Original Research Article

Dementia and Geriatric Cognitive Disorders

Dement Geriatr Cogn Disord 2010;29:356–362
DOI: 10.1159/000296071

Accepted: March 3, 2010
Published online: April 24, 2010

Metabolic Syndrome Is Associated with Learning and Recall Impairment in Middle Age

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Key Words

Metabolic syndrome · Insulin resistance · Memory · Cognitive functioning · Diabetes, type 2 · Glucose tolerance · Cognitive impairment

Abstract

Aims: To determine whether middle-aged individuals with metabolic syndrome, both with and without type 2 diabetes, exhibit cognitive impairments, and to determine the role of each metabolic syndrome component in those associations. ***Methods:*** 143 participants were drawn from ongoing studies of normal aging. Metabolic syndrome was diagnosed in 73 participants (age: 60.4 ± 8.4 years), who were contrasted with 70 age- and education-matched controls. ***Results:*** Metabolic syndrome was associated with reductions in recall ($p = 0.006$), lower overall intellectual functioning ($p = 0.013$), and nearly significant reductions in learning ($p = 0.066$) and executive functioning ($p = 0.050$). These effects were only marginally attenuated when controlling for type 2 diabetes diagnosis. Of the 5 components of the metabolic syndrome, insulin resistance was the only significant predictor of variance in learning and recall. In addition, the number of metabolic syndrome criteria met was inversely associated with cognitive performance. ***Conclusions:*** These results indicate that impairments in cognitive functioning associated with metabolic syndrome and type 2 diabetes may begin as early as middle age and are primarily due to insulin resistance. These results demonstrate the importance of screening at-risk adults for insulin resistance in order to initiate lifestyle modifications to reverse or prevent these cognitive changes.

Introduction

'Metabolic syndrome' is the name given to a cluster of associated risk factors including abdominal obesity, abnormalities in glucose regulation and lipid profile, and hypertension [1]. Metabolic syndrome is associated with type 2 diabetes and cardiovascular disease [2, 3], and some reports indicate an increased risk of dementia, primarily vascular dementia [4]. Cognitive functioning in metabolic syndrome has been the focus of recent studies; however, there are significant limitations to these studies due to the use of mental status examinations to assess cognition, the advanced age of the participants, and gender limitations [5–9]. Metabolic syndrome is extremely prevalent among middle-aged adults and is one of the few clinical syndromes affecting a large portion of the general population that is potentially reversible by established interventions [10]. Therefore, there is considerable interest in assessing whether cognitive changes have begun prior to the onset of more serious clinical diseases associated with advanced age.

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Metabolic syndrome is often studied in nondiabetic populations; however, there is significant overlap with type 2 diabetes. Hyperglycemia is a central characteristic of metabolic syndrome and type 2 diabetes, yet it is rare to see an individual with type 2 diabetes who has no other metabolic syndrome risk factors that may negatively impact brain health, suggesting that the distinction between metabolic syndrome and type 2 diabetes is somewhat unclear [11]. Studies of cognitive performance in type 2 diabetes often overlook metabolic syndrome components despite numerous studies that have linked the individual components to cognitive performance and brain structure. In prior work, we found that obesity, dyslipidemia and hyperglycemia explained variance in cognitive performance and brain volumes among individuals with type 2 diabetes [12]. In addition, a syndrome of insulin resistance, characterized by elevated fasting insulin levels but normal fasting glucose levels, often occurs prior to a diagnosis of type 2 diabetes [13], and we have shown that insulin resistance is associated with cognitive impairment in nondiabetic individuals [14]. Thus, it is likely that components of metabolic syndrome, acting independently or synergistically with hyperglycemia, are associated with cognitive impairment and may have significant impact prior to developing significant hyperglycemia.

