Insulin Resistance and Alzheimer-like Reductions in Regional Cerebral Glucose Metabolism for Cognitively Normal Adults With Prediabetes or Early Type 2 Diabetes

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Background: Insulin resistance is a causal factor in prediabetes (PD) and type 2 diabetes (T2D) and increases the risk of developing Alzheimer disease (AD). Reductions in cerebral glucose metabolic rate (CMRglu) as measured by fludeoxyglucose F 18–positron emission tomography (FDG-PET) in parietotemporal, frontal, and cingulate cortices are associated with increased AD risk and can be observed years before dementia onset.

Objectives: To examine whether greater homeostasis model assessment insulin resistance (HOMA-IR) is associated with reduced resting CMRglu in areas vulnerable in AD in cognitively normal adults with newly diagnosed PD or T2D (PD/T2D), and to determine whether adults with PD/T2D have abnormal patterns of CMRglu during a memory encoding task.

Design: Randomized crossover design of resting and activation FDG-PET.

Setting: University imaging center and Veterans Affairs clinical research unit.

Participants: Twenty-three older adults (mean [SEM] age, 74.4 [1.4] years) with no prior diagnosis of diabetes but who met American Diabetes Association glycemic criteria for PD (n=11) or diabetes (n=12) based on fasting or 2-hour oral glucose tolerance test (OGTT) glucose values and 6 adults (mean [SEM] age, 74.3 [2.8] years) with normal fasting glucose values and glucose tolerance. No participant met Petersen criteria for mild cognitive impairment.

Interventions: Fasting participants underwent resting and cognitive activation FDG-PET imaging on separate days. Following a 30-minute transmission scan, subjects received an intravenous injection of 5 mCi of FDG, and the emission scan commenced 40 minutes after injection. In the activation condition, a 35-minute memory encoding task was initiated at the time of tracer injection. Subjects were instructed to remember a repeating list of 20 words randomly presented in series through earphones. Delayed free recall was assessed once the emission scan was complete.

Main Outcome Measures: The HOMA-IR value was calculated using fasting glucose and insulin values obtained during OGTT screening and then correlated with CMRglu values obtained during the resting scan. Resting CMRglu values were also subtracted from CMRglu values obtained during the memory encoding activation scan to examine task-related patterns of CMRglu.

Results: Greater insulin resistance was associated with an AD-like pattern of reduced CMRglu in frontal, parietotemporal, and cingulate regions in adults with PD/T2D. The relationship between CMRglu and HOMA-IR was independent of age, 2-hour OGTT glucose concentration, or apolipoprotein E ε4 allele carriage. During the memory encoding task, healthy adults showed activation in right anterior and inferior prefrontal cortices, right inferior temporal cortex, and medial and posterior cingulate regions. Adults with PD/T2D showed a qualitatively different pattern during the memory encoding task, characterized by more diffuse and extensive activation, and recalled fewer items on the delayed memory test.

Conclusions: Insulin resistance may be a marker of AD risk that is associated with reduced CMRglu and subtle cognitive impairments at the earliest stage of disease, even before the onset of mild cognitive impairment.

and adults with prodromal AD (amnestic mild cognitive impairment [MCI]) demonstrated lower CMRglu in posterior cingulate, precuneus, parietotemporal, and frontal cortices. Similar patterns have been reported in cognitively normal carriers of the apolipoprotein E ε4 allele (APOE ε4) AD risk factor. Insulin infusion increases whole-brain CMRglu in healthy adults, with relative regional increases in prefrontal and temporal cortices. In rodent models, insulin increases glucose transporter type 4 translocation and glucose uptake in the hippocampus. These regions play an important role in memory; thus, it is not surprising that inducing insulin resistance in animal models and thereby disrupting cerebral insulin function causes memory impairment, a hallmark symptom of AD and a frequently reported characteristic of T2D in older adults. In our study, we examined the hypothesis that, in a sample of cognitively normal adults with newly diagnosed PD or T2D (PD/T2D), greater insulin resistance as indexed by the homeostasis model assessment (HOMA-IR) would be associated with reduced resting CMRglu in areas known to predict AD vulnerability. We also determined whether adults with PD/T2D have abnormal patterns of CMRglu during a memory encoding task.

