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Cognitive Impairment in Non-Diabetic Middle-Aged and Older Adults is Associated with Insulin Resistance

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Abstract

To determine whether the cognitive impairments observed in adults with type 2 diabetes mellitus (T2DM) exist in pre-clinical disease, we compared 38 adult participants with evidence of insulin resistance (IR) to 54 age-, gender- and education-matched control participants on a battery of neuropsychological tests. We found subjects with IR had performance reductions in declarative memory and executive functioning. When we examined IR simultaneously with other biomedical indicators with which it co-occurs, only IR itself was associated with declarative memory and HbA1c was associated with executive functioning and working memory. We conclude that individuals with insulin resistance already demonstrate similar reductions in cognitive performance as those described in T2DM.

Keywords

Insulin resistance; type 2 diabetes; cognition; glycemic control; QUICKI

INTRODUCTION

Type 2 diabetes mellitus (T2DM) has been associated with cognitive impairment in numerous studies. Those studies demonstrate that T2DM predominantly affects hippocampal-based declarative memory performance, but executive functioning, and psychomotor efficiency (Awad, Gagnon, & Messier, 2004) are also often impacted. Some authors have suggested that T2DM results in an increased risk for developing dementia (Leibson et al., 1997), however, this remains an issue of debate. Concomitant with the memory impairments observed in T2DM, four reports (three from our own group) have described hippocampal volume loss in T2DM, suggesting that the hippocampus and

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Conflict of interest

None of the authors has any financial or personal conflict of interest.

Author contribution

H. Bruehl was involved in acquisition of data, analysis and interpretation of data, and preparation of the manuscript. V. Sweat was involved in acquisition of data, analysis and interpretation of data, and preparation of the manuscript. J. Hassenstab was involved in analysis and interpretation of data, and preparation of the manuscript. V. Polyakov was involved in preparation of the manuscript. A. Convit designed and conceptualized the study and was involved in the preparation of the manuscript.

associated declarative memory function are particularly vulnerable to the effects of T2DM (den Heijer et al., 2003; Gold et al., 2007; Bruehl, Wolf, & Convit, 2009; Bruehl et al.,).

Insulin resistance,(IR) which is considered to be etiologically linked to obesity (Ferrannini et al., 1997), is an early phenomenon in the course of developing T2DM and is characterized by high circulating fasting insulin levels with fasting glucose levels still within the normal range (Sesti, 2006). These high fasting insulin levels result from the increased secretion of insulin by the pancreas in an attempt to compensate for the reduced effectiveness of insulin to move glucose from the blood stream into the muscle, liver, and fat tissues. This progressive tissue insulin resistance, when accompanied with an inability of the pancreas to continue to compensate by secreting ever higher insulin levels, results in rising blood glucose levels and a diagnosis of T2DM. Insulin resistance can be easily estimated using the quantitative insulin sensitivity check index (QUICKI), which is a logarithmic scale calculated from fasting insulin and glucose levels that has been well validated against euglycemic-hyperinsulinemic clamps (Mather et al., 2001). A QUICKI of less than 0.350 is considered indicative of insulin resistance (Katz et al., 2000). There is good evidence that IR is directly linked to impairments in glucose tolerance (Lindahl, Asplund, & Hallmans, 1993) and that it is a progressive condition that precedes T2DM (Smith & LeRoith, 2004; Lee, Okumura, Davis, Herman, & Gurney, 2006).

