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ABSTRACT

Objective: To evaluate relationships between HIV-associated neurocognitive disorder and metabolic variables in a subgroup of HIV+ participants examined in a prospective, observational, multicenter cohort study.

Methods: In a cross-sectional substudy of the CNS HIV Anti-Retroviral Therapy Effects Research (CHARTER) cohort, 130 HIV+ participants provided fasting blood samples. Neurocognitive impairment (NCI) was defined by performance on neuropsychological tests adjusting for age, education, gender, and race/ethnicity. Global ratings and global deficit scores were determined. Demographics, biomarkers of HIV disease, metabolic variables, combination antiretroviral therapy (CART) history, other drug exposures, and self-reported diabetes were examined in multivariate models predicting NCI. Separate models were used for body mass index (BMI) alone (n = 90) and BMI and waist circumference (WC) together (n = 55).

Results: NCI (global impairment rating ≥5) was diagnosed in 40%. In univariate analyses, age, longer duration of HIV infection, obesity, and WC, but not BMI, were associated with NCI. Self-reported diabetes was associated with NCI in the substudy and in those >55 in the entire CHARTER cohort. Multivariate logistic regression analyses demonstrated that central obesity (as measured by WC) increased the risk of NCI and that greater body mass may be protective if the deleterious effect of central obesity is accounted for.

Conclusions: As in HIV-uninfected persons, central obesity, but not more generalized increases in body mass (BMI), was associated with a higher prevalence of NCI in HIV+ persons. Diabetes appeared to be associated with NCI only in older patients. Avoidance of antiretroviral drugs that induce central obesity might protect from or help to reverse neurocognitive impairment in HIV-infected persons. ***Neurology*® 2012;78:485–492**

GLOSSARY

AIC = Akaike Information Criterion; **ARV** = antiretroviral; **BMI** = body mass index; **CART** = combination antiretroviral therapy; **Ch** = choline; **CHARTER** = CNS HIV Anti-Retroviral Therapy Effects Research; **DM** = diabetes mellitus; **GDS** = global deficit scores; **HAND** = HIV-associated neurocognitive disorder; **HDL** = high-density lipoprotein; **HOMA-IR** = homeostasis model assessment of insulin resistance; **LDL** = low-density lipoprotein; **MetS** = metabolic syndrome; **NAA** = *N*-acetylaspartate; **NCI** = neurocognitive impairment; **OR** = odds ratio; **WC** = waist circumference; **WHR** = waist to hip ratio; **WMH** = white matter hyperintensity.

Combination antiretroviral therapy (CART) prolongs survival with HIV. Metabolic syndrome (MetS), which is associated with increased risk of type 2 diabetes and atherosclerosis, is a possible complication of CART. MetS components include hyperglycemia attributable to insulin resistance, hypertension, obesity, and dyslipidemias (elevated triglycerides and low-density lipoprotein [LDL] cholesterol and decreased high-density lipoprotein [HDL] cholesterol).[1,2] These features can develop soon after starting CART, especially if regimens include protease inhibitors. Obesity, a component of MetS, may be as common in the HIV-

Supplemental data at www.neurology.org

Supplemental Data

From the University of California (J.A.M., J.A.M.-B., C.A.F., S.L.L., R.J.E., R.K.H., T.W., D.R., T.J.A., I.G.), San Diego; University of Washington (C.M.), Seattle; and Washington University (B.M.A.), St. Louis, MO.

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infected (HIV+) in the CART era as in the general population. Weight distributions are now similar in HIV+ and HIV-uninfected (HIV−) US military populations.[3]

In the CART era, neurocognitive impairment (NCI) remains prevalent in about half of HIV-infected individuals, ranging from mild deficits to severe dementia.[4–6] This persistence suggests that HIV-related CNS damage may be only partially reversible with successful systemic therapy, may be inadequately treated by current CART, or could result from toxicity or secondary metabolic side effects of CART.[7] Links between components of the metabolic syndrome including diabetes and NCI in HIV-uninfected persons has been well-documented.[8–10]

Dementia in older HIV-infected patients has been associated with diabetes, hyperglycemia, and insulin resistance.[8–12] Thus, we studied if metabolic variables, obesity, and diabetes might contribute to risk of NCI in HIV-infected patients in the HAART era.