### METHODS

#### PARTICIPANTS

All study procedures were approved by the institutional review boards of the University of Washington and the Veterans Affairs Puget Sound Health Care System, and written informed consent was obtained from all participants prior to study enrollment. Participants were solicited through community advertising and underwent oral glucose tolerance testing (OGTT), physical examination, and neuropsychological assessment. Participants were excluded if they had previously received a diagnosis of diabetes, had ever been treated with a medication for diabetes, or met criteria for MCI as described by Petersen. Subjects with neurological conditions, uncontrolled hypertension, cardiac disease or dyslipidemia, renal dysfunction, liver dysfunction, or any other significant health condition were excluded. Twenty-three adults met American Diabetes Association glycemic criteria for PD (n=11; 1 with an isolated impaired fasting glucose level and 10 with impaired glucose tolerance) or diabetes (n=12; all with impaired glucose tolerance) based on fasting or 2-hour OGTT glucose values. Six adults with normal fasting glucose values and normal glucose tolerance were included in the cohort for comparison. A validated index of insulin resistance, HOMA-IR, was calculated using fasting glucose and insulin values obtained prior to administration of the beverage for the OGTT.

### PROCEDURES

Participants underwent resting and cognitive activation PET imaging using FDG on separate days approximately 2 weeks apart, in counterbalanced order, at 9 AM after an overnight fast. Participants were placed in the PET scanner in a supine position, with a venous line maintained for radiotracer injection. Plasma glucose was sampled. Throughout the imaging procedure for both the rest and activation conditions, the head was restrained using a neck-conforming support and subjects rested silently with eyes open in a dimly lit and quiet room. Following a 30-minute transmission scan for attenuation correction, subjects received an intravenous injection of 5 mCi of FDG (to convert to millibecquerel, multiply by 3.7 × 10^10). Forty minutes later, the emission scan commenced. In the cognitive activation session, a 33-minute cognitive task was administered immediately after the tracer injection. This allowed brain FDG uptake to represent neuronal activity during cognitive task performance.

The activation task was based on previous work by Alkire et al. Subjects were instructed to remember a repeating list of 20 words that were randomly presented through earphones at a rate of 1 word every 3 seconds. The words were 4 to 8 letters in length, of average linguistic frequency, and neutral in emotional valence. Delayed free recall was assessed when the emission scan was complete and the intravenous lines were removed.

The PET image sets were coregistered and anatomically standardized to Talairach and Tournoux stereotactic coordinates using NEUROSTAT software (Departments of Radiology and Bioengineering, Washington National Primate Research Center, University of Washington, Seattle). Pixel intensity was normalized to global activity and smoothed using a 3-dimensional gaussian kernel (2.25-mm SD) to reduce residual anatomical variences.

Correlations between normalized CMRglu values at rest and HOMA-IR values were calculated on a voxelwise basis, and the correlation coefficients were transformed to Z scores (Fisher transformation). Coordinates for which Z scores exceeded 3.5 were considered to be significant, controlling the type I error rate at approximately P=.05 for multiple comparisons. Associations between regional CMRglu val-
ues and HOMA-IR values, age, APOE ε4 carriage, fasting plasma glucose levels measured prior to radiotracer injection, and degree of hyperglycemia indexed by 2-hour OGTT glucose concentration were examined with correlational and multiple regression analyses.

Groupwise paired subtraction analysis allows the statistical comparison of activation vs a resting baseline in the same subjects. In this study, resting scans were subtracted from activation scans across subjects. One-sample $t$ statistic values were calculated across subjects for each subtracted pixel value. The calculated $t$ statistic values were then converted to $Z$ statistic maps using a probability integral transformation. The resultant $Z$ statistic maps represent the extent and significance of task-related brain activity averaged across all subjects in the group.