A few reports, some animal and some human, indicate that IR itself, before onset of overt diabetes with its associated hyperglycemia, is accompanied by cognitive impairment, however, those reports are methodologically quite heterogeneous and difficult to draw conclusions from. Those reports suggest that the pattern of impairments in IR may resemble the cognitive profile in T2DM. For example, obese insulin resistant rodents exhibit impaired long term spatial memory and reduced hippocampal synaptic plasticity (Stranahan et al., 2008; Winocur et al., 2005). When insulin sensitivity is partly restored pharmacologically, the memory impairments are attenuated (Pathan, Gaikwad, Viswanad, & Ramarao, 2008). In humans with IR, less specific measures of cognitive function have been employed. Elevated insulin levels among non-diabetic individuals have been linked to lower global cognitive performance as assessed with the Mini Mental Status Examination (Vanhanen et al., 1998; Stolk et al., 1997), possibly suggesting that early effects of the metabolic dysregulation associated with IR may be contributing to the cognitive deficits prior to hyperglycemia. Further supporting this notion, studies of subjects with Metabolic Syndrome, which at its core is characterized by impaired glucose tolerance and central obesity, have consistently found reduced performance on mental status exams as well as reduced performance on processing speed, attention, executive functioning, and learning and recall (Dik et al., 2007; van den Berg et al., 2008). Prospective studies have shown that when glycemic control is improved, cognitive functioning improves (i.e., (Gradman, Laws, Thompson, & Reaven, 1993)). Those impairments in glycemic control are generally the result of improvements in IR. A more comprehensive assessment of cognitive function in humans with evidence of IR, short of impaired glucose tolerance or T2DM, remains to be done.

The purpose of this study was to carefully characterize cognitive function in IR by contrasting a group of middle-aged and older adults with clearly defined IR, in the absence of T2DM, with a matched group of individuals with no evidence of clear IR. Based on the existing literature, we hypothesized that IR would be accompanied by lower overall cognitive functioning and specific deficits in hippocampal-based declarative memory. Moreover, we hypothesized that there would be a dose response relationship with more pronounced insulin resistance being associated with a worse cognitive profile. We know that weight loss and/or increased physical activity result in improvements in IR. The clinical relevance of the current study would be to create another rationale, in this case the

prevention of cognitive deficits, for lifestyle modification to halt and reverse the progression of insulin resistance prior to onset of T2DM and significant cardiovascular disease.

METHODS

Ninety-two middle-aged and older non-demented volunteers (38 non-diabetic insulin resistant and 54 controls matched group-wise to the IR group on age, gender, and education) participated in the study. They were either individuals participating in associated longitudinal studies of normal aging or respondents to advertisements on the web. None of the participants showed evidence of neurological, medical (other than dyslipidemia, or hypertension), or psychiatric (including depression and alcohol or other substance abuse) signs and symptoms. None of the participants were being treated with hypoglycemic medications.

All participants were evaluated over two visits. Their first visit included a morning blood draw after a 10–12 hour overnight fast, two blood pressure measurements (once at the beginning of the visit and once at the end), height and weight assessment (for details, see (Wu et al., 2002)), and the first neuropsychological testing session. The remainder of the neuropsychological evaluation took place on a separate subsequent visit. All participants gave informed written consent and were compensated for their participation. The group descriptors are shown in Table 1.

Definition of Insulin resistance

Although some of the insulin resistant participants had fasting glucose levels above 100 mg/dl, none had fasting glucose levels in the diabetic range (≥ 126 mg/dl). All control individuals had fasting glucose levels below 100 mg/dl and HbA1c below 6 %. Individuals were considered to be insulin resistant if they had a quantitative insulin sensitivity check index (QUICKI) of less than 0.350 (Katz et al., 2000). Control subjects all had QUICKI values > 0.350 . The QUICKI is a logarithmic scale calculated from fasting insulin and glucose levels that has been well validated against euglycemic-hyperinsulinemic clamps (Mather et al., 2001). (Mather et al., 2001; Radziuk, 2004)

Definition of hypertension

Hypertension was defined based on current National Cholesterol Education Program guidelines (Expert Panel, 2001) as (1) systolic value greater or equal to 130 mmHg, or (2) diastolic value greater or equal to 85 mmHg, or (3) use of anti-hypertensive medication. The systolic and diastolic blood pressure value used was the average of the two measurements taken on the first day of study evaluation.