METHODS

Study design. CNS HIV Anti-Retroviral Therapy Effects Research (CHARTER), a prospective, cross-sectional and longitudinal, observational cohort study examined the effects of CART on the nervous system in patients who are cared for at the HIV clinic at 6 US academic sites. All participants completed a cross-sectional evaluation consisting of comprehensive neuropsychological and neuromedical assessments and phlebotomy, and most underwent lumbar puncture.

Subjects. Of 1,574 HIV-infected subjects enrolled in the CHARTER study, 145 were selected for the metabolic substudy if they provided a fasting blood specimen and underwent neuropsychological assessment at the same visit between June 2006 and September 2007. Of the 145, 15 were excluded for conditions that confounded the interpretation of their cognitive performance, leaving 130 for this analysis.[13] A senior neuropsychologist (R.K.H.) used guidelines from a consensus panel[14] and available historical and testing data to rate cognitive comorbidity in patients.

Standard protocol approvals, registrations, and patient consents. These procedures were approved by the Human Subjects Protection Committees of each institution. Written informed consent was obtained from all study participants.

HIV disease characteristics. Current blood CD4 cell counts were measured by flow cytometry and HIV RNA concentrations in both plasma and CSF were assayed by ultrasensitive (lower limit of detection, 50 copies/mL) reverse transcriptase PCR (Amplicor®, Roche Diagnostic Systems, Indianapolis, IN).

Details of medical and antiretroviral (ARV) history including the dates, dose, and schedule for each ARV drug were captured through self-report using a structured questionnaire by clinicians. For analysis, CART was categorized as currently on, past use, or never used. Current use of other medications was also assessed at baseline.

Cognitive functioning. All subjects completed a standardized battery of 12 neuropsychological tests that assessed cognitive domains commonly affected by HIV. The battery was administered (average time = 2–2.5 hours) and scored by centrally certified research psychometrists. Details of the battery and adjustments for each subject's age, education, gender, and ethnicity are described elsewhere.[13,15,16] Two approaches to diagnosis of NCI were used: 1) a standardized clinical rating algorithm that conforms to recently published criteria for classifying HIV-associated neurocognitive disorders[13,14] and 2) automated global deficit scores (GDS).[15] These methods agree in most cases, but the standard GDS cutoff of >0.50 is more conservative in classifying impairment because it requires at least mildly impaired performance on at least half of the administered tests for a diagnosis of NCI.

Global ratings were derived using a manualized clinical rating system for classifying the severity of overall neurocognitive impairment that conformed to Frascati criteria for HIV-associated neurocognitive disorder (HAND).[15] Global rating scores range across a 9-point scale from normal (1–4) to mildly impaired (5–6) to moderately or severely impaired (7–9).[14] The GDS ranges in value from 0 to 5; higher scores indicate poorer cognitive functioning. Subjects with GDS greater than or equal to 0.5 were considered cognitively impaired.[15]

Insulin resistance and other metabolic variables. Data of diagnosis of diabetes mellitus and use of medications for diabetes were self-reported. Blood pressure was measured in the sitting position with an automated sphygmomanometer. Height and weight at entry into the larger cohort study were used to calculate body mass index (BMI). Standardized midwaist circumference was measured supine at the level of the upper border of the ilium at full exhalation.

Fasting (>6 hours) blood samples for glucose, total cholesterol, triglycerides, high-density lipoprotein (HDL), and low-density lipoprotein (LDL) were collected, processed, and assayed by standard methods in the certified clinical laboratories of each institution. Insulin and leptin were measured centrally at UCSD using a microbead-based assay (Milliplex MAP, Millipore Corp, Billerica, MA) read by a laser-based analytic system (Luminex, Austin, TX). To evaluate insulin resistance, homeostasis model assessment of insulin resistance (HOMA-IR) was calculated using the formula (insulin in μIU/mL × glucose in nM)/22.5. Insulin, HOMA-IR, and leptin were log-transformed to normalize distribution.

Statistical analysis. Univariate analyses were performed to assess demographic and clinical differences between subjects with and without NCI using the χ^2 test or Fisher exact test for categorical variables and t tests or Wilcoxon rank sum test for continuous variables, depending on whether or not the continuous variable was normally distributed. No correction for multiple comparisons was applied to the univariate analyses, as it was understood the results would require further validation in multivariate modeling that selected factors independently of the bivariate analysis.

