Arterial Wall Function is Associated with Cognitive Performance Primarily in Elderly with Type 2 Diabetes

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Abstract

Regression analyses compared 41 type 2 diabetes (T2D) and 131 non-T2D cognitively normal elderly males on the associations of arterial wall function measures [large artery elasticity index (LAEI), small artery elasticity index (SAEI), systemic vascular resistance (SVR), and total vascular impedance (TVI)] with cognitive performance (memory, language, and executive functions), controlling for socio-demographic and cardiovascular factors. Higher LAEI and lower TVI were significantly associated with better executive functions performance in T2D but not in non-T2D subjects. Lower TVI was more associated with better language performance in T2D. Results suggest that arterial wall function is associated with cognition in T2D.

Keywords

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INTRODUCTION

Type 2 diabetes (T2D) is associated with increased risk for cognitive decline [1] and dementia [2, 3]. Cerebral vasculature involvement in this relationship is plausible given the increased risk for micro- and macrovascular pathology in T2D [4]. Vascular abnormalities have been shown by some [5], but not all [6], to be associated with T2D-related cognitive compromise. A possible explanation for inconsistencies is that vascular abnormalities evolve, with functional typically preceding structural changes [7]. Nevertheless, research usually focuses on structural (primarily MRI), rather than functional assessments of vasculature. Impaired arterial wall function (AWF), which does not necessarily have a structural correlate identifiable by structural brain imaging, has been found in multiple brain regions in neurologically asymptomatic T2D subjects [8–10].

The present study compared T2D and non-T2D elderly subjects on the associations of measures of peripheral AWF with cognitive performance.

METHODS

Subjects

Subjects were recruited from the outpatient lists of the Computerized Patient Records System (CPRS) of the James J. Peters Veterans Affairs Medical Center in Bronx, NY. Subjects with diagnosis of dementia, cerebrovascular disease, or other neuropsychiatric disorders that may impair cognition, or prescribed dementia-related medications, were excluded. Inclusion criteria were: age 75, male (there are very few elderly women veterans), ambulatory patient status, and intact cognition. The study consisted of 172 consecutive participants who completed a neuropsychological assessment and pulse contour analysis to measure AWF. Informed consent was signed by all subjects.

Diagnosis of T2D was based on CPRS records (fully updated with the American Diabetes Association criteria [11]) and confirmation by the subjects.

Verification of intact cognition was based on the Clinical Dementia Rating (CDR) scale [12] and the Mini Mental State Examination (MMSE) [13]. The CDR assesses the severity of cognitive and functional impairment in six domains, through an interview with the subject and an informant. Subjects were required to have a CDR score of 0, reflecting absence of dementia or questionable dementia. The subjects' score on the MMSE was required to be better than the 10th percentile of age and education adjusted norms [14]. Normal cognitive status was then confirmed by a clinical consensus conference.

Arterial pressures

Arterial pressures were measured using the HDI/Pulse-Wave CardioVascular Profiling Instrument (Hypertension Diagnostics, Eagan, MN). Following 5 min of rest, left brachial blood pressure was measured by oscillometer, with the patient in the supine position with head inclined up 30º. Tracing of the arterial waveforms from the right radial artery was performed using a calibrated stainless steel applanation tonometer with a connected ceramic piezoelectric element. A computer-based diastolic pulse wave contour analysis of radial

artery was performed by evaluating the average diastolic pressure curve by a nonlinear parameter-estimating algorithm using a third-order, four-element Windkessel model of the circulation. The diastolic decay of a waveform was quantified for the large artery elasticity index (LAEI), representing capacitive or large arterial compliance (C1), and for the small artery elasticity index (SAEI), representing oscillatory or small arterial compliance (C2). The values of the C1 and C2 indices are weighted averages of the values obtained from waveforms recorded over 30 s.

Arterial wall function was measured with a noninvasive device that uses blood pressure waveform analysis. Brachial and radial arterial elasticity measurements were obtained using a standard blood pressure cuff and an automated tonometer using an oscillometric technique. Systemic vascular resistance (SVR) was calculated as mean arterial pressure (MAP) divided by estimated cardiac output (ECO). ECO is obtained applying a multivariate algorithm considering patient age, heart rate, body surface area and cardiac ejection time, derived from the pulse wave analysis. The MAP is derived from waveform analysis by integrating the area under each beat and then calculating the average of all beats included in the analysis of recordings during 30 s. Total vascular impedance was determined from the modified Windkessel model evaluated at the frequency of the measured heart rate [15].