Neuropsychological assessment

All cognitive assessments used standardized neuropsychological tests described in detail elsewhere (Bruehl et al., 2007; Bruehl et al., 2007). Briefly, declarative memory was assessed with the Guild Memory Test, California Verbal Learning Test and the Logical Memory subtest from the Wechsler Memory Scale-Revised (WMS-R). Working memory was tested using the Digit Span Backward and the Visual Memory Span Backward from the WMS-R. Executive Function was measured with the Controlled Oral Word Association Test (COWAT), the Stroop task, and the Tower of London. Attention was assessed with the Digit Symbol Substitution Test from the WAIS-R and the Perceptual Speed Test. General Intellectual Functioning was assessed using the Shipley Institute of Living Scale and WAIS-R full scale IQ score estimates were derived from the Shipley score. For each test (e.g., logical memory), the raw score was first converted to a z-score based on the group mean. From these individual z-scores, composite z-scores were then created for each domain

(declarative memory, attention, working memory, and executive function) by averaging the z-transformed data of the individual tests. These composite z-scores were used to assess the differences between groups.

Assays

Glucose was measured using a glucose oxidase method (VITROS 950 AT, Amersham, England) and insulin by chemiluminescence (Advia Centaur, Bayer Corporation).

Statistical analysis

All analyses were conducted using SPSS version 16. Student's t-tests and χ^2 tests were used for comparing the groups on demographic and medical descriptors. Biomedical and physiological variables were selected based on existing literature and our hypotheses. Briefly, hypertension was selected because of its known impact on cognition. QUICKI and HbA1c were selected to ascertain the contribution of IR and hyperglycemia on cognition.

Cognitive performance was contrasted between groups using student's t-tests and Analysis of Covariance (ANCOVA) for each *a priori* cognitive domain (Declarative Memory, Executive Functioning, Attention, and Working Memory).

Multivariate stepwise regression models were constructed to determine the relative contribution of biomedical indicator variables to cognitive performance as represented by composite z-scores for each domain.

RESULTS

Group differences

Demographics—Groups were well-matched on age, education, gender and IQ as is shown in Table 1. As expected, the IR group had significantly higher BMIs, glucose, insulin, HbA1c and QUICKI values, as well as more lipid abnormalities, and higher rates of hypertension. Please refer to Table 1 for a summary of the individual group characteristics.

Cognition—Individuals with IR performed worse on all cognitive tests than did control subjects, except for one test of working memory, where scores were equivalent. Table 2 shows the means and standard deviations for all the individual cognitive tests administered.

When we contrasted the groups based on the summary z-scores for the four different cognitive domains, we found that individuals with insulin resistance showed significant reductions on measures of declarative memory as well as executive function, although effect sizes were small (refer to Table 3). Since groups also differed on BMI and percentage with dyslipidemia, even though a higher BMI is closely associated with insulin resistance, to be conservative, we controlled for BMI and dyslipidemia, respectively. Controlling for BMI in the analysis of declarative memory differences enhanced the group differences ($p=0.018$), whereas the differences on executive function became non-significant ($p=0.147$). Conversely, controlling for dyslipidemia reduced the differences on declarative memory to a statistical trend ($p=0.059$), whereas the differences on executive function became more significant ($p=0.025$).

Given that 27% of our participants did not have all three test scores that comprised the executive function z-score; we re-analyzed the data including only participants with all three scores and found that the reductions in executive function among the IR group was actually more significant (data not shown).

Associations between cognition and physiological variables

Given that many of our physiological variables are expected to be interrelated (for example, IR is related to hypertension, and to long-term glucose control), to better understand the relative contribution of HbA1c, QUICKI and hypertension to cognitive performance, we constructed a stepwise multivariate regression model for each of cognitive domains. For declarative memory, we found that QUICKI was the most significant contributor ($R^2\Delta = 0.050$, $p = 0.034$, $\beta = 4.538$). However, HbA1c was the main contributor to the frontal lobe-mediated domains of executive function ($R^2\Delta = 0.103$, $p = 0.002$, $\beta = -0.587$) and working memory ($R^2\Delta = 0.048$, $p = 0.037$, $\beta = -0.423$). When we conducted a very conservative analysis, where we also controlled for age and education, the only model that remained significant was that of HbA1c predicting frontal lobe-mediated executive function ($R^2\Delta = 0.061$, $p = .013$, $\beta = -0.046$).