The goal of this study was to examine performance on a comprehensive battery of cognitive tests in a sample of well-educated middle-aged and older adults with metabolic syndrome, including individuals with type 2 diabetes who met criteria for metabolic syndrome. In addition to fasting glucose, we included fasting insulin and calculated the quantitative insulin sensitivity check index (QUICKI) to diagnose insulin resistance, providing a more sensitive measure of glucose regulation. We hypothesized that metabolic syndrome would be associated with worse overall performance on tests of memory, psychomotor speed and executive functioning, and this association would exist in subjects with and without a diagnosis of type 2 diabetes. We further hypothesized that of the 5 risk factors that comprise metabolic syndrome, insulin resistance would explain a large portion of the variance associated with cognitive performance.

Participants and Methods

Participants

Participants were consecutively screened community-residing nondemented individuals drawn from ongoing studies of normal aging and type 2 diabetes at the Brain, Obesity and Diabetes Laboratory, Department of Psychiatry, New York University School of Medicine. A total of 143 participants, ranging from 43 to 79 years of age, with a minimum of 12 years of education, were enrolled in the study. The participants underwent medical, endocrine, neurological, psychiatric and neuropsychological assessments. The New York University School of Medicine institutional board of research associates approved the study; all participants provided informed written consent and were compensated for their time and inconvenience. Based on data from blood tests and physical examinations, 73 participants were identified as satisfying the requirements for a diagnosis of metabolic syndrome using a slightly modified version of the National Cholesterol Education Program criteria [1]. In these criteria for metabolic syndrome, fasting glucose is used as a measure of insulin resistance, presumably as a matter of practical convenience for clinicians, but fasting glucose levels alone are somewhat insensitive markers of insulin resistance. Insulin resistance is a substantial contributor to cardiovascular disease risk and has been directly linked to impairments in glucose tolerance [15, 16]. Insulin resistance can be easily estimated using the QUICKI, which is a logarithmic scale calculated from fasting insulin and glucose levels that has been well validated against the gold standard, the euglycemic-hyperinsulinemic clamp [17]. A QUICKI of less than or equal to 0.350 is considered an indicator of insulin resistance [18].

Seventy healthy control participants were included in the present study. The participants in this group met no more than 2 of the metabolic syndrome criteria, and the majority (70%) met 1 or none of the criteria.

To receive a diagnosis of metabolic syndrome, participants met at least 3 of the following 5 risk factors:

(1) Abdominal obesity – waist circumference above the specified values for women (>88 cm) and for men (>102 cm);
(2) Hypertriglyceridemia – serum triglyceride levels of ≥1.7 mmol/l;
(3) Decreased high-density lipoprotein (HDL) levels – serum HDL levels below the specified values for men (<1.03 mmol/l) and for women (<1.29 mmol/l);
(4) Hypertension – systolic blood pressure of ≥130 mm Hg, diastolic blood pressure of ≥85 mm Hg, or use of antihypertensive medication;
(5) Insulin resistance: QUICKI of ≤0.350 (1/ [log (fasting insulin) + log (fasting glucose)]), or a diagnosis of type 2 diabetes.

Exclusion Criteria

The participants were screened for psychiatric diseases using a standard psychiatric interview schedule, and further screening was completed by the Mini-Mental State Examination [19] and standard depression questionnaires. Participants with significant psychiatric, neurological (e.g. stroke, seizure disorder, traumatic brain injury) or other medical diseases (apart from type 2 diabetes, hypertension, dyslipidemia or obesity) were excluded from participation in the study. Participants with a diagnosis of type 2 diabetes that otherwise did not meet criteria for metabolic syndrome were excluded from participation.

Measures

Cognitive Assessments

All participants completed a battery of standard neuropsychological tests as part of ongoing studies of type 2 diabetes and normal aging. The battery included tests of attention/working memo-

ry, executive functioning, psychomotor speed and declarative memory. Intellectual abilities were assessed by the Shipley Institute of Living Scale and converted to an age-adjusted IQ estimate [20]. Attention/working memory was assessed by the digit span, spatial span and mental control tests from the Wechsler Memory Scale-Revised (WMS-R) [21]. Psychomotor speed was assessed by the perceptual speed test (a cancellation task) and the digit symbol substitution test from the Wechsler Adult Intelligence Scale-Revised [22]. Executive functioning was assessed using the Stroop interference test, phonemic fluency and category fluency tests. Memory was assessed by the primary subtests of the WMS-R and the California Verbal Learning Test (CVLT) [23]. Memory was separated *a priori* into 2 domains: learning and recall. Learning included the initial trials of the logical memory, verbal paired associates, visual paired associates and visual reproduction subtests from the WMS-R, and the total learning score from the CVLT (sum of learning trials 1–5). Recall included the delayed trials of the WMS-R tests included in the learning domain, as well as the short-delay free recall and long-delay free recall scores from the CVLT.