Neuropsychological testing

Neuropsychological testing was administered by certified psychometricians. Factor analysis using Varimax rotation derived three cognitive factors from principal components with eigenvalues >1, loading on the following tests: memory (Word List Memory Immediate Recall [16], Delayed Recall, Word List Recognition [16]), language (Verbal Fluency Test [17], Short Version of the Boston Naming Test [18], Shipley [19]), and executive functions (Trail Making Test (Parts A and B) [20], Diamond cancellation, TMX Cancellation [21]). All neuropsychological tests' scores were transformed into Z scores and each cognitive domain was calculated as the sum of the z-scores of the cognitive tests pertaining to the particular domain based on the factor analyses results.

Statistical analysis

Statistical analysis was regression analyses of each cognitive factor (language, memory, and executive functions), evaluating the interaction of each AWF measure (LAEI, SAEI, SVR, and TVI) with the T2D dichotomy, controlling for sociodemographic and cardiovascular characteristics (age, years of education, body mass index (BMI), and average diastolic and systolic blood pressure). The interaction variables were calculated as the product of the T2D dichotomy and the AWF, both of which were additional control variables in the regressions. The effect size of the interaction was its partial correlation, with a positive sign if the association of the AWF with cognition was more positive in T2D than non-T2D. The Holm enhancement of the Bonferroni procedure was used to adjust significance for 12 interactions. For descriptive purposes, partial correlations of each cognitive factor with each AWF, with the same control variables, were calculated separately by T2D status. (Since the T2D and non-T2D partial correlations used the control variables differently, their interactions with T2D were also included as control variables in the regressions.) Student's *t*-test was used to compare means of demographic, cardiovascular, and general cognitive measures.

RESULTS

The study included 172 subjects: 131 non-T2D and 41 T2D. Sample characteristics are presented in Table 1: mean age was 82.0 years and the MMSE averaged 28.2, reflecting normal cognitive function.

Compared to non-T2D, T2D subjects had higher BMI ($p = 0.026$), higher rates of hypertension ($p = 0.042$), higher values of glucose ($p < 0.0001$) and Hemoglobin A1c ($p < 0.0001$), lower diastolic blood pressure ($p = 0.037$), lower HDL-cholesterol levels ($p = 0.025$), higher LAEI ($p = 0.016$), higher SAEI ($p = 0.050$), lower SVR ($p < 0.0001$), and lower TVI ($p = 0.020$) The groups did not differ in other socio-demographic, cardiovascular factors, or cognitive scores (Table 1).

Regression analysis showed a significant interaction for LAEI in executive functions ($p = 0.004$)—higher LAEI was associated with better performance in T2D (partial $r = 0.47$; $p = 0.007$) but not in non-T2D subjects (partial $r = 0.05$, $p = 0.58$) (Fig. 1). TVI results were similar, with the direction of association reversed—higher TVI was significantly associated with worse performance in T2D (p for interaction = 0.003; partial $r = -0.39$, $p = 0.03$ for T2D and $r = 0.02$, $p = 0.82$ for non-T2D). Both results had $p < 0.05$ after adjusting for multiple comparisons. Language interaction for TVI was in the same direction as for executive functions (p for interaction = 0.039; $r = -0.27$, $p = 0.13$ for T2D and $r = 0.04$, $p = 0.67$ for non-T2D). The interactions of T2D with SAEI and SVR were not significant in any cognitive domains (Table 2).

There were 3 subjects with T2D for whom LAEI was > 30. Excluding them from the analysis did not change substantially the results for executive function and LAEI (partial $r = 0.42$, $p = 0.02$) and for executive function with TVI (partial $r = -0.37$, $p = 0.04$), reflecting the robustness of the results. In addition, for 70% of the subjects, we had data on creatinine, triglycerides, total cholesterol, and smoking. Results of analysis including these variables were essentially unchanged (data not shown).

DISCUSSION

In cognitively normal very old male subjects, significant interactions were demonstrated between measures of AWF and T2D in executive functions and language. Higher large arterial compliance and lower total vascular impedance were significantly associated with better executive functions performance in T2D but not non-T2D subjects. Lower total vascular impedance was also more associated with better language performance in T2D than non-T2D subjects. These analyses accounted for socio-demographic and cardiovascular factors that have been associated with cognition and with vascular disease [22]. The cognitive domain most strongly involved in this relationship, executive functions, is consistent with a profile of vascular insults to the brain [23].