Multivariate logistic regression analysis was used to model categorical diagnosis of NCI as a function of demographic, medical, and metabolic factors. Stepwise regression based on Akaike Information Criterion (AIC) was used to select the optimal models. The AIC combines the models' overall accuracy with a penalty for overfitting that allows competing models to be

ranked in terms of estimated predictive accuracy. This method is a preferred alternative to coefficient-based stepwise regression since it avoids selecting models on the basis of apparent significance of the individual terms or global fit, both of which are likely to be overstated. The best model may contain a predictor (or predictors) that do not reach statistical significance and still perform better, on average, than available alternatives.

Table 1 Demographic and clinical characteristics for the CHARTER metabolic substudy group combined and stratified by cognitive impairment

	Metabolic group (n = 130)	Impaired (n = 52)	Unimpaired (n = 78)	*p* Value[a]
Demographic characteristics				
Age, y, mean ± SD[b]	46.2 ± 8.8	48.3 ± 7.5	44.9 ± 9.4	0.02
Gender, male, n (%)[b]	113 (87)	45 (87)	68 (87)	0.92
Ethnicity, white, n (%)[b]	74 (57)	35 (67)	39 (50)	0.07
Education, y, mean ± SD	13.1 ± 2.6	13 ± 2.4	13 ± 2.8	0.68
HIV disease status				
AIDS diagnosis, n (%)[b]	91 (70)	41 (79)	50 (64)	0.08
Duration of HIV infection, y, mean ± SD[b]	13 ± 6.5	14.5 ± 6.0	12.0 ± 6.7	0.03
Current CD4, cells/mm^3, median (IQR)[b]	501 (305–708)	556 (326–757)	458 (305–669)	0.09
Nadir CD4, cells/mm^3, median (IQR)[b]	120 (50–250)	101 (50–217)	175 (58–254)	0.20
Plasma viral load				
Cells/mL (log_{10}), median (IQR)	1.7 (1.7–2.4)	1.7 (1.7–2.1)	1.7 (1.7–2.4)	0.51
Detectable, n (%)[b]	40 (35)	16 (33)	24 (36)	0.84
CSF viral load (n = 99)				
Cells/mL (log_{10}), median (IQR)	1.7 (1.7–1.7)	1.7 (1.7–1.7)	1.7 (1.7–1.7)	0.65
Detectable, n (%)	15 (17)	6 (15)	9 (18)	0.78
Antiretroviral characteristics				
ARV status, n (%)[b]				0.90
Currently on	107 (82)	43 (83)	64 (82)	
Past use only	14 (11)	6 (12)	8 (10)	
ARV naive	9 (7)	3 (6)	6 (8)	
Duration of current regimen, mo, median (IQR)	21 (13–40)	23 (14–46)	21 (11–38)	0.57
Metabolic parameters				
Body mass index, kg/m^2, mean ± SD[b]	26 ± 5	26 ± 5	25 ± 5	0.34
Waist circumference, cm, mean ± SD	93 ± 12	99 ± 14	88 ± 9	0.0005
Systolic blood pressure, mm Hg, mean ± SD[b]	127 ± 16	126 ± 17	127 ± 16	0.75
Diastolic blood pressure, mm Hg, mean ± SD[b]	80 ± 11	81 ± 12	80 ± 10	0.54
Total cholesterol, mg/dL, mean ± SD	185 ± 50	192 ± 55	180 ± 45	0.17
HDL, mg/dL, mean ± SD[b]	48 ± 22	46 ± 14	49 ± 26	0.38
LDL, mg/dL, mean ± SD[b]	100 ± 36	104 ± 42	98 ± 31	0.46
Triglycerides, median (IQR)[b]	148 (84–223)	174 (102–252)	136 (79–203)	0.19
Fasting glucose, mg/dL, mean ± SD				
Plasma[b]	89.2 ± 21.7	89.5 ± 22.1	89.0 ± 21.6	0.91
CSF	61.3 ± 9.6	61.7 ± 11.0	61.0 ± 8.7	0.72
Insulin, median (IQR)	17.8 (11.1–36.3)	23.6 (9.7–44.1)	16 (11.2–31.2)	0.24
HOMA-IR, median (IQR)	3.7 (2.1–8.5)	5.8 (1.9–10.7)	3.4 (2.2–7.8)	0.34
Leptin, median (IQR)	435 (209–848)	574 (230–1135)	377 (201–703)	0.10
Diagnosis of diabetes mellitus, n (%)[b]	10 (8)	8 (15)	2 (3)	0.007

Abbreviations: ARV = antiretroviral; CHARTER = CNS HIV Anti-Retroviral Therapy Effects Research; HDL = high-density lipoprotein; HOMA-IR = homeostasis model assessment of insulin resistance; IQR = interquartile range; LDL = low-density lipoprotein.