DISCUSSION

We found among our group of individuals with IR a pattern of cognitive impairments resembling those described among middle-aged individuals with type 2 diabetes (T2DM). Insulin resistant participants performed descriptively worse on all cognitive domains, but showed statistically significant decrements on measures of declarative memory and executive function. Although these were statistically significant group differences, the effects sizes were relatively small. This is not completely surprising given that IR is an intermediate state between normal insulin function and T2DM. Given that insulin resistance is a progressive pre-diabetic condition (e.g., (Smith et al., 2004; Lee et al., 2006)), our findings are also in keeping with the results from another study that reported that hyperinsulinemia at baseline was associated with cross-sectional declarative memory impairments and greater cognitive decline over a 6 year follow-up (Young, Mainous, III, & Carnemolla, 2006). This suggests that perhaps as metabolic impairments progress, cognitive decrements may become more pronounced.

Declarative memory has well-established associations with the hippocampal formation. Therefore, our findings suggest that hippocampal function is already negatively affected in IR. Hippocampal-based memory impairments, as well as hippocampal atrophy have been described in T2DM (den Heijer et al., 2003; Gold et al., 2007). Moreover, cognitive function and hippocampal volume have been related to degree of long term glucose control in T2DM (Gold et al., 2007). Given the high vulnerability of the hippocampus to metabolic insults of all sorts (e.g., (Mattson, Gurthrie, & Kater, 1989)), and our findings of hippocampal-based declarative memory dysfunction among individuals with IR (a risk category for T2DM), we propose that the hippocampus might be one of the first brain regions affected by the metabolic abnormalities of T2DM, even during its pre-clinical stages. Moreover, although somewhat speculative at this point, our finding of a relationship between degree of IR and declarative memory provides indirect evidence that the early damaging effects on the hippocampal formation observed in T2DM may be due at least in part to the marked insulin resistance that lies at the heart of T2DM. Hyperglycemia may later add to the harmful effects that have started in the pre-clinical IR-stages of the illness.

Insulin resistance may contribute to hippocampal dysfunction through several possible mechanisms including impaired insulin signaling and endothelial dysfunction. The animal literature on IR has demonstrated that insulin signaling pathways are impaired throughout the cerebral cortex and in particular the hippocampus (Mielke et al., 2005), where insulin-binding sites are concentrated (Dore, Kar, Rowe, & Quirion, 1997). These lines of evidence suggest that insulin and insulin receptors may be involved in learning and memory consolidation (Zhao, Chen, Quon, & Alkon, 2004). Although not yet examined in the

human, it is possible that some of the declarative memory deficits we observed in our IR group may be related to impaired insulin receptor signaling in the hippocampus.

Insulin, in addition to its putative role in learning and memory and its well-known key role in peripheral glucose metabolism, also acts as a vasodilator by the regulation of nitric oxide production in endothelial cells (Muniyappa, Iantorno, & Quon, 2008). It has been well-documented that endothelial function is compromised in peripheral tissues of individuals with IR (e.g., (Yki-Jarvinen, 2003)) (Tooke & Goh, 1998; Vinik et al., 2001; Yki-Jarvinen, 2003; Muniyappa et al., 2008) and that this dysfunction occurs early on in the condition (Hsueh, Lyon, & Quinones, 2004). Given the crucial role that vascular reactivity may play in maintaining well-regulated cerebral blood flow, which in turn is vital for maintaining energy-dependent processes such as cognitive function (Drake & Iadecola, 2007), it is possible that the vascular reactivity problems expected in the cerebral microcirculation during IR may lead to CNS dysfunction, particularly during periods of increased metabolic demand that occur during cognitive demand. Therefore, we propose that in IR, disruptions in insulin signaling at the level of the hippocampus in combination with endothelial dysfunction may lead to decreased substrate delivery and perhaps result in cognitive dysfunction (please also see (Convit, 2005)). These hypotheses remain to be formally tested in future work.

Other researchers have speculated that the associations between IR and cognitive impairments may be due to the increased risk of developing dementia in individuals with IR (Young et al., 2006). To that point, some potential mechanistic associations have been reported (Craft, 2007). However, autopsy studies in T2DM argue against such a link (e.g., (Heitner & Dickson, 1949; Beeri et al., 2005; Nelson et al., 2009))(Heitner et al., 1949; Beeri et al., 2005; Beeri et al., 2008).

