Published in final edited form as:

J Alzheimers Dis. 2018 ; 62(2): 833–840. doi:10.3233/JAD-170767.

Longitudinal Changes in Serum Glucose Levels are Associated with Metabolic Changes in Alzheimer's Disease Related Brain Regions

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Abstract

Background: The association between longitudinal changes in serum glucose level and longitudinal changes in [¹⁸F] Fluorodeoxyglucose-PET (FDG PET) measurements of Alzheimer's disease (AD) risk are unknown.

Objective: To investigate whether variation in serum glucose levels across time are associated with changes in FDG PET measurements of cerebral metabolic rate for glucose (rCMRgl) in brain regions preferentially affected by Alzheimer's disease (AD).

Methods: Participants are a subset of a prospective cohort study investigating FDG PET, apolipoprotein E (APOE) $\epsilon 4$, and risk for AD which includes data from baseline, interim, and follow up visits over 4.4 ± 1.0 -years. An automated brain-mapping algorithm was utilized to characterize and compare associations between longitudinal changes in serum glucose levels and longitudinal changes in rCMRgl.

Results: This study included 80 adults aged 61.5 ± 5 years, including 38 carriers and 42 non-carriers of the APOE $\epsilon 4$ allele. Longitudinal increases in serum glucose levels were associated with longitudinal CMRgl decline in the vicinity of parietotemporal, precuneus/posterior cingulate,

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Authors' disclosures available online (<https://www.j-alz.com/manuscript-disclosures/17-0767rl>).

SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: <http://dx.doi.org/10.3233/JAD-170767>.

and prefrontal brain regions preferentially affected by AD ($p < 0.05$, corrected for multiple comparisons). Findings remained significant when controlled for APOE $\epsilon 4$ status and baseline and advancing age.

Conclusions: Additional studies are needed to clarify and confirm the relationship between longitudinal changes in peripheral glucose and FDG PET measurements of AD risk. Future findings will set the stage on the use of FDG PET in the evaluation of possible interventions that target risk factors for the development of AD.

Keywords

Alzheimer's disease; blood glucose; longitudinal studies; positron emission tomography

INTRODUCTION

[^{18}F]-Fluorodeoxyglucose (FDG PET) measurements of reduced regional cerebral metabolic rate for glucose (rCMRgl) have been proposed as a “presymptomatic quantitative endophenotype” of Alzheimer's disease (AD) [1], defined as a biological measure more related to disease predisposition than to the clinical syndrome itself [2]. Reduced rCMRgl has been demonstrated in precuneus/posterior cingulate, parietal, temporal, and prefrontal brain regions in studies of AD patients [3]. Cognitively healthy, older individuals with 1 or 2 copies of the apolipoprotein E (APOE) $\epsilon 4$ allele, an established risk factor for the development of AD, have exhibited similar reductions in these AD-affected areas [1,4, 5].

Several cross-sectional FDG PET studies have investigated the non-genetic, genetic, and potentially interacting factors contributing to AD risk in cognitively healthy individuals. For example, similar patterns of reduced CMRgl in AD relevant regions were evident in samples with pre-diabetes, insulin resistance, and elevated serum glucose irrespective of APOE $\epsilon 4$ status [6–9]. In the present study, we utilized FDG PET to test the hypothesis that, in middle aged to older cognitively healthy adults with a family history of AD, longitudinal increases in serum glucose across time would be associated with decreasing rCMRgl in brain regions previously demonstrated to be affected by AD [3]. As in our cross sectional study, [7] we expected these associations to be independent of APOE $\epsilon 4$ allele status.

A secondary aim of the study was preliminary exploration of changes in neuropsychological outcomes. Delayed recall deficits are evident early in the preclinical course of the disease, and are predictive of those who are shown to meet criteria for diagnosis several years later [10]. Although it was expected that neuropsychological findings would remain within normal limits in this cognitively healthy cohort, it was hypothesized that increases in serum glucose across time would be associated with declines in measures of delayed recall.