The cognitive impairment observed in T2D has previously been attributed to neurodegenerative and to cerebrovascular mechanisms [24]. However, the structural component of these mechanisms, as detected by MRI scans, cannot fully explain the lower cognitive performance observed in T2D, suggesting the involvement of additional factors

[24]. Measurement of AWF can demonstrate the functional precedents of structural vascular pathology. Moreover, AWF may also contribute to neurodegeneration [6],[25] and brain atrophy [25]. Thus its assessment may enhance understanding of the direct and indirect roles of functional vascular pathology in T2D-related cognitive compromise.

Previous cross-sectional studies showed that higher pulse wave velocity (PWV)—a marker of arterial wall stiffness—was associated with lower cognitive performance, neurodegenerative and vascular [26] pathologies in stroke- and dementia-free subjects. PWV was significantly higher in subjects with dementia or mild cognitive impairment compared with normal cognition [27]. Higher PWV was associated with lower scores in episodic memory in cognitively normal subjects aged 45–65[28] and with lower performance in executive functions, and—in contrast to our results—worse verbal episodic memory (primarily affected by AD) in similarly aged T2D subjects [29]. In non-T2D, untreated hypertensive subjects, lower MMSE scores were associated with increased large artery stiffness [30]. In longitudinal studies, higher PWV was associated with a faster rate of cognitive decline in community dwelling older adults [31], very old institutionalized subjects [32] and AD patients [33]. Our study innovates by directly comparing large and small artery compliance measures in elderly with and without T2D and suggests that results of studies that included T2D patients or other subjects prone for vascular pathology (e.g., hypertensive subjects) may be primarily led by them. Lower cognitive performance, even within the normal range, is associated with increased risk for dementia [34]. Thus improvement of AWF, which is modifiable [35], could potentially contribute to prevention or postponement of dementia in elderly T2D subjects.

Worse glycemic control has previously been demonstrated to be associated with increased arterial stiffness [36]. In the present study, T2D subjects had higher large and small artery elasticity, perhaps reflecting more aggressive treatment of other factors affecting arterial stiffness (e.g., hypertension) as advised by international clinical practice guidelines which recommend lower target blood pressure levels in T2D compared to non-T2D subjects [37]. Such an approach may underlie the observed lower values of diastolic blood pressure in T2D subjects participating in the current study despite higher prevalence of hypertension diagnosis. The differences between T2D and non-T2D subjects in the relationship of cognitive performance with worse AWF have not been reported previously. Hyperglycemic and insulin resistance have been more strongly associated with cognitive performance in T2D subjects compared to non-T2D subjects supporting our findings, and, perhaps pointing to a greater vulnerability of the brain in T2D [38]. The mechanisms underlying this vulnerability are beyond the scope of the present study.

Increased intracranial vascular resistance has previously been shown to be associated with poorer cognitive performance in dementia-free individuals [39]. Thus, use of peripheral rather than central nervous system measures of AWF is a limitation of the present study. Nevertheless, the heterogenic effect of vasculopathy on different organs, as demonstrated by the 10-year difference between the peak incidence of myocardial infarction and that of stroke [40, 41], suggests that cerebral vessels are affected at a later stage than coronary vessels and stresses the relevance of the relationship of peripheral extra-cranial vessels function with cognition. An additional limitation is lack of data on carotid artery stenosis,

previously demonstrated to be associated with cognitive function, independently of intracranial vascular changes (e.g., silent MRI infarcts, white matter lesions) [39, 42–44], and lack of structural imaging of brain parenchyma and vasculature, precluding any conclusions about the relationship of peripheral AWF with these factors. The study included only male subjects, limiting the generalizability of the findings to women. Nevertheless, this cohort pertains to the very elderly—the most rapidly growing segment of the population [45] with the highest rates of cognitive decline and dementia [46], and thus of particular importance when developing tailored dementia preventive strategies.

