Obesity, Diabetes, and HIV: Intersecting Epidemic Contributing to NeuroAIDS?

Barcelona, May, 2013

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UC, San Diego
Background

- In HIV-uninfected populations, risk of neurocognitive impairment (NCI), is increased by components of the metabolic syndrome:
  - obesity (central > generalized),
  - diabetes and glucose intolerance
  - atherogenic hyperlipidemias
  - hypertension

- Mechanisms for these effects are unknown, but may include:
  - Macro- or micro-vascular disease +/- stroke, or
  - Neurotoxicity of insulin resistance or hyperglycemia, or
  - Encephalopathy of systemic inflammation
Background

- In HIV-infected persons, additional mechanisms of neurocognitive impairment (NCI) may be also come directly from HIV and/or by exposure to ART through:
  - Failure: Continued HIV replication in the brain
  - Side effects: Subclinical IRIS to residual HIV in the brain
  - Possible neural toxicity: specific drugs such as efavirenz have clinical and in vitro neurotoxicity

- Diabetes and insulin resistance increased risk of NCI in older (>55) HIV-infected patients in the Hawaiian cohort. (Valcour, Sacktor, Paul, et al, J Acquir Immune Defic Syndr 2006;43:405-41)
Could obesity be contributing to NCI by direct mechanisms or through increasing prevalence of diabetes in HIV patients?

- Obesity, diabetes, and HIV have increased dramatically over the last 3 decades.
- Obesity affects the HIV-infected, antiretroviral-treated populations
  
Proportion of Overweight Adults by Country
Prevalence of Obesity by Educational Levels in Spanish Adults 2008-2010

Obesity Reviews (2012) 13, 388–392
Anatomic Divisions of Abdominal Fat

- **Subcutaneous fat (SAT)** is divided into superficial and deep.
- **Visceral (VAT)** is fat lying within the peritoneum.
- Histology of deep SAT resembles that of VAT.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Superficial</th>
<th>Deep</th>
<th>Visceral</th>
</tr>
</thead>
<tbody>
<tr>
<td>A = lean</td>
<td>144</td>
<td>126</td>
<td>84</td>
</tr>
<tr>
<td>B = obese</td>
<td>141</td>
<td>273</td>
<td>153</td>
</tr>
</tbody>
</table>

Prevalence of Abdominal Obesity in Spanish Adults by Educational Levels 2008-2010

Obesity Reviews (2012) 13, 388–392
Weight categories in HIV+ US Navy personnel

## Body Mass Index (BMI) in HIV+ and HIV- American Women

<table>
<thead>
<tr>
<th>BMI</th>
<th>HIV - N=573</th>
<th>%</th>
<th>HIV+ N=1208</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low &lt;18.5</td>
<td>11</td>
<td>1.9</td>
<td>3</td>
<td>0.25</td>
</tr>
<tr>
<td>Normal 18.5-4</td>
<td>135</td>
<td>23</td>
<td>411</td>
<td>34</td>
</tr>
<tr>
<td><strong>Overweight 25-30</strong></td>
<td><strong>152</strong></td>
<td><strong>27</strong></td>
<td><strong>347</strong></td>
<td><strong>29</strong></td>
</tr>
<tr>
<td>Obese &gt;30</td>
<td>251</td>
<td>44</td>
<td>371</td>
<td>31</td>
</tr>
</tbody>
</table>
Increased Global Absolute Prevalence of Diabetes from 2010 to 2030

World
2010 = 285 million
2030 = 439 million
Increase 54%
Global Projected Diabetes Prevalence (ages 20-79) in 2030
Prevalence of Obesity and Diabetes in the US Adults 1994 to 2009

**Obesity (BMI \geq 30 \text{ kg/m}^2)**

1994 | 2000 | 2009

No Data | <14.0% | 14.0-17.9% | 18.0-21.9% | 22.0-25.9% | \geq 26.0%

**Diabetes**

1994 | 2000 | 2009

No Data | <4.5% | 4.5-5.9% | 6.0-7.4% | 7.5-8.9% | \geq 9.0%
Has the obesity epidemic caused the diabetes epidemic?

Population-wide weight loss and regain in relation to diabetes burden in Cuba 1980-2010: repeated cross sectional surveys and ecological comparison of secular trends

Franco, M et al BMJ 2013

- **Design:** Repeated cross sectional surveys and ecological comparison of secular trends.
- **Setting:** Cuban province of Cienfuegos from 1991, 1995, 2001 in representative samples of 1657, 1351, 1667, and 1492 adults.
- **Economic recession following loss of Soviet support (1990-1995) with decreased availability of food and documented population-wide weight loss.**
Weight distributions in Cuba caused by economic reversals in 1991-95
Diabetes prevalence followed obesity prevalence
Diabetes incidence followed obesity prevalence
Conclusions

- During periods of population-wide loss followed by gain in weight in Cuba, the incidence and prevalence of diabetes closely followed the prevalence of obesity.