In addition to the declarative memory impairments and in line with a recent report on executive dysfunction among an older group (65–93 years) with IR (Abbatecola et al., 2004), we found that executive function was also moderately compromised among our insulin resistant participants, with higher degree of IR being associated with worse executive function. Given that Insulin resistance tends to co-occur with several other factors that make up what is called the metabolic syndrome, which includes problems with glucose control (HbA1c), lipid problems, abdominal obesity, and high blood pressure (Expert Panel, 2001), it may be important to determine the relative contribution of each of the various biomedical indicators to the cognitive summary scores.

When we evaluated all of these possible contributing variables simultaneously in a multivariate regression analysis we found that declarative memory was only predicted by the measure of insulin resistance (QUICKI) and that long term glucose control (HbA1c) was the main contributor to the frontal lobe-mediated domains of executive function and working memory. In T2DM, elevated HbA1c levels have been linked to executive dysfunction (i.e., (Mogi et al., 2004)), but of interest here is that none of our participants had HbA1c values in the diabetic range, although some values were high (slightly above 6%). Adding support to our reported associations between HbA1c and decreased executive function, is another report in healthy middle-aged non-diabetics, where elevations in HbA1c were related to decreased cognitive function, although not executive function specifically (MacLulich, Deary, Starr, Walker, & Secki, 2004). HbA1c has been shown to reflect postprandial glucose elevations more than fasting glucose values in T2DM (Woerle et al., 2007) and recently, it has been demonstrated that oscillations in glucose are associated with accelerated oxidative stress and deleterious effects on endothelial in both non diabetics and individuals with T2DM (Ceriello et al., 2008). Therefore, one could speculate that in IR, where fasting glucose values are within the normal range, somewhat more sustained post-prandial glucose

elevations could particularly affect those brain regions, such as the frontal lobe, where there is less vascular redundancy, and contribute to the frontal lobe-based cognitive dysfunction. Although this is a plausible explanation, it is speculative at this point, and these phenomena will need to be better characterized by longitudinal observation.

In conclusion, we present novel data suggesting that otherwise healthy middle-aged and older individuals with IR have subtle cognitive impairments similar to those observed in well-controlled T2DM, namely decreases in declarative memory and executive function. Those abnormalities likely reflect the damaging effects of IR and its associated hypertension on the hippocampal formation and frontal lobe. It appears that prior to onset of T2DM and sustained hyperglycemia, the effects of IR put the brain at risk for damage, possibly via a subtle vascular abnormalities including endothelial dysfunction and even possible alterations in insulin receptor functioning. Because, like hypertension, IR itself is a silent condition, patients are likely unaware that they are at risk for negative health consequences prior to onset of T2DM. We hope that these data will stress the importance that more attention needs to be paid to fasting insulin levels and HbA1c among older patients who are overweight or obese. Given the potential to reverse IR through lifestyle modification prior to the development of T2DM and possible irreversible peripheral and CNS damage, emphasis should also be placed on improving fitness and reducing excess body weight among individuals at high risk for T2DM. For example, interventions including diet modification and aerobic exercise have been found to be effective in improving insulin function in middle-aged and elderly adults (i.e., (Benedict et al., 2008))

This study is limited by its modest sample size, which does not allow a thorough investigation of possible gender effects. In addition, the cross-sectional design of the study limits our ability to make more causal inferences. Further longitudinal work should evaluate possible mechanisms and ascertain whether the impairments associated with IR are reversible with reversal of the IR through pharmacological treatment or lifestyle modification.