To determine whether recall performance was associated with CMRglu, Pearson correlations were conducted between delayed recall scores and mean global-normalized CMRglu values of stereotactically defined volumes of interest for frontal, temporal, parietal, and posterior cingulate cortices.

## RESULTS

### RESTING CMRglu

For adults with PD/T2D, greater insulin resistance as indexed by HOMA-IR values was associated with reduced CMRglu in regions known to be affected early in AD, including posterior cingulate cortex, the precuneus region, parietal cortices (Brodmann areas [BAs] 7 and 40), the temporal/angular gyri (BA 39), and the anterior and inferior prefrontal cortices (BAs 10, 45, and 47) (Figure 1). Stereotactic cortices for brain regions exhibiting significant correlations between resting CMRglu and HOMA-IR values and the associated significance values are provided in Table 2. Multiple regression analyses indicated that the significant relationship between HOMA-IR values and CMRglu for adults with PD/T2D was unaffected by age, pre-PET fasting glucose values, hyperglycemia (2-hour OGTT glucose values), or APOE ε4 allele carriage. Scatterplots show the negative relationship between insulin resistance and CMRglu for the PD/T2D group in 2 representative areas (frontal and cingulate cortices) (Figure 2). Correlations between CMRglu and HOMA-IR values were not significant for healthy adults, likely owing to the restricted range of HOMA-IR values and the small sample size.

Table 2. Talairach and Tournoux Stereotactic Atlas Coordinates and Associated $P$ Values for Brain Regions in Which Lower Cerebral Glucose Metabolic Rate Was Associated With Greater Insulin Resistance

<table>
<thead>
<tr>
<th>Brain Region</th>
<th>Atlas Coordinates, mm$^3$</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Posterior cingulate/precuneus</td>
<td>$-6$ $-76$ $40$</td>
<td>.000365</td>
</tr>
<tr>
<td>Medial cingulate</td>
<td>$-3$ $-8$ $38$</td>
<td>.00131</td>
</tr>
<tr>
<td>Right parietal</td>
<td>$-26$ $-67$ $50$</td>
<td>.000336</td>
</tr>
<tr>
<td>Left temporal</td>
<td>$37$ $-55$ $25$</td>
<td>.000142</td>
</tr>
<tr>
<td>Right frontal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BA 10</td>
<td>$-39$ $44$ $-2$</td>
<td>.000048</td>
</tr>
<tr>
<td>BA 45</td>
<td>$-55$ $32$ $0$</td>
<td>.000025</td>
</tr>
<tr>
<td>BA 47</td>
<td>$-39$ $32$ $-4$</td>
<td>.000032</td>
</tr>
<tr>
<td>Left frontal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BA 10</td>
<td>$35$ $48$ $2$</td>
<td>.000024</td>
</tr>
<tr>
<td>BA 47</td>
<td>$42$ $35$ $-4$</td>
<td>.000630</td>
</tr>
</tbody>
</table>

Abbreviation: BA, Brodmann area.

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Figure 1. Brain regions in which a lower cerebral glucose metabolic rate was associated with greater insulin resistance as indexed by the homeostasis model assessment of insulin resistance. Regions in which the strongest negative associations were observed are represented in yellow. The vertical bar shows image color vs $Z$ score scale. Image views are labeled as follows: R, right; L, left; Lat, lateral; Sup, superior; Inf, inferior; Ant, anterior; Post, posterior; and Med, medial.