- This ecological study supports that hypothesis that the obesity epidemic is a major factor causing the diabetes epidemic.
How are diabetes and obesity related to neurocognitive impairment (NCI)?

In HIV-uninfected persons,

- Diabetes, BMI and central obesity (WC or WHR) all correlate with:
  - Prevalence of NCI in cross sectional studies
  - Incidence of NCI in longitudinal studies
- Diabetes is consistently associated with NCI and cortical atrophy in MRI.
- In statistical models, central obesity is better than BMI in predicting NCI.
Since obesity and diabetes contribute to NCI in HIV-uninfected persons, do they contribute to NCI in HIV-infected patients?

Role of Obesity, Metabolic Variables, and Diabetes in HIV-Associated Neurocognitive Disorder (HAND)


Objective

To examine the relationship between HAND and metabolic variables in HIV+ participants in CHARTER, an observational, multicenter cohort study of patients on HAART.
Methods

- In a cross-sectional study 130 HIV+ CHARTER participants
- Neurocognitive impairment (NCI) was defined by performance on neuropsychological tests adjusting for age, education, gender and race/ethnicity.
- Global ratings and global deficit scores (GDS) were determined by standardized demographically corrected tests.
Methods

- Demographics, biomarkers of HIV disease, metabolic variables, anthropomorphic measures, CART history, other drug exposures, and self reported diabetes were collected.

- Multivariate models predicted NCI using variables that are selected for best overall goodness of fit criteria in two subgroups limited by availability of measures of obesity:
  - Model 1- Body Mass Index (BMI) alone, n=90
  - Model 2- BMI and waist circumference (WC), n=55
### Results: Impaired versus unimpaired

<table>
<thead>
<tr>
<th>Demographic Characteristics</th>
<th>Metabolic Group (n=130)</th>
<th>Impaired (n=52)</th>
<th>Unimpaired (n=78)</th>
<th>p-value #</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years¹</td>
<td>46.2 (8.8)</td>
<td>48.3 (7.5)</td>
<td>44.9 (9.4)</td>
<td>0.02</td>
</tr>
<tr>
<td>Gender, Male²</td>
<td>113 (87%)</td>
<td>45 (87%)</td>
<td>68 (87%)</td>
<td>0.92</td>
</tr>
<tr>
<td>Ethnicity, White²</td>
<td>74 (57%)</td>
<td>35 (67%)</td>
<td>39 (50%)</td>
<td>0.07</td>
</tr>
<tr>
<td>Education, years¹</td>
<td>13.1 (2.6)</td>
<td>13 (2.4)</td>
<td>13 (2.8)</td>
<td>0.68</td>
</tr>
<tr>
<td>AIDS diagnosis²</td>
<td>91 (70%)</td>
<td>41 (79%)</td>
<td>50 (64%)</td>
<td>0.08</td>
</tr>
<tr>
<td>Duration of HIV Infection: years¹</td>
<td>13 (6.5)</td>
<td>14.5 (6.0)</td>
<td>12.0 (6.7)</td>
<td>0.03</td>
</tr>
<tr>
<td>Current CD4³: cells/mm³</td>
<td>501 (305-708)</td>
<td>556 (326-757)</td>
<td>458 (305-669)</td>
<td>0.09</td>
</tr>
<tr>
<td>Nadir CD4³: cells/mm³</td>
<td>120 (50-250)</td>
<td>101 (50-217)</td>
<td>175 (58-254)</td>
<td>0.20</td>
</tr>
<tr>
<td>Plasma viral load c/mL (log₁₀)³</td>
<td>1.7 (1.7-2.4)</td>
<td>1.7 (1.7-2.1)</td>
<td>1.7 (1.7-2.4)</td>
<td>0.51</td>
</tr>
<tr>
<td>Detectable²</td>
<td>40 (35%)</td>
<td>16 (33%)</td>
<td>24 (36%)</td>
<td>0.84</td>
</tr>
<tr>
<td>CSF viral load (n=99)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current CD4³: cells/mm³</td>
<td>1.7 (1.7-1.7)</td>
<td>1.7 (1.7-1.7)</td>
<td>1.7 (1.7-1.7)</td>
<td>0.65</td>
</tr>
<tr>
<td>Detectable²</td>
<td>15 (17%)</td>
<td>6 (15%)</td>
<td>9 (18%)</td>
<td>0.78</td>
</tr>
<tr>
<td>Antiretroviral Characteristics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARV status²</td>
<td></td>
<td></td>
<td></td>
<td>0.90</td>
</tr>
<tr>
<td>Currently on</td>
<td>107 (82%)</td>
<td>43 (83%)</td>
<td>64 (82%)</td>
<td></td>
</tr>
<tr>
<td>Past use only</td>
<td>14 (11%)</td>
<td>6 (12%)</td>
<td>8 (10%)</td>
<td></td>
</tr>
<tr>
<td>ARV naïve</td>
<td>9 (7%)</td>
<td>3 (6%)</td>
<td>6 (8%)</td>
<td></td>
</tr>
<tr>
<td>Duration of current regimen, mths³</td>
<td>21 (13-40)</td>
<td>23 (14-46)</td>
<td>21 (11-38)</td>
<td>0.57</td>
</tr>
</tbody>
</table>
Results:
BMI and WC are highly correlated (rho = .79) and WC increases NCI at all levels of BMIs.
### Results: Multiple Regression Analysis