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Table 1

Group descriptors

	Controls n = 54	IR n = 38	p
	Mean/SD (Range)	Mean/SD (Range)	
Age (yrs)	60.71 ± 8.69 (45.38–78.53)	62.87 ± 7.21 (46.63–79.10)	0.210
Education (yrs)	16.15 ± 1.93 (12–20)	15.95 ± 2.12 (12–19)	0.638
Gender (% F)	59.3	42.1	0.105
IQ	114.90 ± 10.13 (85.94–139.56)	113.67 ± 9.52 (90.61–132.13)	0.564
BMI (kg/m²)	24.86 ± 3.49 (19–38)	28.98 ± 4.62 (19–40)	<0.001
Glucose (mmol/L)	4.45 ± 0.40 (4–5)	5.15 ± 0.60 (4–7)	<0.001
Insulin (pmol/L)	38.13 ± 9.88 (20.84–57.64)	92.02 ± 10.56 (48.62–236.13)	<0.001
QUICKI	0.382 ± 0.019 (0.351–0.417)	0.328 ± 0.017 (0.290–0.349)	<0.001
HbA1c (%)	5.16 ± 0.30 (4.10–5.50)	5.61 ± 0.42 (4.90–6.70)	<0.001
HDL (mmol/L)	1.59 ± 0.395 (1–3)	1.26 ± 0.33 (1–2)	<0.001
LDL (mmol/L)	2.97 ± 0.79 (1.45–5.10)	2.98 ± 0.87 (1.45–5.36)	0.966
Triglycerides (mmol/L)	1.02 ± 0.42 (0–3)	1.60 ± 0.98 (1–5)	<0.001
Statin use (%)	13.0	28.9	0.057
Dyslipidemia (%)	46.3	84.2	<0.001
Systolic BP (mmHg)	122.65 ± 16.50 (94.5–172.0)	127.36 ± 14.05 (102–165)	0.156
Diastolic BP (mmHg)	72.78 ± 9.41 (56–96)	74.83 ± 8.02 (56–90)	0.278
HTN Med (%)	11.1	26.3	0.058
HTN (%)	53.7	68.4	0.156

Table 2

Raw cognitive scores used to compute domain-wide z-scores

	Controls n = 54	IR n = 38
	Mean/SD (Range)	Mean/SD (Range)
Declarative Memory		
Logical Memory Immed.	31.59 ± 5.72 (19–42)	29.79 ± 6.74 (19–43)
Verbal Paired Immed.	21.17 ± 3.47 (6–24)	19.74 ± 3.75 (11–24)
Visual Paired Immed.	15.91 ± 2.45 (7–18)	14.13 ± 4.16 (3–18)
Visual Rep. Immed.	34.07 ± 4.87 (17–41)	33.53 ± 4.03 (23–40)
CVLT Immediate Recall	12.87 ± 2.39 (5–16)	11.39 ± 3.94 (2–16)
Logical Memory Delayed	27.75 ± 7.36 (12–41)	24.92 ± 7.49 (10–35)
Verbal Paired Delayed	7.72 ± 0.92 (5–12)	7.29 ± 1.06 (4–8)
Visual Paired Delayed	5.87 ± 0.44 (4–6)	5.34 ± 1.21 (1–6)
Visual Rep. Delayed	32.57 ± 5.09 (22–41)	30.74 ± 7.49 (13–40)
CVLT Delayed Recall	12.69 ± 2.61 (4–16)	11.53 ± 3.70 (2–16)
Executive Functioning		
COWAT Total Score	50.69 ± 13.69 (24–76)	43.13 ± 14.28 (21–83)
Stroop Color-Word	39.98 ± 9.44 (21–69)	36.61 ± 9.66 (16–53)
London Excess Moves	10.21 ± 8.53 (0–37)	12.67 ± 10.81 (1–47)
Attention		
Perceptual Speed	76.80 ± 10.37 (50–106)	76.61 ± 17.50 (35–122)
Digit-Symbol Substitution	56.77 ± 10.10 (32–76)	54.87 ± 10.03 (31–76)
Working Memory		
Digit Span Backwards	8.02 ± 2.27 (3–12)	7.32 ± 2.40 (3–12)
Visual Span Backwards	7.74 ± 1.78 (4–11)	7.79 ± 1.70 (4–11)

Table 3

Summary of z-scores differences for the 4 cognitive domains

	95% Confidence Interval			<i>p</i>	<i>d</i>
	Mean Diff	Lower	Upper		
Declarative Memory	0.29	0.01	0.58	0.045	0.462
Executive Function	0.32	0.01	0.63	0.044	0.433
Attention/Concentration	0.14	0.26	0.54	0.477	0.152
Working Memory	0.13	0.21	0.47	0.461	0.157