Figure 2. Scatterplots for cerebral glucose metabolic rate (CMRglu) and homeostasis model assessment of insulin resistance (HOMA-IR) values in frontal (A) and cingulate (B) cortices for adults with prediabetes or type 2 diabetes.
Healthy adults showed task-related change in CMRglu activity in right anterior and inferior prefrontal cortices (BA 10, 45, and 47), right inferior temporal cortex (BA 20), and medial and posterior cingulate regions (BA 23, 24, and 31) (Table 3 and Figure 3A). This pattern is consistent with previous imaging results using similar encoding paradigms in healthy adults.\(^1\) In contrast, the PD/T2D group had a more widespread pattern of activation including bilateral orbitomedial and inferior prefrontal regions (BA 11, 25, and 47) that were adjacent to regions activated for healthy adults. The PD/T2D group also showed task-specific activation of subcortical regions (right putamen, left thalamus) and right cerebellar vermis (Figure 3B). The percentage of increase in mean global-normalized CMRglu values from resting to activation conditions for these regions was generally consistent with the pattern described earlier. That is, healthy adults showed a greater CMRglu percentage increase than did adults with PD/T2D in right frontal regions (healthy adults: mean [SEM] change, +3.65% [1.20%]; adults with PD/T2D: mean [SEM] change, +0.16% [0.71%]; \(P = .02\)) and right temporal regions (healthy adults: mean [SEM] change, +1.44% [0.98%]; adults with PD/T2D: mean [SEM] change, −0.40% [0.61%]; \(P = .12\)). We were unable to conduct definitive statistical between-group comparisons for most regions, however, owing to the small number of healthy participants.

Delayed recall for words presented during the activation condition was recorded after the scan was completed. The healthy group recalled more words than did the PD/T2D group (healthy group: mean [SEM] recall, 19.60 [2.45] words; PD/T2D group: mean [SEM] recall, 13.96 [1.17] words; \(P = .047\)). To determine whether recall performance was related to task-related CMRglu for the PD/T2D group, delayed recall scores were correlated with mean global-normalized CMRglu for frontal, temporal, parietal, and posterior cingulate volumes of interest. Better recall was associated with greater CMRglu for right frontal and posterior cingulate cortices (\(r=0.52\) and 0.46, respectively; \(P < .04\)) and for left frontal, temporal, and parietal cortices (\(r=0.63, 0.47,\) and 0.51, respectively; \(P < .03\)).

### Insulin Resistance and CMRglu in PD/T2D

Insulin resistance was associated with a pattern of reduced CMRglu in frontal, parietotemporal, and cingulate regions in cognitively normal adults with PD/T2D. This pattern of hypometabolism has also been observed in patients with MCI and AD, in middle-aged carriers of the APOE ε4 genetic risk factor who do not have dementia, and in presymptomatic adults with the AD-causative presenilin-1 gene.\(^3\) In our sample, the relationship between CMRglu and insulin resistance indexed by HOMA-IR was independent of age, 2-hour OGTT glucose concentration, or APOE ε4 allele carriage. Adults with PD/T2D also showed an activation pattern during a memory encoding task that was qualitatively different from that observed in healthy adults, characterized by more widespread activation. Our participants received careful neuropsychological assessment and were not cognitively impaired according to current criteria for MCI.\(^2\) However, their ability to recall words encoded during the activation scan was reduced relative to adults who were not insulin resistant, despite being of similar age and education levels. Taken together, these results suggest that increased insulin resistance may be a marker of AD risk that is associated with reduced CMRglu and subtle cognitive impairments at the earliest stage of disease, even before the onset of MCI.

Although reduced CMRglu has been reported in several rodent models of diabetes,\(^1\) few human studies have examined this possibility in T2D and none to our knowledge have examined it in PD. Reduced cerebral blood flow in all cortical areas has been noted, with prominent reduction in frontal areas for more severely affected patients who were treated with insulin.\(^20\) In contrast, participants in our study had milder, newly diagnosed PD or T2D and had never received treatment for diabetes. Thus, the AD-like pattern of hypometabolism we observed is likely related to the underlying pathophysiology of insulin resistance and diabetes as opposed to secondary effects of diabetic treatment.