[a] *p* Value from *t* test, Fisher exact test, χ^2, or Wilcoxon rank sum.

[b] Variables examined in multivariate analysis of neurocognitive impairment described in the Results section.

Odds ratios (OR) for NCI were obtained from the final models. Because of missing data, the 2 logistic regression analyses were limited to 90 and 55 subjects depending on the availability of data for specific variables. Analyses were performed using JMP statistical package (version 6.0, SAS Institute Inc.) and *R* statistical software (version 2.10.1, R Foundation for Statistical Computing, Vienna, Austria).

RESULTS In table 1, demographic, clinical, and metabolic characteristics are presented for all 130 participants in the substudy who had no confounding neurologic history or conditions. This substudy group differed at first CHARTER visit in some demographic and HIV-related variables from the remainder of the CHARTER participants who were also free of serious confounding neurologic conditions (n = 1,195). However, their metabolic profiles were similar to those of the CHARTER cohort except for lower BMI and higher triglycerides. The metabolic substudy group also differed from all US HIV-infected patients based on the CDC 2005 HIV/AIDS surveillance report.[17] For example, our study subjects were on average 9 years older (mean age of 46 vs 37 years) and more likely to be Caucasian (57% vs 31%) and male (87% vs 74%).

The majority of participants had experienced CART-induced immune reconstitution based on having ARV therapy at the time of their study visit (82%), high current CD4 counts (median = 501 cells/mm^3) compared to either much lower nadir CD4 counts (median = 120 cells/mm^3) or AIDS diagnoses (70%), and median plasma HIV concentrations below the limit of detection (1.7 log copies/mL). The average duration of known HIV infection was 13 years.

Cognitive impairment (global rating ≥5) was common (52/130 = 40%). When demographic and clinical characteristics were compared between cognitively impaired and unimpaired subjects (table 1), impaired subjects were older (age 48.3 vs 44.9 years, $p = 0.02$), had longer self-reported durations of HIV infection (14.5 vs 12.0 years, $p = 0.04$), had larger waist circumferences (WC) (99 vs 88 cm, $p = 0.0005$), and were more likely to have been diagnosed with diabetes mellitus (DM II) (15% vs 3%, $p = 0.007$). Impaired and unimpaired participants were similar in other demographics and HIV disease indicators including current and nadir CD4 count, plasma and CSF viral loads, and ARV exposure.

Levels of most metabolic variables were also similar for the 2 groups, but several were nonsignificantly higher in the impaired group. DM II was self-reported by 10 of 130 (8%) subjects. DM II patients were more likely to be cognitively impaired than nondiabetic patients (80% [8/10] vs 37% [44/120], OR = 6.9, $p = 0.01$). Similarly, cognitive GDS were higher in diabetic than nondiabetic patients (median GDS = 0.60 vs 0.13, $p = 0.0012$). These differences appear unrelated to CART because diabetic and nondiabetic participants were similar for proportions on antiretroviral therapy currently, time on their current regimen, and class of CART drugs taken (data not shown, $p > 0.18$ for all comparisons).

To examine the association between diabetes and NCI further, we assessed 1,325 participants in the entire CHARTER cohort who had self-reported diabetes and had no conditions that confounded their cognitive assessment. In these participants, prevalence of NCI by global rating was similar in diabetic and nondiabetic patients (55/115 [48%] vs 563/1,210 [47%], $p = 0.79$). Because the effects of diabetes on NCI had been demonstrated in older HIV-infected patients in a prior study,[12] we examined effects of diabetes in patients aged >55 years (table 2). Prevalence of NCI was significantly higher in these older HIV+ diabetic patients as diagnosed by GDS of >0.5 (11/21 [52%] vs 29/97 [30%], $p = 0.05$), but not when diagnosed by global ratings (13/21 [62%] vs 43/97 [44%], $p = 0.14$). Thus, if diabetes contributes to NCI, it may do so only in older patients.