METHODS

The present study is based on an existing data set (National Institute on Mental Health R01 MH57899 to EMR; National Institute on Aging 9R01AG031581-10 and P30 AG19610 to EMR) designed to investigate APOE $\epsilon 4$ and the preclinical course of AD utilizing FDG PET and neuropsychological measures [11–13]. All participants provided informed consent and

participated under guidelines provided by the Human Subjects Committees at Banner Good Samaritan Medical Center and Mayo Clinic Scottsdale.

PARTICIPANTS

As described previously [11–13], recruitment materials for these studies included newspaper and magazine ads, direct mail advertising, newspaper articles, and community presentations. In order to be eligible for the study, volunteers needed to be cognitively healthy without any self-reported history of stroke, neurologic conditions, head injury, diabetes, or use of glucose lowering medications. In order to be able to adequately observe longitudinal changes in this cohort prior to the onset of possible changes related to AD, our original inclusion criteria (at baseline) targeted late middle-aged adults, aged 50–65 [11]. However, we found that we needed to extend the age range in order to address attrition as the study progressed. Therefore, the baseline inclusion age was modified to 47–68 years of age. Hachinski ischemic scores [14] were calculated for all participants. A family history of AD in a first-degree family member was required for participation. All study volunteers participated in initial APOE ϵ 4 testing, a medical exam, clinical ratings, neuropsychological tests, volumetric MRI, and FDG PET. The participants returned for neuropsychological and imaging visits approximately once every two years.

All participants understood that they would not be informed of their APOE ϵ 4 genotype. All participants denied memory or other cognitive impairment, had a minimum score of 27 on the Mini-Mental State Examination (MMSE), [15] and were classified as normal following a neurological exam. Based on a structured psychiatric interview, study participants did not satisfy criteria for a current psychiatric disorder and had a score of less than 10 on the Hamilton Depression Rating Scale (HAM-D) [16]. For the purpose of the present project, participants were eligible for analyses if they had at least three consecutive FDG PET scans acquired every two-years from the same HR+ scanner (Siemens, Knoxville, TN).

Brain imaging

PET was performed using the HR+ scanner (Siemens, Knoxville, TN) in the 3D mode and included a transmission scan, the intravenous injection of 5–8 mCi of [^{18}F] fluorodeoxyglucose, and an emission scan as the participants lay quietly with eyes closed in a darkened room. The reconstructed images consisted of 63 horizontal slices with a center-to-center slice separation of 2.46 mm, an axial field of view of 15.5 cm, an in-plane resolution of 4.2–5.1 mm full width at half-maximum (FWHM), and an axial resolution of 4.6–6.0 mm FWHM. Voxel based analyses were performed using the PET images acquired during the last 30 min.

Automated algorithms (SPM8, Wellcome Department of Cognitive Neurology, London, U.K.) were utilized to align the sequential PET images from each subject, deform the images into the coordinates of a standard brain atlas [17] and normalize PET data for the variation in absolute measurements by proportional scaling using global as the reference region. Changes in serum glucose and longitudinal rCMRgl change were defined as the respective slope of the linear regression model for these variables across the three time points for each subject. General Linear Model (GLM) based voxel-wise analyses were performed using

SPM to generate the statistical parametric maps of a) change in rCMRgl in the entire sample and b) change in rCMRgl in each of the APOE $\epsilon 4$ carrier groups. Voxel-wise GLM multiple regression analyses examined linear relationships between changes in serum glucose and longitudinal rCMRgl changes within the entire sample, and within each of the APOE $\epsilon 4$ sub-groups. Findings in the overall group were corrected for age at baseline, advancing age and APOE $\epsilon 4$ status.