Laboratory Tests and Physical Examinations

Weight (in pounds) and height (in inches) were measured using a standard scale. Waist circumference (in centimeters) was recorded as the greatest circumference between the lowest rib margin and the iliac crest. Fasting glucose concentration was measured in venous plasma using a glucose oxidase method (VITROS 950 AT; Amersham, Bucks, UK). Blood pressure was taken twice on the first day of the study evaluation, and the systolic and diastolic blood pressure values used were the averages of those 2 measurements. Insulin sensitivity was calculated using the QUICKI. Triglycerides and HDL were determined from fasting blood samples by standard enzymatic techniques.

Statistical Analysis

Between-group differences in population characteristics were analyzed by independent sample t tests for continuous variables and Mann-Whitney U tests for categorical data. Where appropriate, missing values (<5%) were replaced with gender-specific mean values. Excluding cases with missing values did not significantly alter results or conclusions. Each cognitive domain was examined by omnibus multivariate analysis of variance; univariate analysis of variance was used for subsequent pairwise contrasts. Effect sizes were reported using partial eta squares (η_p^2), where 0.02–0.05 is considered a small effect, 0.05–0.08 is a medium effect, and >0.08 is considered a large effect [24]. Due to the significant between-group difference in gender distribution and well-established associations between gender and verbal abilities [25], gender was included as a covariate in all analyses.

The relation of the 5 individual risk factors of the metabolic syndrome with memory and executive function performance was analyzed across the whole sample using hierarchical, multiple linear regression, adjusting for age, gender and education. To limit the number of analyses, composite Z scores were created for learning, recall and executive functioning domains. Additional models were also adjusted for a diagnosis of type 2 diabetes. Finally, the association between learning and recall performance and the number of metabolic syndrome risk factors present (i.e. 0–5) was modeled. All analyses were conducted using PASW Statistics 18.0 for Macintosh (SPSS Inc., Chicago, Ill., USA).

Table 1. Demographic characteristics, metabolic syndrome risk factors and other descriptive variables of the sample (n = 143)

	Metabolic syndrome	Controls	p
Demographic variables			
Number	73	70	–
Female, %	43	60	0.045
Age, years	60.4 ± 8.4	60.1 ± 8.5	0.840
Education, level[1]	3.8 ± 1	4.0 ± 1	0.127
Metabolic syndrome criteria			
Number of criteria present (median)	4	1	<0.001
Insulin resistance, %	94.5	17.1	<0.001
Abdominal obesity, %	90.4	30.0	<0.001
Hypertension, %	80.8	32.9	<0.001
Low HDL, %	63.0	21.4	<0.001
Hypertriglyceridemia, %	39.7	4.3	<0.001
Other descriptive variables			
Type 2 diabetes, %	53.4	0	<0.001
Fasting glucose, mmol/l	6.64 ± 2.82	4.57 ± 0.55	<0.001
Fasting insulin, pmol/l	95.8 ± 56.9	44.4 ± 21.5	<0.001
QUICKI	0.32 ± 0.03	0.38 ± 0.03	<0.001
HbA1c, %	6.75 ± 1.8	5.35 ± 0.6	<0.001
Antidiabetic medication, %	52.1	1.4	<0.001
Body Mass Index, score	32.1 ± 6.5	25.0 ± 3.4	<0.001
Waist circumference, cm	110.7 ± 13.5	91.0 ± 11.4	<0.001
Systolic blood pressure, mm Hg	126.8 ± 15.1	119.1 ± 15.2	0.003
Diastolic blood pressure, mm Hg	74.9 ± 9.3	71.4 ± 9.2	0.029
Antihypertensive medication, %	52.1	10	<0.001
HDL cholesterol, mmol/l	1.16 ± 0.31	1.59 ± 0.40	<0.001
LDL cholesterol, mmol/l	2.78 ± 0.81	3.01 ± 0.84	0.105
Triglycerides, mmol/l	1.79 ± 1.11	1.00 ± 0.37	<0.001
Lipid-lowering medication, %	47.9	10	<0.001
C-reactive protein, nmol/l	30.5 ± 39.0	19.2 ± 29.2	0.051
Depression score (0–63)	2.7 ± 3.1	2.5 ± 3.1	0.732