Acknowledgments

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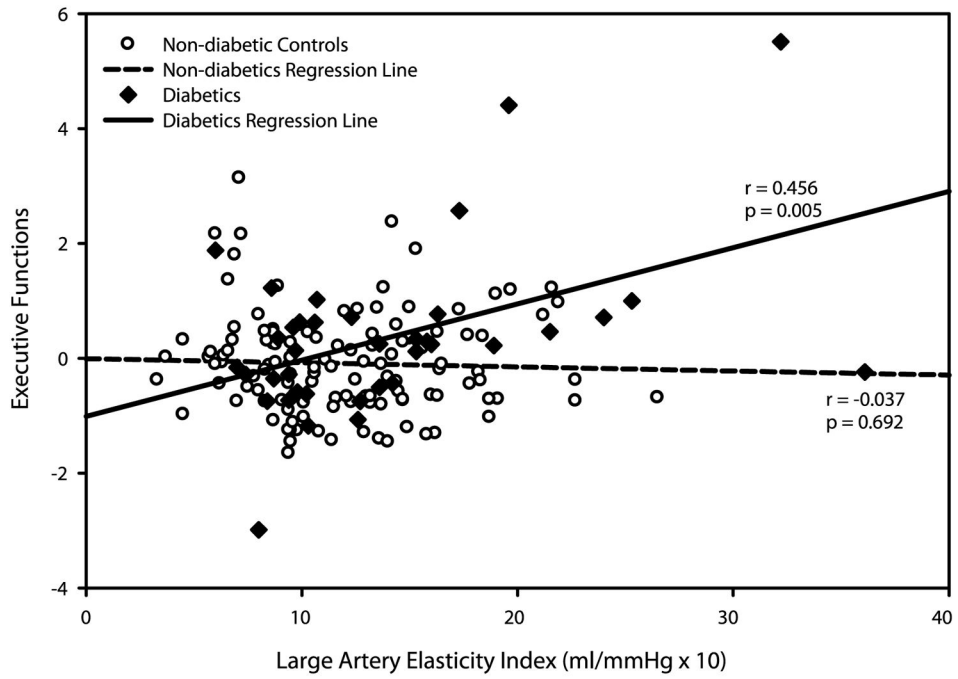
Fig. 1.
Partial correlations of LAEI with executive functions in T2D and non-T2D subjects (unadjusted).

Table 1

Socio-demographic, cardiovascular, and general cognitive characteristics of the sample

Variable	Diabetes status	Mean (SD)	significance
Age (years)	Total ($n = 172$)	82.01 (4.41)	
	Non-T2D ($n = 131$)	82.23 (4.59)	0.249
	T2D ($n = 41$)	81.32 (3.76)	
BMI (kg/m^2)	Total ($n = 171$)	26.84 (4.08)	
	Non-T2D ($n = 130$)	26.39 (3.71)	0.026
	T2D ($n = 41$)	28.27 (4.85)	
Systolic blood pressure (mmHg)	Total ($n = 172$)	136.12 (20.02)	
	Non-T2D ($n = 131$)	135.92 (20.54)	0.81
	T2D ($n = 41$)	136.78 (18.49)	
Diastolic blood pressure (mmHg)	Total ($n = 172$)	71.42 (10.39)	
	Non-T2D ($n = 131$)	72.41 (9.96)	0.037
	T2D ($n = 41$)	68.24 (11.19)	
Diagnosis of hypertension % [*]	Total ($n = 143$)	65.6	
	Non-T2D ($n = 108$)	60.7	0.042
	T2D ($n = 35$)	84.4	
Cholesterol levels [*]	Total ($n = 143$)	170.85 (37.88)	
	Non-T2D ($n = 108$)	173.75 (36.69)	0.108
	T2D ($n = 35$)	161.91 (40.60)	
HDL cholesterol [*]	Total ($n = 143$)	52.27 (14.93)	
	Non-T2D ($n = 108$)	53.58 (15.93)	0.025
	T2D ($n = 35$)	48.23 (10.49)	
LDL cholesterol [*]	Total ($n = 143$)	97.86 (57.30)	
	Non-T2D ($n = 108$)	101.94 (62.98)	0.131
	T2D ($n = 34$)	84.89 (30.67)	
Triglycerides [*]	Total ($n = 143$)	136.94 (73.15)	
	Non-T2D ($n = 108$)	131.08 (69.33)	0.092
	T2D ($n = 35$)	155.03 (82.30)	
Glucose [*]	Total ($n = 154$)	113.91 (47.87)	
	Non-T2D ($n = 117$)	97.13 (15.83)	<0.0001
	T2D ($n = 37$)	166.97 (71.56)	
HbA1c [*]	Total ($n = 154$)	5.9 (105)	
	Non-T2D ($n = 120$)	5.62 (0.45)	<0.0001
	T2D ($n = 34$)	7.03 (1.69)	
Creatinine	Total ($n = 154$)	1.22 (0.46)	
	Non-T2D ($n = 117$)	1.15 (0.32)	P=0.01
	T2D ($n = 37$)	1.47 (0.69)	
LAEI	Total ($n = 173$)	12.53 (5.51)	
	Non-T2D ($n = 132$)	11.98 (4.72)	0.016