Multivariate logistic regression analysis was performed using the 90 substudy participants with complete data for 17 of the 26 variables that are marked with superscript b in table 1. As the measure of obesity in our first model, we used BMI instead of WC

Table 2 Relationship of diabetes and NCI (by GDS and global rating) in the CHARTER cohort and in those aged 55+ (excluding cognitively impaired group)

	CHARTER cohort (n = 1,325)			Age ≥55 y (n = 118)		
	Diabetic (n = 115)	Nondiabetic (n = 1,210)	*p* Value[a]	Diabetic (n = 21)	Nondiabetic (n = 97)	*p* Value[a]
GDS ≥0.5, n (%)	44 (38.3)	418 (34.6)	0.43	11 (52.4)	29 (29.9)	0.05
Global rating, n (%)	55 (47.8)	563 (46.5)	0.79	13 (61.9)	43 (44.3)	0.14

Abbreviations: CHARTER = CNS HIV Anti-Retroviral Therapy Effects Research; GDS = global deficit scores; NCI = neurocognitive impairment.
[a] *p* Value from χ^2 or Fisher exact test.

Table 3 Multivariate regression model selected based on AIC to model NCI as a function of demographic, medical, and metabolic predictors of interest including BMI (n = 90)

Variable	Odds ratio	95% CI	*p* Value
Age, year	1.06	1.01, 1.12	0.027
Diabetes	6.08	0.61, 60.7	0.12
BMI, kg/m^2	1.12	1.01, 1.24	0.039

Abbreviations: AIC = Akaike Information Criterion; BMI = body mass index; CI = confidence interval; NCI = neurocognitive impairment.

because only 55 subjects had WC measurements and WC is highly correlated with BMI ($r = 0.83$). This model which used AIC as a selection criterion contained age (OR = 1.06/per year, $p = 0.027$) and BMI (OR = 1.12/kg/m^2, $p = 0.039$) as predictors of NCI (table 3). Diabetes appeared to increase the goodness of fit for the model, but its individual effect did not reach statistical significance ($p = 0.12$). However, the overall fit of this model based on the AIC was better with diabetes included than in competing models.

Finally, we examined WC in a second model of NCI based on the 55 patients with measurements of this and all other variables (table 4). BMI (OR = 0.69, $p = 0.038$) and WC (OR = 1.34 per cm, $p = 0.001$) both entered the model with the best goodness of fit along with diagnosis of AIDS (OR = 49.6, $p = 0.027$), diabetes (OR = 17.6, $p = 0.07$), and triglycerides (OR = 0.32, $p = 0.09$) (table 4). In this model both BMI and triglycerides have ORs less than 1.0 and thus appear protective rather than predisposing, an unexpected finding. The C-statistic (area under the curve of the receiver operating characteristic curve) for this model (0.893) was greater than that of the first model (0.722).

Table 4 Multivariate regression model selected based on AIC to model NCI as a function of demographic, medical, and metabolic predictors of interest including BMI and average mid waist circumference (n = 55)

Variable	Odds ratio	95% CI	*p* Value
AIDS	49.57	2.26, 1089	0.013
Diabetes	17.6	0.76, 409	0.07
BMI, kg/m^2	0.69	0.49, 0.98	0.038
Waist circumference, cm	1.34	1.13, 1.60	0.001
Triglycerides, mg/dL	0.32	0.09, 1.21	0.09

Abbreviations: AIC = Akaike Information Criterion; BMI = body mass index; CI = confidence interval; NCI = neurocognitive impairment.

Reversal of the effect of BMI when WC enters the model suggests that WC is the component of obesity that is most correlated with NCI and that BMI may correlate only because it is a marker of WC. As expected, BMI and WC were highly correlated ($r = 0.83$). The impaired group had larger WC than the unimpaired group at any level of BMI, consistent with findings from the multivariate models.

DISCUSSION This study examined multiple demographic, HIV-associated, and metabolic factors for their effects on prevalence of NCI in HIV-infected patients in care at 6 US academic centers. Age, duration of HIV infection, WC, and self-reported DM were significantly associated with NCI in univariate comparisons, but BMI was not. When BMI was the only measure of obesity in a multivariate model, higher BMIs were associated with NCI. However, the best multivariate model for predicting NCI included both WC and BMI. Greater WC and lower BMI, as well as a diagnosis of AIDS or diabetes and lower serum triglycerides, were significant predictors of NCI. Thus, of the 2 measures of obesity, only WC, a measure of central obesity and a risk factor for insulin resistance and atherosclerosis,[18] contributed to NCI. The reversal of the effect of BMI on NCI when WC is accounted for suggests that central rather than generalized obesity conveys increased risk factor for NCI. These findings suggest that selection of CART that induces less central obesity might reduce the risk of HIV-associated brain damage and cognitive impairment.