Values denote means ± SD unless specified otherwise.

[1] Educational level defined as 1 = less than 12 years, 2 = 12 years, 3 = 12–15 years, 4 = 16 years (college graduate), 5 = more than 16 years (at least some graduate degree).

Results

The demographics, metabolic syndrome risk factor prevalence and medical variables are presented in table 1. The metabolic syndrome group had significantly more men than women. In the metabolic syndrome group, insulin resistance and abdominal obesity were the most common risk factors. In the control group, hypertension was the most common risk factor.

Table 2. Between-group multivariate analyses of covariance and univariate contrasts after controlling for gender

	Omnibus F ratio	d.f.	p	η_p^2	Univariate contrasts	F	p	η_p^2
Intelligence	n/a					6.36	0.013	0.04
Attention/working memory	1.732	3, 138	0.163	0.04	n/a			
Psychomotor speed	1.98	2, 139	0.141	0.03	n/a			
Executive functions	2.68	3, 136	0.050	0.06	Stroop interference	3.55	0.062	0.03
					category fluency	3.14	0.079	0.02
					phonemic fluency	4.57	0.034	0.03
Learning	2.13	5, 136	0.066	0.07	logical memory (immediate)	9.24	0.003	0.06
					verbal paired (immediate)	3.74	0.055	0.03
					visual paired (immediate)	4.86	0.029	0.03
					visual reproduction (immediate)	1.39	0.241	0.01
					CVLT trials 1–5 (total)	4.21	0.042	0.03
Recall	3.18	6, 135	0.006	0.12	logical memory (delayed)	9.73	0.002	0.07
					verbal paired (delayed)	3.45	0.065	0.02
					visual paired (delayed)	6.83	0.010	0.05
					visual reproduction (delayed)	7.31	0.008	0.05
					CVLT short-delay recall	11.86	0.001	0.08
					CVLT long-delay recall	6.43	0.012	0.04

For both groups, the estimated overall IQ was in the average-to-high-average range; however, the metabolic syndrome group demonstrated a slightly, but statistically significantly, lower overall IQ (p = 0.013) (table 2). Multivariate analysis of variance, with gender as a covariate, revealed a significant overall difference between the groups in recall ($F_{5, 136} = 3.18$; p = 0.006) (table 2). Univariate contrasts revealed significant group differences on each test in recall, with the exception of verbal paired associates recall, which exhibited a trend (p = 0.065). The most substantial differences were found in paragraph recall (WMS-R: logical memory) and the short- and long-delay recall of the CVLT. A large effect size ($\eta_p^2 = 0.12$) was seen for the overall model, and medium-to-large effect sizes ($\eta_p^2 = 0.05–0.08$) were seen for individual tests. Metabolic syndrome was associated with slightly lower performance on learning measures ($F_{5, 136} = 2.13$; p = 0.066). Although not statistically significant, a robust effect size ($\eta_p^2 = 0.07$) for this model indicates a trend towards lower performance. Univariate contrasts revealed a significantly lower performance on paragraph learning, visual paired associates learning, and the total learning score from the CVLT. There was a trend towards lower performance on the verbal paired associates learning test in the metabolic syndrome group (p = 0.055). There was no difference between groups in the learning trials of the visual reproduction task. Metabolic syndrome was associated with slightly lower overall executive functioning ($F_{3, 136} = 2.68$; p = 0.050; $\eta_p^2 = 0.06$) and lower performance on phonemic fluency (p = 0.034), and trends on the Stroop (p = 0.062) and category fluency tests (p = 0.079).