The identification of specific metabolic factors that are associated with abnormal CMRglu patterns may elucidate important pathogenetic pathways. Reiman et al\(^23\) investigated the relationship between cholesterol and CMRglu in late middle-aged adults with varying APOE genotypes. They reported an AD-like pattern of parieto-temporal and frontal hypometabolism that was more prominent in APOE ε4 carriers than in noncarriers. In

### Table 3. Talairach and Tournoux Stereotactic Atlas Coordinates and Associated P Values for Brain Regions Activated During the Memory Encoding Task Compared With Resting Baseline

<table>
<thead>
<tr>
<th>Brain Region</th>
<th>Atlas Coordinates, mm(^3)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medial cingulate</td>
<td>(-8) −10 34 (\times)10(^3)</td>
<td>0.00054</td>
</tr>
<tr>
<td>Right frontal</td>
<td>(-35) 57 −4 (\times)10(^3)</td>
<td>0.00003</td>
</tr>
<tr>
<td>BA 10</td>
<td>(-53) 26 0 (\times)10(^3)</td>
<td>0.00009</td>
</tr>
<tr>
<td>BA 47</td>
<td>−44 44 −9 (\times)10(^3)</td>
<td>0.00002</td>
</tr>
<tr>
<td>Right temporal</td>
<td>−44 1 −36 (\times)10(^3)</td>
<td>0.00028</td>
</tr>
<tr>
<td>PD/T2D group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left frontal</td>
<td>(-35) 41 −18 (\times)10(^3)</td>
<td>0.00002</td>
</tr>
<tr>
<td>BA 11</td>
<td>19 23 −16 (\times)10(^3)</td>
<td>0.00007</td>
</tr>
<tr>
<td>Right frontal</td>
<td>−44 50 −9 (\times)10(^3)</td>
<td>0.00017</td>
</tr>
<tr>
<td>BA 11</td>
<td>−24 1 0 (\times)10(^3)</td>
<td>0.00084</td>
</tr>
<tr>
<td>Right cerebellum</td>
<td>−37 −60 −38 (\times)10(^3)</td>
<td>0.00104</td>
</tr>
<tr>
<td>Left thalamus</td>
<td>8 −13 0 (\times)10(^3)</td>
<td>0.00172</td>
</tr>
</tbody>
</table>

Abbreviations: BA Brodmann area; PD, prediabetes; T2D, type 2 diabetes.

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our study, the relationship between insulin resistance and CMRglu was not mediated by APOE ε4 carriage, suggesting that insulin resistance and APOE ε4 may be independent factors associated with AD-related CMRglu abnormalities. This possibility has been suggested in other studies in which insulin resistance and APOE genotype have been shown to be independent risk factors for AD.1 Support for insulin resistance–related CMRglu reductions was also provided by a recent study in which a cognitively mixed group of adults showed reduced frontal CMRglu that was associated with increased cardiovascular risk as assessed by the Framingham Cardiovascular Risk Profile, a measure that is correlated with insulin resistance.24,25

There are several possible mechanisms through which insulin resistance may affect CMRglu.26 Insulin resistance is associated with reduced insulin levels and/or activity in the central nervous system.1 Insulin modulation affects brain glucose use in animal models7,27; thus, reduced insulin levels or activity may interfere with this process. Insulin resistance is also associated with impaired cerebrovascular function, which may affect glucose delivery to the central nervous system, even in the absence of frank infarcts.1 A final potential mechanism with direct relevance to AD concerns the relationship between insulin and Aβ. Increased Aβ burden has been linked to reduced CMRglu, and insulin modulates levels of Aβ in part through its effects on Aβ clearance.1,28 Indeed, the pattern of prominent frontal correlations is in a region of intense Aβ deposition in AD as measured by Pittsburgh compound B imaging, raising an interesting question of potential correlations between Pittsburgh compound B retention and measures of insulin resistance.28