Voxel-based analyses of this type, which involve a large number of comparisons, are subject to Type-1 error rate inflation. Previous research has indicated that an uncorrected $p < 0.005$ provides an optimal trade-off between Type 1 and Type 2 errors [18]. The present study has retained this threshold for all imaging-related analyses. Additionally, in order to correct for multiple comparisons, the small volume correction with family wise error procedure in SPM was utilized, as indicated, to adjust significance levels for the number of resolution elements in *a priori* areas of interest including the precuneus, posterior cingulate, parietal, temporal, prefrontal, and occipital brain regions. The small volume correction procedure utilized a $p < 0.05$ threshold.

Serum glucose levels

Acquisition of serum glucose levels occurred consistently throughout every PET procedure to permit the quantification of cerebral glucose utilization, as per convention in the field. At each visit, the Lifescan SureStepFlexx hand-held glucometer acquired and analyzed five venous blood samples over the course of the sixty-minute scan (at 7, 12, 20, 25, and 45 min post-FDG injection). As in the previously published report [7], the glucose level acquired at the 7-min time mark was the serum glucose value used in analyses. Fasting status was required for the scan; fasting was defined as a minimum of 4 h, which is consistent with guidelines provided by the Society of Nuclear Medicine for FDG PET brain imaging [19].

Neuropsychological test scores

In the present study, the Auditory Verbal Learning Test Long Term Memory score (AVLT-LTM) [20] and the Complex Figure Test Recall (CFT-R) [21] were selected to assess memory (delayed recall) and the Controlled Oral Word Association Test (COWAT) [22] was selected to assess verbal fluency.

RESULTS

A description of the participant sample can be found in Table 1. This longitudinal study (4.4 ± 1.0 years on average) characterized 80 cognitively normal, non-diabetic, 61.5 ± 4.8 -year-old persons with a first-degree family history of AD, including 38 carriers and 42 non-carriers of the APOE $\epsilon 4$ allele. Baseline serum glucose levels (minimum of 4 h fasting) ranged from 75 to 115mg/dl with an average serum glucose value of 91.0 ± 8.0 . There were no statistically significant differences between APOE $\epsilon 4$ subgroups in age, gender, education, neuropsychological test scores, or baseline serum glucose levels. There was a significant difference between APOE $\epsilon 4$ carriers and non-carriers on their HAM-D scores ($p = 0.03$) with non-carriers scoring higher than carriers. Although the difference in scores was statistically significant, the scores themselves are low for both groups, and do not reflect

clinically significant depression [23]. Hachinski scores ranged from 0–1 with 20% of the sample receiving a score of 1. Every score of 1 was attributed to history of hypertension.

Mean serum glucose levels increased from 91.0 ± 8.0 mg/dl to 95.2 ± 8.6 mg/dl over the course of the study. This increase was statistically significant (Table 2, $p < 0.001$). Table 3 lists the brain atlas coordinates and magnitude of the brain regions in with the strongest correlations between changes in serum glucose and changes in rCMRgl in AD-related locations. Longitudinal changes in serum glucose were inversely associated with changes in rCMRgl in left prefrontal and left parietotemporal regions, and bilaterally in precuneus and posterior cingulate brain regions that have previously been implicated in AD. Left prefrontal, left parietotemporal, and bilateral precuneus regions survived statistical correction for multiple comparisons ($p < 0.05$; Fig. 1). Negative association of the changes over time between FSG and CMRgl were independent of APOE $\epsilon 4$ status and independent of the variation in baseline and advancing age ($p > 0.005$, *results not shown*).

