
- Subjects were further categorized by baseline HbA1c as non-diabetic (<5.7%), pre-diabetic (5.7-6.4%), or diabetic (≥6.5%).
- Outcomes included plasma amyloid-β (Aβ42, Aβ40, and Aβ42/40 ratio) and phosphorylated tau biomarkers (p-tau) across multiple assay platforms, amyloid and tau PET measures, cerebral white matter and meta-temporal volumetric measures, and WMH volume.
- Associations were evaluated using multivariable linear regression adjusted for follow-up time and demographic and clinical covariates.

Baseline Measurements				
Variables (n= 1,266)	Healthy (A1c < 5.7)	Pre-Diabetes (A1c: 5.7-6.4)	Diabetes (A1c: ≥ 6.5)	p-value
N (%)	594 (46.9)	546 (43.1)	126 (9.95)	
Age at First visit, years, (mean, SD)	68.55 (7.32)	69.95 (7.35) ¹	69.65 (6.81)	0.004
Sex				0.31
Male	226 (38.1)	230 (42.1)	54 (42.9)	
Female	368 (61.9)	316 (57.9)	72 (57.1)	
Race				<0.001
White	404 (68.0)	294 (53.9) ¹	52 (41.3) ²	
Black/African American	135 (22.7)	179 (32.8)	52 (41.3)	
Asian	26 (4.38)	42 (7.69)	13 (10.3)	
AI/AN	5 (0.84)	2 (0.37)	1 (0.79)	
NH/PI	0 (0.0)	0 (0.0)	0 (0.0)	-----
More than 1	12 (2.02)	25 (4.58)	5 (3.97)	
Unknown	12 (2.02)	4 (0.73)	3 (2.38)	
Ethnicity				0.95
Non-Hispanic/Latino	528 (88.9)	489 (89.5)	112 (88.9)	
Hispanic/Latino	64 (10.8)	56 (10.3)	14 (11.1)	
Education				0.087
Highschool or Less	93 (15.7)	90 (16.5)	30 (23.8)	
Associates/Undergrad Degree	246 (41.5)	229 (41.9)	57 (45.2)	
Graduate or Professional Degree	254 (42.8)	227 (41.6)	39 (30.9)	
Height, cm (mean, SD)	169.26 (25.8)	167.97 (21.2)	167.93 (10.1)	0.60
Weight, kg (mean, SD)	76.52 (17.2)	81.92 (19.9) ¹	88.47 (21.9) ^{2,3}	<0.001
BMI (n, %)				<0.001
Underweight/Normal	227 (38.41)	153 (28.2) ¹	18 (14.4) ^{2,3}	
Overweight	215 (36.4)	199 (36.7)	47 (37.6)	
Obese	126 (21.3)	150 (27.7)	46 (36.8)	
Severely obese	23 (3.89)	40 (7.38)	14 (11.2)	

One-Way ANOVA to compare continuous variables. Chi-squared Or Fisher’s Exact Test to compare categorical variables.
¹Statistical difference between Healthy and Pre-Diabetic following Bonferroni Correction (p < 0.016)
²Statistical difference between Healthy and Diabetic following Bonferroni Correction (p < 0.016)
³Statistical difference between Pre-Diabetic and Diabetic following Bonferroni Correction (p < 0.016)



Baseline PET imaging and Plasma Measurements				
Variables	Healthy (A1c < 5.7)	Pre-Diabetes (A1c: 5.7-6.4)	Diabetes (A1c: ≥ 6.5)	p-value
N (%)	594 (46.9)	546 (43.1)	126 (9.95)	
PET (n = 1,835)	Mean (SD)	Mean (SD)	Mean (SD)	
Centiloids (Amyloid)	24.36 (40.02)	21.44 (37.28)	15.26 (25.56)	0.15
Summary SUVR (Amyloid)	1.13 (0.24)	1.12 (0.23)	1.08 (0.15)	0.20
Composite Reference SUVR (Amyloid)	1.48 (0.09)	1.49 (0.08) ¹	1.49 (0.07)	0.043
Cerebellum Cortex SUVR (Amyloid)	0.86 (0.04)	0.86 (0.05)	0.86 (0.04)	0.51
Eroded Subcortical WM SUVR (Amyloid)	1.90 (0.18)	1.93 (0.18) ¹	1.96 (0.16) ²	0.007
Cerebral White Matter SUVR (Amyloid)	1.62 (0.17)	1.63 (0.20)	1.62 (0.18)	0.88
Cerebral White Matter Volume, mm ³ (Amyloid)	419171.05 (59073.18)	410840.97 (59202.06)	396915.07 (56928.82) ²	0.007
Meta-Temporal SUVR (n = 835) (Tau)	1.37 (0.59)	1.32 (0.53)	1.25 (0.43)	0.33
Meta-Temporal Volume, mm ³ (n = 835) (Tau)	69268.26 (8659.27)	67647.49 (8465.26)	66949.27 (7403.44)	0.042*
Plasma	Mean (SD)	Mean (SD)	Mean (SD)	
Abeta 40	17379.58 (5746.4)	18522.91 (5488.6)	17365.71 (7006.8)	0.06
Abeta 42	1303.06 (696.4)	1441.39 (606.9)	1444.59 (921.4)	0.21
TAU	226.05 (92.1)	223.61 (91.6)	213.80 (76.3)	0.84
pTAU	20.63 (9.97)	19.90 (9.27)	19.90 (7.12)	0.81
WMH volume				
Total White Matter Hyperintensity Volume	3.17 (6.86)	2.87 (5.61)	2.69 (3.11)	0.77
Total Brain Volume	1435.96 (154.84)	1409.48 (139.93)	1407.28 (143.11)	0.072

One-Way ANOVA to compare continuous variables. Chi-squared Or Fisher’s Exact Test to compare categorical variables.
¹Statistical difference between Healthy and Pre-Diabetic following Bonferroni Correction (p < 0.016)
²Statistical difference between Healthy and Diabetic following Bonferroni Correction (p < 0.016)
³Statistical difference between Pre-Diabetic and Diabetic following Bonferroni Correction (p < 0.016)
*Pairwise comparisons were not significant following Bonferroni Correction.

RESULTS

Baseline demographic and clinical characteristics stratified by HbA1c category are shown in Table 1. Baseline plasma amyloid-β measures (Aβ42, Aβ40, and the Aβ42/40 ratio) and p-tau levels generally did not differ significantly across HbA1c categories (Table 2). Differences were observed in select volumetric and PET measures (Table 3), specifically composite reference SUVR, eroded subcortical white matter SUVR, and cerebral white matter volume, which remained significant after multiple-comparison correction. Tau meta-temporal volume was different across groups but was not sustained after correction. No significant associations were observed with meta-temporal tau PET burden, total brain volume, or WMH volume.

DISCUSSION

Baseline HbA1c levels are generally not associated with AD biomarkers, nor with cerebrovascular disease as measured by WMH. Most amyloid PET, tau PET, and volumetric measures did not maintain significant differences across groups. Generally, plasma Aβ42/40 ratio did not show overwhelming differences across groups. Our results indicate a minimal association between T2DM pathophysiology and in vivo neuropathological markers of AD, suggesting a different mediating mechanism.