Studies of HIV-uninfected persons have revealed complex, nonlinear relationships of obesity (BMI) to cognitive functioning. For example, impairment was more prevalent in persons with either lower or higher than normal BMIs.[19] In a study of 2606 Finnish twins, BMI, cardiovascular disease, hypertension, and diabetes in midlife were each associated with cognitive impairment in old age when adjusted for sex, education, birth year, and age at interview.[20] In contrast, higher BMI later in life appears to be associated with better cognitive function.[21] This latter association could be related to "frailty," a syndrome with components of decreased body mass and impaired cognition.

Recent studies have identified nonlinear effects on cognition by central obesity as measured by WC or waist to hip ratio (WHR).[22–24] In a cross-sectional study of 7,163 normal and overweight (BMI = 20.0–29.9 kg/m^2) women aged 65 to 80 without dementia, increased WHRs (≥0.80) were associated with greater risk of cognitive impairment than were higher BMIs. BMI had the most pronounced association with poorer cognitive functioning in women

with less central obesity (WHR). In contrast, for women with the highest WHR, cognitive scores actually increased with BMI, suggesting that more general increased body mass was protective. This observation is consistent with the protective effect of high BMI that we found when WC was entered into our second model.[22,23]

The mechanisms underlying these relationships are unclear. Both white matter hyperintensities (WMH) and decreased hippocampal volume have been associated with central obesity. In healthy middle-aged adults, visceral fat volume was associated with lower overall brain volume, but not with volume of WMH, temporal horn volume (reflecting hippocampal volume), or number of brain infarcts.[25] Higher midlife body mass index was associated with lower concentrations of *N*-acetylaspartate (NAA) and choline (Ch) in the frontal white matter on MRI spectroscopy, suggesting axonal and myelin injury.[26] Thus, one or more of the multiple consequences of obesity including systemic inflammation, diabetes, insulin resistance, or adipose tissue–derived hormones may mediate generalized or focal cerebral degeneration that leads to cognitive dysfunction.

Self-reported diabetes was associated with NCI in univariate analysis in our metabolic substudy group and in patients older than 55 years within the larger CHARTER cohort. In the younger HIV-infected persons in the CHARTER cohort, the association was not statistically significant. Diabetes entered both of our models selected by the AIC method for maximal predictive accuracy for NCI, but alone was not a statistically significant contributor. Surprisingly, several correlates of diabetes such as fasting blood levels of glucose and insulin and insulin resistance (HOMA-IR) were not significantly related to NCI. Moreover, variables related to atherosclerosis such as blood levels of high- and low-density cholesterol and systolic and diastolic blood pressure were also not significantly associated with NCI.

Likely mechanisms for the effect of diabetes on risk of NCI are either direct damage to the brain from hyperglycemia or increased risk for cerebral atherosclerosis. The decades required for diabetes to cause atherosclerosis could explain the why diabetes increased risk only in older persons. Greater BMI and WC predispose to insulin resistance and diabetes and diabetes increases risk of cognitive impairment.[27,28] Another possible explanation is disruption of the blood–brain barrier by HIV since HIV proteins[29] alter the tight junctions of the blood–brain barrier, potentially increasing brain exposure to higher levels of glucose or other damaging molecules. While we found that CSF glucose levels were higher in diabetic than nondiabetic patients, the difference was not dramatic and seems unlikely to account for the dysfunction. However, glucose levels in CSF may not reflect those in the brain.

Diabetes has been associated in some imaging studies with cerebral macrovascular and microvascular disease that damages the brain in a predominantly subcortical pattern similar to the pattern of HIV damage.[30–32] Moreover, 2 recent studies have associated both risk factors for atherosclerosis (prior cardiovascular disease, hypercholesterolemia, and hypertension) or structural evidence for it (increased carotid artery intima–media thickness) with cognitive impairment in patients with HIV. Alternatively, insulin resistance in the brain may attenuate the intracerebral neuroprotective effects of insulin.[33]

This effect of diabetes on NCI is similar to, but larger than, that reported by other studies of both HIV-infected and HIV-uninfected adults.[9,10,12,34–37] NCI has been correlated with abnormal glucose metabolism, including diabetes and less severe abnormalities, in HIV-infected individuals.[12]

Limitations of the study include its cross-sectional design, relatively small size and few diabetic patients, and lack of an HIV-uninfected comparison group or direct measures of body composition. Moreover, we may have been underpowered to detect effects of some metabolic variables because our substudy population was relatively young.[38–40]