In APOE $\epsilon 4$ non-carriers, there was an inverse association between changes in serum glucose across time and changes in rCMRgl in left prefrontal and left parietal, and bilaterally in precuneus AD related brain regions. Findings in each of these brain regions survived correction for multiple comparisons. In carriers of the APOE $\epsilon 4$ allele, there was an inverse association between serum glucose changes and changes in rCMRgl across time in left prefrontal, left parietotemporal, left precuneus, and bilateral posterior cingulate AD related brain regions. However, none of these findings survived correction for multiple comparisons (Supplementary Figure 1). In order to further explore a possible interaction between changes in serum glucose levels and APOE $\epsilon 4$ on changes in rCMRgl across time, we performed additional exploratory analyses by including a serum glucose by APOE $\epsilon 4$ interaction term in our model. At the uncorrected 0.005 level, we noted that there was an interaction between APOE $\epsilon 4$ status and serum glucose such that as serum glucose increased across time, APOE $\epsilon 4$ non-carriers had a greater decline in rCMRgl left medial frontal gyrus and non-AD related left postcentral gyrus regions; APOE $\epsilon 4$ carriers had a greater decline in rCMRgl relative to non-carriers in cerebellar regions.

Preliminary analyses reveal that there was a significant inverse correlation between changes in serum glucose levels across time and changes in the CFT-R ($r = -0.3$, $p = 0.002$). This relationship remained significant when age, education, and APOE $\epsilon 4$ status were entered into a hierarchical regression analysis (in that order) to address their association with this measure of visual memory (Table 4). There were no additional significant findings in tests of verbal memory (AYLT-LTM) or verbal fluency (COWAT).

In summary, increasing serum glucose levels across time were associated with reduced rCMRgl across time in AD-related brain regions. In the overall cohort, these findings remained significant when controlled for APOE $\epsilon 4$ status, and baseline and advancing age. Increase in serum glucose across time was associated with decreased performance on a measure of visuospatial memory.

DISCUSSION

This study of cognitively normal older adults without diabetes demonstrated an association between longitudinal increases in serum glucose levels and longitudinal decrease in rCMRgl in precuneus/posterior cingulate, prefrontal, and parietal brain regions previously determined to be preferentially affected by AD [3]. The present study extends our original cross sectional observations regarding the relationship between serum glucose and rCMRgl [7] to a longitudinal sample. Findings from the cross sectional and longitudinal samples provides additional evidence that higher serum glucose levels may be related to brain changes related to AD risk.

Declarative memory function is sensitive to factors that regulate glucose control [24]. In the present study, increasing glucose levels across time were associated with decreased performance on a measure of visual memory. While the majority of studies suggest verbal memory as particularly sensitive to changes in glucose control [25, 26], there is evidence of elevated fasting serum glucose's impact on visual memory in studies that specifically assess pre-diabetic [27] and diabetic participants [28, 29].

Serum glucose levels did increase over time in this cognitively normal, non-diabetic cohort, and, on average, remained within the normal level based on true fasting serum glucose estimates reported in larger scale population studies [30, 31]. Therefore, these increases likely do not reflect clinically meaningful changes. As in our original study, [7] the major limitation of the present study is that the parent project was not prospectively designed to assess glucose control in study participants; it was designed to investigate the natural history of APOE $\epsilon 4$ and risk for development of AD. Therefore, we are unable to comment on whether the rise in glucose over time represents elevated risk for glucoregulatory dysfunction. Findings remain consistent however, if one considers that higher estimates of glucose *exposure* over time (that include random or non-fasting glucose levels) have been associated with increased risk of dementia [32].

Our findings support previous cross sectional and longitudinal FDG PET studies that associate poor glucose control with changes in AD related brain regions. In cross sectional studies, individuals that fulfilled criteria for pre-diabetes or diabetes, higher levels of insulin resistance, as measured by the HOMA-IR model, [33] were also associated with reduced FDG PET rCMRgl uptake in AD relevant regions in both older (mean age 74.4 years) cognitively normal adults [6] and in late middle aged (mean age 60.7 years) cognitively normal adults with a family history of AD [9]. In terms of longitudinal studies, over the course of 8 years, ^{15}O -water PET has demonstrated that impaired glucose tolerance in cognitively normal adults at midlife (mean age of 57.2 years) is associated with changes in cerebral blood flow in AD relevant regions [34].

