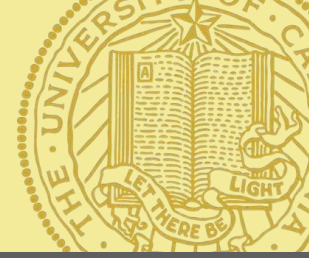


Metabolic Syndrome, Diabetes, and Cognitive Impairment in the Era of Combination Antiretroviral Therapy



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OBJECTIVE

To evaluate the relationship of cognitive impairment in HIV-infection to components of the metabolic syndrome (MS).

BACKGROUND AND SIGNIFICANCE

- Metabolic syndrome, a common complication of combination antiretroviral therapy (CART), includes components such as:
 - insulin resistance (glucose intolerance and type II diabetes),
 - dyslipidemias (high total cholesterol, triglycerides and LDL and low HDL),
 - lipodystrophy (truncal obesity), and
 - hypertension.
- In HIV-uninfected populations, both diabetes and high body mass index (BMI) have been correlated with prevalent cognitive impairment.
- In two studies of the Hawaii Aging with HIV Cohort, diabetes, insulin resistance and elevated glucose levels were linked to dementia in older HIV+ patients.
- We examined the relationship of cognitive impairment to components of the metabolic syndrome in a substudy of the CHARTER Cohort.

METHODS

- This was a prospectively designed substudy of CHARTER, an observational cohort study at 6 North American academic HIV clinics, that examines the effects of combination antiretroviral therapy (CART) on the nervous system.

Enrolled in CHARTER
June 2006-Sept 2007
(n=1,534)

Participants were selected for this metabolic
substudy based on willingness to return
for a fasting blood draw
(n=145)

Neuromedical Assessment:

Metabolic factors: waist circumference, body mass index (BMI), and clinically diagnosed type II diabetes (DMII)
HIV factors: CD4 nadir, antiretroviral (ARV) history, and diagnosis of AIDS

Neuropsychological (NP) Assessment:

All subjects completed a comprehensive battery of NP tests aimed at assessing cognitive functioning in domains commonly affected by HIV. In order to adjust for subject age, education, gender and ethnicity, raw test scores were converted to deficit scores using published methods and normative data. The individual deficit scores from each test were then averaged into a Global Deficit Score (GDS). The GDS ranges in value from 0-5; higher scores indicate poorer cognitive functioning and subjects with scores greater than or equal to 0.5 are considered cognitively impaired.

Laboratory Measurements:

Fasting Blood Draw: cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), glucose, insulin, HOMA-IR (I), HIV viral load (VL), CD4 count
Lumbar Puncture: in a subset of subjects, CSF HIV viral load

RESULTS

Characteristics of Participants

- Most had experienced CART-induced prolonged and sustained immune reconstitution based on:
 - 81% of subjects were taking ARVs
 - current median CD4 count was 498 cells/mm³ in spite of low median CD4 nadir (130 cells/mm³) and high percentage of prior AIDS diagnoses (70%).
 - 38% has detectable plasma HIV in (>1.7 log₁₀ copies/mL),
- About 1/4 of subjects (41/145 = 27%) were cognitively impaired (GDS ≥ 0.5)

Univariate Analyses (see table at lower right)

Impaired and unimpaired participants were similar in demographics... HIV disease indicators based on a) current and nadir CD4 count b) plasma and CSF viral loads, and c) CART exposure.

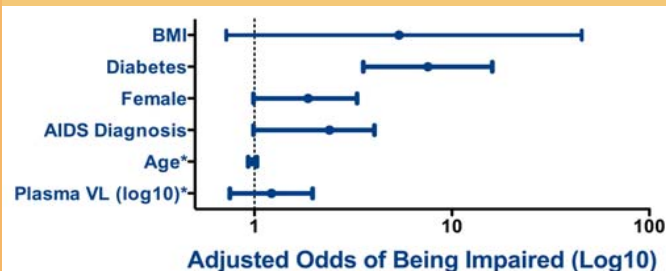
Impaired participants had more abnormal levels in some, but not all, components of the metabolic syndrome:

- higher average BMI (27 vs. 25, p = 0.07), and
- lower high density lipoproteins (43 vs 50, p = .05), and
- higher triglycerides (184 vs. 136, p = .03),
but also
- lower average LDL cholesterol (90 vs 103, p = .03).

- Type II diabetics (DM II) were more likely to be cognitively impaired than non-diabetics (17 vs.42 %, p = .01, OR = 5.1). Similarly, median GDS was higher in diabetics compared to non-diabetics (median GDS = 0.67 vs 0.20, p < 0.01).
- However, neither fasting blood glucose, insulin, and leptin nor insulin resistance (HOMA-IR) were related to cognitive impairment (p ≥ 0.2 or all measures).