AUTHOR CONTRIBUTIONS

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DISCLOSURE

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REFERENCES

1. Aboud M, Elgalib A, Kulasegaram R, Peters B. Insulin resistance and HIV infection: a review. Int J Clin Pract 2007;61:463–472.
2. Grinspoon S, Carr A. Cardiovascular risk and body-fat abnormalities in HIV-infected adults. N Engl J Med 2005; 352:48–62.
3. Crum-Cianflone N, Tejidor R, Medina S, Barahona I, Ganesan A. Obesity among patients with HIV: the latest epidemic. AIDS Patient Care STDS 2008;22:925–930.
4. Cysique LA, Maruff P, Brew BJ. Prevalence and pattern of neuropsychological impairment in human immunodeficiency virus-infected/acquired immunodeficiency syndrome (HIV/AIDS) patients across pre- and post-highly active antiretroviral therapy eras: a combined study of two cohorts. J Neurovirol 2004;10:350–357.
5. McCutchan JA, Wu JW, Robertson K, et al. HIV suppression by HAART preserves cognitive function in advanced, immune-reconstituted AIDS patients. Aids 2007;21: 1109–1117.
6. Tozzi V, Balestra P, Lorenzini P, et al. Prevalence and risk factors for human immunodeficiency virus-associated neurocognitive impairment, 1996 to 2002: results from an urban observational cohort. J Neurovirol 2005;11:265–273.
7. Schweinsburg BC, Taylor MJ, Alhassoon OM, et al. Brain mitochondrial injury in human immunodeficiency virus-seropositive (HIV+) individuals taking nucleoside reverse transcriptase inhibitors. J Neurovirol 2005;11:356–364.
8. Craft S, Watson GS. Insulin and neurodegenerative disease: shared and specific mechanisms. Lancet Neurol 2004;3:169–178.
9. Cukierman-Yaffe T, Gerstein HC, Williamson JD, et al. Relationship between baseline glycemic control and cognitive function in individuals with type 2 diabetes and other cardiovascular risk factors: the action to control cardiovascular risk in diabetes-memory in diabetes (ACCORD-MIND) trial. Diabetes Care 2009;32:221–226.
10. Peila R, Rodriguez BL, Launer LJ. Type 2 diabetes, *APOE* gene, and the risk for dementia and related pathologies: The Honolulu-Asia Aging Study. Diabetes 2002;51: 1256–1262.
11. Valcour VG, Sacktor NC, Paul RH, et al. Insulin resistance is associated with cognition among HIV-1-infected patients: the Hawaii Aging With HIV cohort. J Acquir Immune Defic Syndr 2006;43:405–410.
12. Valcour VG, Shikuma CM, Shiramizu BT, et al. Diabetes, insulin resistance, and dementia among HIV-1-infected patients. J Acquir Immune Defic Syndr 2005;38:31–36.
13. Heaton RK, Clifford DB, Franklin DR, Jr., et al. HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy: CHARTER Study. Neurology 2010;75:2087–2096.
14. Antinori A, Arendt G, Becker JT, et al. Updated research nosology for HIV-associated neurocognitive disorders. Neurology 2007;69:1789–1799.
15. Carey CL, Woods SP, Gonzalez R, et al. Predictive validity of global deficit scores in detecting neuropsychological impairment in HIV infection. J Clin Exp Neuropsychol 2004;26:307–319.
16. Heaton RK, Grant I, Butters N, et al. The HNRC 500: neuropsychology of HIV infection at different disease stages: HIV Neurobehavioral Research Center. J Int Neuropsychol Soc 1995;1:231–251.