Results from the overall sample continue to support previous work that suggests glucose dysregulation may exert a risk that is independent of the genetic risk associated with APOE $\epsilon 4$ status [6, 9]. However, in our APOE $\epsilon 4$ subgroup analyses, only the APOE $\epsilon 4$ non-carrier findings survived correction for multiple comparisons. While our study did not include individuals with diabetes, a similar pattern of results was demonstrated in an FDG PET

study from the Mayo Clinic Study of Aging. In cognitively healthy older adults (mean age of 79), the association between diabetes and an AD related pattern of hypometabolism was stronger in APOE $\epsilon 4$ non-carriers than carriers, leading authors to posit that perhaps there is a shared mechanism between possession of the APOE $\epsilon 4$ and diabetes-related risk as it relates to cerebral hypometabolism [8]. Exploratory analyses performed for this study further revealed interactions between changes in serum glucose and APOE $\epsilon 4$ group on rCMRgl in cerebellar, frontal, and parietal locations outside the regions that are preferentially affected by AD. However, we will continue to consider a possible interaction in AD-related regions as we move forward with study of this cohort. Notably, our lack of findings in the APOE $\epsilon 4$ carriers may also be related to power, as there were fewer carriers in the study relative to non-carriers.

As mentioned in our cross sectional findings [7], although fasting status (a minimum of 4h) was adhered to per standard FDG-PET imaging procedures, [19] stringent protocols for fasting serum glucose and other relevant laboratory values (e.g., HBA1c) are recommended for studies that prospectively study insulin resistance and related processes [6, 8, 9]. We caution that while longitudinal increases in serum glucose levels may be associated with progressive rCMRgl declines, elevated serum glucose may exert an acute and potentially reversible effect on regional rCMRgl or on the competition between labeled FDG and circulating, endogenous glucose levels. For example, reduced rCMRgl in AD-relevant brain regions has been demonstrated upon induction of hyperglycemia in younger healthy adults [35, 36]. It is likely a more reasonable claim that AD related brain regions are particularly sensitive to peripheral glucose control, and further studies are needed to determine the extent to which acute changes may exert an increased vulnerability to neurodegenerative and/or cerebrovascular changes associated with increased risk for dementia. This study did not employ the use of PET amyloid imaging, which also has been utilized to assess glucoregulatory risk for the development of AD with mixed results [8, 37, 38]. Lastly, the present findings are generalizable only to individuals with a first-degree history of AD.

Conclusions

This study contributes to accumulating research evidence suggesting that elevated levels of serum glucose and other indicators of poor peripheral glucose control may be associated with neuroimaging and neuropsychological measures related to AD risk. It complements and extends previous studies by virtue of its longitudinal design. Lastly, this study continues to support the use of neuroimaging measures, like PET, as an additional approach by which to identify and assess risk for AD, and to inform the design and timing of prospective trials of preventative interventions [39, 40].

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

The authors would like to thank study participants. We acknowledge Patti Aguilar, Candy Monarrez, and Katie DeMarco for their hard work in coordinating this study.

Funding for this work was provided by National Institute on Mental Health ROI MH57899 (EMR), National Institute on Aging 9R01AG031581-10 (EMR) and P30 AG19610 (EMR).

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Fig. 1. Longitudinal increases in serum glucose are associated with decreases in rCMRgl in AD related brain regions. Statistical maps generated from this study were projected onto the lateral and medial surfaces of the left and right cerebral hemispheres, and feature brain regions in which increases in serum glucose levels over time are associated with decreases in rCMRgl in the entire sample. Blue areas (shaded in the print version) reflect findings in regions that have previously been determined to demonstrate reduced rCMRgl in AD patients (Alexander et al. [3]; $p < 0.05$, corrected for multiple comparisons). Findings remained significant when controlled for age and APOE $\epsilon 4$ status.