Interesting differences in activation patterns were observed during the memory encoding task for healthy and PD/T2D groups. For healthy adults, activation was observed in BAs 10, 45, and 47, that is, in the right frontal cortex, right inferior temporal cortex, and medial and posterior cingulate regions. This right-sided lateralization may appear surprising given that the encoding paradigm used auditorily presented verbal stimuli. Several reviews have noted, however, that lateralization patterns during encoding differ for older adults and include regions observed in our study.16 Furthermore, selective right prefrontal activation, particularly involving BA 10, has been noted in a variety of verbal memory tasks.29 These patterns may reflect different strategic approaches to encoding or recruitment of different regions to compensate for age-related metabolic dysfunction. Additionally, because it was necessary to obtain a resting scan to explore relationships of basal CMRglu with insulin resistance, task activation was compared with a resting state rather than with a control task that accounted for nonspecific attentional and working memory demands; consequently, activation includes cognitive processes in addition to memory encoding, processes that may preferentially activate right-hemisphere neurocognitive networks. Use of a matched control task in future studies may more clearly delineate activation patterns due specifically to encoding processes. It is also worth noting that our healthy group may be healthier than control groups included in many neuroimaging studies; it is likely that many studies of “normal” older adults include adults with undiagnosed PD/T2D in their sample as it is estimated that more than 50% of adults older than 60 years with these conditions are unaware of their abnormal glycemic status30 and screening OGTTs are not routinely administered. The inclusion of such subjects undoubtedly contributes to heterogeneous results in neuroimaging studies of older adults.

In contrast to the pattern observed for the healthy group, the PD/T2D group showed diffuse activation that included bilateral medial and inferior frontal regions adjacent to regions activated for healthy adults. The PD/T2D group also showed activation of subcortical regions (right putamen, left thalamus) and right cerebellar vermis. Diffuse activation or hyperactivation of areas not typically engaged in a cognitive task have been reported in adults with prodromal or early AD as well as in non-symptomatic APOE ε4 carriers and may be a compensatory mechanism invoked following dysfunction of the neuroarchitectural network that typically would support a cognitive task.31,32 A recent meta-analysis reported that patients with AD showed extensive prefrontal activation during memory encoding tasks, including activa-
tion in BA 11 as well as thalamic and cerebellar activation, a pattern very similar to that observed in our PD/T2D group. Positive correlations were also observed between recall and CMRglu for several stereotactically defined, globally normalized volumes of interest that included frontal, parietal, temporal, and posterior cingulate cortices.

A key limitation of our study is its relatively small sample size, particularly with regard to the healthy group. Clearly, our results need to be replicated with a larger sample. The reduced power associated with the small sample size also affected our ability to directly compare healthy and PD/T2D group changes in CMRglu with task activation.

Our results suggest that insulin resistance may be a risk factor for AD in part owing to detrimental effects on CMRglu. Efforts to understand the role of insulin resistance in AD are hampered by the lack of specific criteria defining this syndrome. Should such criteria become available, they would provide a relatively low-cost, noninvasive means for identifying adults at risk as well as a rationale for examining the potential benefits of interventions directed at improving insulin resistance. Many interventions such as exercise are low risk with numerous documented health benefits and improve cognitive function in adults with MCI and AD. Our results also provide a strong rationale for further study of the mechanisms underlying the association between insulin resistance and reduced CMRglu.

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Author Contributions: Dr Baker had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Baker, Minoshima, Watson, and Craft. Acquisition of data: Baker, Cross, Minoshima, Belongia, Watson, and Craft. Analysis and interpretation of data: Baker, Cross, Minoshima, and Craft. Drafting of the manuscript: Baker and Craft. Critical revision of the manuscript for important intellectual content: Baker, Cross, Minoshima, Belongia, Watson, and Craft. Statistical analysis: Baker, Cross, Minoshima, and Craft. Obtained funding: Baker, Watson, and Craft. Administrative, technical, and material support: Baker, Cross, Belongia, Watson, and Craft. Study supervision: Baker, Minoshima, and Craft.

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REFERENCES


Announcement

Trial Registration Required. As a member of the International Committee of Medical Journal Editors (ICMJE), Archives of Neurology will require, as a condition of consideration for publication, registration of all trials in a public trials registry (such as http://ClinicalTrials.gov). Trials must be registered at or before the onset of patient enrollment. The trial registration number should be supplied at the time of submission.

For details about this new policy, and for information on how the ICMJE defines a clinical trial, see the editorials by DeAngelis et al in the September 8, 2004 (2004; 292:1363-1364) and June 15, 2005 (2005;293:2927-2929) issues of JAMA. Also see the Instructions to Authors on our Web site: www.archneurol.com.