The association between the 5 individual risk factors of metabolic syndrome and learning, recall and executive functioning (using composite Z scores) was examined in hierarchical linear regression models across the whole sample (table 3). Each model was initially adjusted for age, gender and education, and additional models were adjusted for type 2 diabetes diagnosis. The results indicated that insulin resistance was significantly associated with learning (p = 0.02) and recall (p = 0.001), but not with executive functioning (p = 0.141). When type 2 diabetes was added to the model, insulin resistance was no longer significantly associated with learning performance (p = 0.174), but remained significantly associated with recall performance (p = 0.034). Finally, the number of metabolic syndrome criteria met (0–5) was significantly inversely associated with both learning (p = 0.038) and recall (p = 0.007).

Table 3. Association of individual metabolic syndrome risk factors and metabolic syndrome risk factor total with learning, recall and executive functioning

Independent variables (n = 143)	Learning composite Z score, β	Recall composite Z score, β	EF composite Z score, β
Model 1			
Insulin resistance	–0.179*	–0.250**	–0.127
Hypertension	–0.095	–0.123	–0.103
Abdominal obesity	–0.120	–0.152	0.029
Low HDL	–0.186	–0.191	0.001
Hypertriglyceridemia	0.005	–0.003	0.024
Model 2			
Insulin resistance	–0.124	–0.190*	–0.112
Hypertension	–0.028	–0.039	–0.079
Abdominal obesity	–0.064	–0.082	0.074
Low HDL	–0.125	–0.107	0.056
Hypertriglyceridemia	0.050	0.053	0.051
Model 3			
Risk factor total (0–5)	–0.164*	–0.212**	–0.057

All models adjusted for age, gender and education. Model 2 also adjusted for type 2 diabetes diagnosis.

* $p < 0.05$, ** $p < 0.01$. EF = Executive functioning.

Discussion

Our results provide evidence of an association between metabolic dysfunction and subtle cognitive impairment in a group of mostly middle-aged, highly educated adults with metabolic syndrome. We hypothesized that participants with metabolic syndrome would perform significantly worse than controls on standardized tests of declarative memory and executive functions. The results confirmed that after adjusting for variance associated with gender, the metabolic syndrome group performed worse than the control group on learning and recall on the CVLT and the WMS-R. Trends towards lower performance emerged on tests of executive functions including phonemic fluency, Stroop interference and category fluency. In addition, the metabolic syndrome group had slightly lower overall intellectual abilities. Of the 5 individual risk factors of metabolic syndrome, only insulin resistance emerged as a significant predictor of performance on learning and recall across the sample. After accounting for type 2 diabetes, insulin resistance remained a significant predictor of recall performance. In addition, the number of metabolic syndrome criteria met was inversely associated with learning and recall performance. Our results are unique in that we focused on a primarily middle-aged sample that included males and females and tested for differences in cognitive performance using well-validated and sensitive measures. Given that lower education has been associated with metabolic syndrome [26, 27], this study, utilizing only highly educated individuals, removes educational achievement as a possible explanatory variable and suggests that it is metabolic syndrome itself that is associated with brain dysfunction. Moreover, we included a cohort of subjects with verified type 2 diabetes and relied upon the QUICKI instead of fasting glucose alone to allow a more accurate classification of participants with metabolic disruptions involving more subtle forms of insulin resistance.

Small reductions in overall IQ have been found in prior studies of diabetes and metabolic syndrome [28–30]. We hypothesize that metabolic dysregulation affects neurocognitive performance in general, and intellectual ability, which is measured using neurocognitive tests, is no exception. Intellectual ability has also been shown to predict dietary choices, substance use and physical activity, which suggests that the verbal comprehension and abstract reasoning skills measured in traditional IQ tests may influence lifestyle behaviors that could contribute to the development of metabolic syndrome and type 2 diabetes [30]. However, the high level of education in our sample (most participants were college graduates) could argue against this effect. The causal order of these associations will need to be elucidated in longitudinal prospective studies starting prior to the age of 40 years.