Table 1

Baseline participant characteristics, clinical ratings, serum glucose measurements, and neuropsychological test scores for older adults

Characteristic	Total sample		APOE ε4 subgroups	
	Mean	Non-carriers (n = 42)	Carriers (n = 38)	p-value ^b
Age, mean (SD)	61.5 (4.8)	61.5 (5.2)	61.4 (4.3)	0.94
Gender (%F)	52 (65%)	27 (64%)	25 (66%)	0.90
Education, mean (SD)	16.1 (2.0)	16.3 (1.9)	15.8 (2.2)	0.23
Serum glucose, mean (SD), mg/dL	91.0 (8.0)	91.5 (8.6)	90.4 (7.4)	0.55
History of hypertension (% Yes) ^c	16 (20%)	5 (11.9%)	11 (28.9%)	0.06
BMI, mean (SD)	26.7 (4.5)	26.5 (4.8)	27.0 (4.2)	0.63
Years between V ₁ and V ₃ ^d , mean (SD)	4.4 (1.0)	4.6 (1.2)	4.2 (0.8)	0.13
MMSE, mean (SD)	29.7 (0.7)	29.6 (0.8)	29.8 (0.6)	0.36
HAM-D, mean (SD)	1.5 (2.3)	2.1 (2.8)	1.0 (1.2)	0.03
AVLT, Long term memory, mean (SD)	9.4 (3.0)	9.1 (2.9)	9.6 (3.2)	0.43
Complex Figure Test, Recall, mean (SD)	19.0 (7.5)	18.8 (7.8)	19.2 (7.2)	0.80
COWAT, mean (SD)	46.9 (10.4)	44.8 (9.3)	47.9 (11.4)	0.19

^aRaw scores are reported.

^bUnless otherwise indicated, values are mean ± SD. p-values were calculated with analysis of variance (ANOVA) or chi square test, uncorrected for multiple comparisons ($p < 0.05$), as appropriate.

^cReported as number (and percentage) of participants with a history of hypertension (based on information retrieved from Hachinski score).

^dV₁ and V₃ are Visits 1 and 3 respectively.

Table 2

Serum glucose values over time

	Visit 1	Visit 2	Visit 3	p value ^a
Serum glucose (mg/dl)	91.0 ± 8.0	93.6 ± 9.1	95.2 ± 8.6	p <0.001
Minimum (mg/dl)	75	76	79	
Maximum (mg/dl)	115	117	116	

^a simple t test.

Table 3

Location and magnitude of the most significant correlations between serum glucose levels and rCMRgl in older adults

AD-related brain region	Atlas coordinates (mm) ^a			Brodmann area	<i>r</i>	<i>p</i> -value ^b
	X	Y	Z			
Parietotemporal	Left	-57	-57	29	40	-0.5 3.3×10^{-7} *
Precuneus/Posterior Cingulate	Left	-20	-71	55	7	-0.4 8.5×10^{-4} *
	Right	12	-55	32	31	-0.4 7.7×10^{-4} *
Prefrontal	Left	-36	5	59	6	-0.5 2.4×10^{-6} *

The data were extracted from voxels associated with the most significant correlations in regions previously found to be associated with abnormally low rCMRgl in patients with AD.6.

^aThe coordinates were obtained from Talairach and Tournoux [17]. × is the distance to the right (+) or left (-) of the midline, Y is the distance anterior (+) or posterior (-) to the anterior commissure, and Z is the distance superior (+) or inferior (-) to a horizontal plane through the anterior and posterior commissures.

^bThe reported significance levels are one-tailed and uncorrected for multiple comparisons ($p < 0.005$).

*Correlations that remained significant ($p < 0.05$) after correcting for multiple comparisons are marked with an asterisk. Findings remained significant when controlled for APOE ε4 status.

Table 4

Correlation between changes in serum glucose and neuropsychological measures over time

Measure	Pearson's <i>r</i>	<i>p</i> -value
AVLT-LTM	0.02	0.42
CFT-Recall	−0.32	0.002 *
COWAT	0.05	0.33

* Remained significant when controlled for age, education, and APOE ε4 status.