Multivariate Analysis (see figure below)

In multivariate logistic regression analysis (n=121), DM II (OR=7.6) was significantly associated with increased odds of being impaired (p < 0.01) after adjusting for BMI, gender, AIDS diagnosis, age and plasma VL, none of which were independently associated with impairment.



Multivariate Logistic Regression Analysis of the Relationship Between Cognitive Impairment and Selected Demographics, HIV Disease Characteristics and Metabolic Parameters.

SUMMARY AND CONCLUSIONS

- In HIV patients, Type II diabetes (DM II) and multiple components of metabolic syndrome were associated with prevalent cognitive impairment in HIV-infected persons, but the mechanism is unclear.
- In contrast to findings in an older Hawaiian cohort, increased insulin resistance, a causal mechanism for DM II, did not correlate with cognitive impairment in our patients.
- Thus, CART drugs that are less likely to induce the metabolic syndrome might reduce the risk of cognitive impairment in HIV-infected persons.

Demographic and Clinical Characteristics for the Entire Cohort Combined and Stratified by Cognitive Impairment Status

	Entire Cohort (n=145)	Impaired (n=41)	Unimpaired (n=104)	p-value*
Demographic Characteristics				
Age, years ¹	45.9 (8.9)	45.0 (7.9)	46.1 (9.3)	0.47
Gender, Male ¹	124 (86%)	32 (78%)	92 (88%)	0.12
Ethnicity, White ²	83 (58%)	26 (63%)	57 (55%)	0.36
Education, years ¹	13.1 (2.7)	13.3 (2.8)	13.0 (2.7)	0.53
HIV Disease Status				
AIDS diagnosis ²	101 (70%)	32 (78%)	69 (66%)	0.23
Current CD4 ² , cells/mm ³	498 (312-712)	550 (305-816)	477 (312-692)	0.47
Nadir CD4 ² , cells/mm ³	130 (5.0-250)	110 (5.0-257)	146 (5.2-250)	0.62
Plasma viral load				
c/mL (log ₁₀) ³	1.7 (1.7-2.4)	1.7 (1.7-2.7)	1.7 (1.7-2.4)	0.43
Detectable ²	48 (38%)	16 (43%)	32 (36%)	0.27
CSF viral load (n=99)				
c/mL (log ₁₀) ³	1.7 (1.7-1.7)	1.7 (1.7-1.7)	1.7 (1.7-1.7)	0.80
Detectable ²	18 (18%)	6 (19%)	12 (18%)	1.00
Antiretroviral Characteristics				
ARV status ²				
Currently on	118 (81%)	32 (78%)	86 (83%)	0.42
Past use on ly	17 (12%)	7 (17%)	10 (10%)	
ARV naive	10 (7%)	2 (5%)	8 (8%)	
Duration of current regimen, months ³	21 (12-38)	19 (11-42)	21 (14-38)	0.55
Metabolic Parameters				
Body mass index ¹ , kg/m ²	26 (5)	27 (5)	25 (5)	0.07
Waist Circumference: cm	93 (15)	97 (23)	91 (10)	0.28
Systolic Blood Pressure ¹	126 (16)	125 (19)	127 (16)	0.42
Diastolic Blood Pressure ¹	80 (11)	80 (12)	80 (10)	0.84
Total cholesterol ¹ , mg/dL	184 (9.4)	178 (4.8)	186 (4.9)	0.38
HDL ¹ , mg/dL	48 (2.2)	43 (1.5)	50 (2.4)	0.05
LDL ¹ , mg/dL	99 (3.5)	90 (2.9)	103 (3.7)	0.03
Triglycerides ³	148 (9.1-219)	184 (124-236)	136 (7.9-212)	0.03
Fasting glucose ¹ , mg/dL	89.4 (21.9)	91.1 (25.8)	88.8 (20.3)	0.60
Insulin (log ₁₀)	1.3 (0.4)	1.4 (0.4)	1.3 (0.4)	0.51
HOMA-IR (log ₁₀)	0.65 (0.45)	0.69 (0.46)	0.63 (0.45)	0.26
Leptin (log ₁₀)	2.6 (0.5)	2.7 (0.6)	2.6 (0.5)	0.41
Diagnosis of diabetes mellitus ²	11 (8%)	7 (17%)	4 (4%)	0.01

*Mean (Standard Deviation), ¹Number (%), ²Median (Inter-quartile Range)
³p-value from t-test, Fisher's Exact test, Chi-square or Wilcoxon Rank Sum

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