Our finding of impaired declarative memory in metabolic syndrome is similar to findings from the type 2 diabetes literature [31]. In a prior study of cognitive performance in middle-aged participants with carefully diagnosed type 2 diabetes, we found that poor glycemic control was associated with poorer performance on declarative memory tests and with hippocampal volume reductions [28]. Also, we have found that subjects with insulin resistance that do not meet current definitions of type 2 diabetes have impairments in declarative memory and executive functioning [14]. The present study expands upon these findings by including a broader range of participants across the metabolic risk factor spectrum, including those with verified type 2 diabetes and those with what could be considered 'prediabetes' [11]. It is possible that we have detected early stages of brain dysfunction in metabolic syndrome, even among participants who are at risk for, but do not yet have, type 2 diabetes.

Regression analyses revealed that of the 5 components of metabolic syndrome, insulin resistance was the only significant determinant of lower performance in declara-

tive memory tasks. Declarative memory has well-established associations with the structure and the function of the hippocampus. Several possible mechanisms underlying the role of insulin resistance in disruptions in hippocampal-based declarative memory have recently come to light. Although not yet established in humans, animal studies suggest that the supply of glucose during periods of 'high demand' in brain regions such as the hippocampus may not be optimal during acute periods of increased neuronal activity, which may be exacerbated by the disruptions in glucose availability that are characteristic of insulin resistance [32]. In patients with insulin resistance, there is clear evidence of microvascular endothelial dysfunction [33], which can lead to reductions in vascular reactivity [34, 35] and perhaps inefficient transport of glucose across the blood-brain barrier. Thus, during periods of increased neuronal activity, such as during a declarative memory task, patients with insulin resistance may exhibit poor compensation for acute drops in cerebral glucose following neuronal activation, effectively creating a functional hypoglycemic cerebral state [36]. Over time, chronic functional cerebral hypoglycemia may lead to neuronal damage, abnormal brain response and volume loss.

Insulin resistance may also damage the brain via other mechanisms including superoxidative states, advanced glycation end products (AGEs), and by disruption of insulin signaling pathways. Brownlee [37] has suggested that the metabolism of excess glucose in individuals with hyperglycemia may produce a systemic superoxidative state that damages neurons directly. Emerging evidence from neurobiological studies on rodents, primates and humans has focused on the role of AGEs, which are sugar-derived toxic substances that form at a slow but constant rate in the normal body. In insulin resistance, AGEs formation is markedly accelerated because of the increased availability of glucose [38]. AGEs cause damage by altering proteins, which can interfere with cell structure and function throughout the body and brain. In animal models of insulin resistance, insulin signaling pathways are disrupted throughout the cerebral cortex and, in particular, in the hippocampus, where insulin-binding sites are concentrated, suggesting that insulin signaling in the hippocampus may be compromised in patients with insulin resistance.

There are several limitations to the current study. Our sample was composed of mostly highly educated and white individuals, which may limit the external validity of the findings for the broader population with metabolic syndrome. However, given the associations between metabolic syndrome and low educational achievement, this could be seen as a strength of this study. Gender was controlled for when possible, but as expected from the increased prevalence of metabolic syndrome among males, there were slightly more men in the metabolic syndrome group; however, a detailed analysis of gender effects was limited due to sample size. Similarly, a greater sample size may have allowed a more detailed analysis of possible interactions between metabolic syndrome components and cognitive function.

Conclusions

Our results suggest that middle-aged and older individuals with metabolic syndrome exhibit subtle cognitive impairment, independent of type 2 diabetes diagnosis. Of the 5 factors of metabolic syndrome, insulin resistance appears to best explain this association. Impairments in declarative memory performance in insulin resistance are likely related to damage to the medial temporal lobe. Several mechanisms may explain this effect, including endothelial dysfunction, superoxidative stress, AGEs and disrupted insulin signaling pathways. Our results are unique in that they provide evidence that declarative memory impairments in metabolic syndrome may begin earlier in the disease course of type 2 diabetes and as early as in middle age.

Acknowledgements

This study was supported by a grant from the National Institutes of Health DK064087 and supported in part by grant 1UL1RR029893 from the National Center for Research Resources.

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