17. Centers for Disease Control and Prevention. HIV/AIDS Surveillance Report, 2005. US Department of Health and Human Services. Centers for Disease Control and Prevention; 2007:1–54.
18. Distiller LA, Joffe BI, Brown V, Distiller GB. The effect of features of the metabolic syndrome on atherosclerotic risk in relatively long-surviving patients with type 1 diabetes. Metab Syndr Relat Disord 2010;8:539–543.
19. Gustafson D. A life course of adiposity and dementia. Eur J Pharmacol 2008;585:163–175.
20. Laitala VS, Kaprio J, Koskenvuo M, Raiha I, Rinne JO, Silventoinen K. Association and causal relationship of midlife obesity and related metabolic disorders with old age cognition. Curr Alzheimer Res 2011;8:699–706.
21. Fitzpatrick AL, Kuller LH, Lopez OL, et al. Midlife and late-life obesity and the risk of dementia: Cardiovascular Health Study. Arch Neurol 2009;66:336–342.
22. Kerwin DR, Gaussoin SA, Chlebowski RT, et al. Interaction between body mass index and central adiposity and risk of incident cognitive impairment and dementia: results from the Women's Health Initiative Memory Study. J Am Geriatr Soc 2011;59:107–112.
23. Kerwin DR, Zhang Y, Kotchen JM, et al. The cross-sectional relationship between body mass index, waist-hip ratio, and cognitive performance in postmenopausal women enrolled in the Women's Health Initiative. J Am Geriatr Soc 2010;58:1427–1432.
24. Wolf PA, Beiser A, Elias MF, Au R, Vasan RS, Seshadri S. Relation of obesity to cognitive function: importance of central obesity and synergistic influence of concomitant hypertension: The Framingham Heart Study. Curr Alzheimer Res 2007;4:111–116.
25. Debette S, Beiser A, Hoffmann U, et al. Visceral fat is associated with lower brain volume in healthy middle-aged adults. Ann Neurol 2010;68:136–144.
26. Gazdzinski S, Kornak J, Weiner MW, Meyerhoff DJ. Body mass index and magnetic resonance markers of brain integrity in adults. Ann Neurol 2008;63:652–657.
27. Gautier A, Roussel R, Ducluzeau PH, et al. Increases in waist circumference and weight as predictors of type 2 diabetes in individuals with impaired fasting glucose: influence of baseline BMI: data from the DESIR study. Diabetes Care 2010;33:1850–1852.
28. Vazquez G, Duval S, Jacobs DR Jr, Silventoinen K. Comparison of body mass index, waist circumference, and waist/hip ratio in predicting incident diabetes: a meta-analysis. Epidemiol Rev 2007;29:115–128.
29. Kanmogne GD, Primeaux C, Grammas P. HIV-1 gp120 proteins alter tight junction protein expression and brain endothelial cell permeability: implications for the pathogenesis of HIV-associated dementia. J Neuropathol Exp Neurol 2005;64:498–505.
30. Akisaki T, Sakurai T, Takata T, et al. Cognitive dysfunction associates with white matter hyperintensities and subcortical atrophy on magnetic resonance imaging of the elderly diabetes mellitus Japanese elderly diabetes intervention trial (J-EDIT). Diabetes Metab Res Rev 2006;22:376–384.
31. Roman GC, Erkinjuntti T, Wallin A, Pantoni L, Chui HC. Subcortical ischaemic vascular dementia. Lancet Neurol 2002;1:426–436.
32. Schmidt R, Launer LJ, Nilsson LG, et al. Magnetic resonance imaging of the brain in diabetes: the Cardiovascular Determinants of Dementia (CASCADE) Study. Diabetes 2004;53:687–692.
33. Duarte AI, Proenca T, Oliveira CR, Santos MS, Rego AC. Insulin restores metabolic function in cultured cortical neurons subjected to oxidative stress. Diabetes 2006;55:2863–2870.
34. Gregg EW, Yaffe K, Cauley JA, et al. Is diabetes associated with cognitive impairment and cognitive decline among older women? Study of Osteoporotic Fractures Research Group. Arch Intern Med 2000;160:174–180.
35. Grodstein F, Chen J, Wilson RS, Manson JE. Type 2 diabetes and cognitive function in community-dwelling elderly women. Diabetes Care 2001;24:1060–1065.
36. Leibson CL, Rocca WA, Hanson VA, et al. Risk of dementia among persons with diabetes mellitus: a population-based cohort study. Am J Epidemiol 1997;145:301–308.
37. Yaffe K, Blackwell T, Kanaya AM, Davidowitz N, Barrett-Connor E, Krueger K. Diabetes, impaired fasting glucose, and development of cognitive impairment in older women. Neurology 2004;63:658–663.
38. Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. JAMA 2002;287:356–359.
39. Becker JT, Lopez OL, Dew MA, Aizenstein HJ. Prevalence of cognitive disorders differs as a function of age in HIV virus infection. AIDS 2004;18(suppl 1):S11–S18.
40. Cherner M, Ellis RJ, Lazzaretto D, et al. Effects of HIV-1 infection and aging on neurobehavioral functioning: preliminary findings. AIDS 2004;18(suppl 1):S27–S34.