Variable	Diabetes status	Mean (SD)	significance
	T2D ($n = 41$)	14.33 (7.31)	
SAEI	Total ($n = 172$)	3.41 (2.10)	
	Non-T2D ($n = 131$)	3.24 (1.92)	0.05
	T2D ($n = 41$)	3.98 (2.54)	
SVR	Total ($n = 172$)	1848.30 (427.044)	
	Non-T2D ($n = 131$)	1907.63 (437.89)	<0.0001
	T2D ($n = 41$)	1658.73 (328.74)	
TVI	Total ($n = 172$)	190.49 (76.56)	
	Non-T2D ($n = 131$)	197.23 (79.58)	0.02
	T2D ($n = 41$)	168.95 (62.06)	
Education (years)	Total ($n = 168$)	13.68 (3.51)	
	Non-T2D ($n = 129$)	13.69 (3.49)	0.971
	T2D ($n = 39$)	13.67 (3.62)	
MMSE score	Total ($n = 169$)	28.20 (1.60)	
	Non-T2D ($n = 129$)	28.16 (1.53)	0.897
	T2D ($n = 40$)	28.20 (1.74)	
Language z score	Total ($n = 172$)	−0.093 (1.10)	
	Non-T2D ($n = 131$)	−0.06 (1.0)	0.42
	T2D ($n = 41$)	−0.22 (1.29)	
Episodic memory z score	Total ($n = 172$)	0.04 (0.93)	
	Non-T2D ($n = 131$)	0.02 (0.94)	0.54
	T2D ($n = 41$)	0.12 (0.91)	
Executive function z score	Total ($n = 172$)	0.01 (1.07)	
	Non-T2D ($n = 131$)	−0.08 (0.93)	0.08
	T2D ($n = 41$)	0.32 (1.39)	

[*] data on diagnosis of hypertension, Total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, blood glucose levels and HbA1c (hemoglobin A1c) was available for $n = 108$–120 non-T2D subjects and for $n = 34$–35 T2D subjects. T2D, type 2 diabetes; BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LAEI, large artery elasticity index; SAEI, small artery elasticity index; SVR, systemic vascular resistance; TVI, total vascular impedance; MMSE, Mini-Mental State Examination.

Table 2

Interactions of AWF with T2D, and partial correlations* of AWF with cognitive domains by T2D status

AWF	Cognitive domain	Interaction of AWF with T2D effect size (p)	Non-T2D partial r (p)	T2D partial r (p)
LAEI	Language	0.096 (0.250)	0.016 (0.865)	0.201 (0.269)
	Memory	0.026 (0.752)	0.094 (0.315)	0.202 (0.267)
	Executive functions	0.238 (0.004)	0.052 (0.581)	0.467 (0.007)
SAEI	Language	0.014 (0.867)	0.036 (0.703)	0.059 (0.749)
	Memory	−0.069 (0.410)	0.230 (0.013)	0.137 (0.455)
	Executive functions	0.118 (0.159)	0.076 (0.417)	0.270 (0.135)
SVR	Language	−0.135 (0.102)	0.033 (0.723)	−0.211 (0.239)
	Memory	−0.034 (0.686)	−0.146 (0.117)	−0.180 (0.315)
	Executive functions	−0.075 (0.363)	−0.072 (0.442)	−0.147 (0.414)
TVI	Language	−0.170 (0.039)	0.040 (0.669)	−0.271 (0.127)
	Memory	−0.047 (0.572)	−0.154 (0.098)	−0.248 (0.164)
	Executive functions	−0.246 (0.003)	0.022 (0.818)	−0.386 (0.027)

*
Controlling for age, years of education, body mass index, and average diastolic and systolic blood pressure. AWF, arterial wall function; T2D, type 2 diabetes; LAEI, large artery elasticity index; SAEI, small artery elasticity index; SVR, systemic vascular resistance; TVI, total vascular impedance.