**Model 1**: Multivariate regression based on AIC to model NCI as a function of demographic, medical and metabolic predictors of interest including BMI (n=90)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.06</td>
<td>1.01, 1.12</td>
<td>0.027</td>
</tr>
<tr>
<td>Diabetes</td>
<td>6.08</td>
<td>0.61, 60.7</td>
<td>0.12</td>
</tr>
<tr>
<td>BMI</td>
<td>1.12</td>
<td>1.01, 1.24</td>
<td>0.039</td>
</tr>
</tbody>
</table>

**Model 2**: Multivariate Regressions 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)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIDS</td>
<td>49.57</td>
<td>2.26, 1089</td>
<td>0.013</td>
</tr>
<tr>
<td>Diabetes</td>
<td>17.6</td>
<td>0.76, 409</td>
<td>0.07</td>
</tr>
<tr>
<td>BMI</td>
<td>0.69</td>
<td>0.49, 0.98</td>
<td>0.038</td>
</tr>
<tr>
<td>WC</td>
<td>1.34</td>
<td>1.13, 1.60</td>
<td>0.001</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>0.32</td>
<td>0.09, 1.21</td>
<td>0.09</td>
</tr>
</tbody>
</table>

AIC = Akaike Information Criterion
NCI = Neurocognitive Impairment
Summary of Results

- NCI (global impairment rating ≥ 5) was diagnosed in 40%.
- In univariate analyses, NCI was associated with:
  - age,
  - longer duration of HIV infection,
  - central obesity (waist circumference (WC), but not general obesity (BMI),
  - Diabetes: self-reported diabetes was also associated with NCI in those aged >55 years in the CHARTER cohort with n=1325.
- Multivariate logistic regression analyses using BMI alone and BMI plus WC demonstrated that only central obesity independently increased risk of NCI.
Conclusions

- As in HIV-uninfected persons, either BMI or WC increases the risk of NCI in HIV+ persons.
- When both BMI and WC are in the model, the effect of BMI is reversed, i.e., it protects from NCI.
- Diabetes increased risk of NCI most clearly in older (> 55 years) HIV-infected persons.
- Reduction of central adiposity might protect from or help to reverse neurocognitive impairment in HIV-infected persons.
Neuroimaging Morphometric Correlates of Metabolic Variables in HIV: The CHARTER Study

Sarah L. Archibald, Christine Fennema-Notestine, J. Allen McCutchan et al
In preparation
### Metabolic Characteristics of 223 participants

<table>
<thead>
<tr>
<th>Metabolic Factor</th>
<th>Mean (stdev.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg/m²)</td>
<td>25.9 (4.5)</td>
</tr>
<tr>
<td>C-LDL (mM)</td>
<td>99.9 (35.4)</td>
</tr>
<tr>
<td>C-HDL (mM)</td>
<td>48.7 (20.6)</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>125.3 (15.2)</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>76.4 (10.8)</td>
</tr>
<tr>
<td>Blood glucose (mM)</td>
<td>95.8 (24.1)</td>
</tr>
<tr>
<td>Diabetes (prevalence in %)</td>
<td>7.2</td>
</tr>
</tbody>
</table>
Imaging Protocol and Analysis

- Ventricular CSF
- Subarachnoid CSF
- Abnormal White
- Total White Matter
- Cortex
- Subcortical Gray
Statistical Analyses

- **Multiivariate regression models to predict each brain volume from each metabolic factor:**
  - Control: age, gender, ethnicity, education, scanner/site, cranial vault, Current CD4, CD4 nadir
  - Metabolic variables: BMI, TC, LDL-C, HDL-C, blood pressure (diastolic and systolic), blood glucose level and diabetes

- **Regression model to predict each metabolic variable from CD4 change**
  - Control: age, gender, ethnicity, education, site, CD4 nadir, vault
  - Immune response: CD4 change (current - six months prior)
## Results: Regression Analyses

<table>
<thead>
<tr>
<th></th>
<th>Total White Matter</th>
<th>Cortical Gray Matter</th>
<th>Subcortical Gray Matter</th>
<th>Ventricular Fluid</th>
<th>Sulcal Fluid</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n=223</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Abnormal White Matter</strong></td>
<td>t ratio</td>
<td>p</td>
<td>t ratio</td>
<td>p</td>
<td>t ratio</td>
</tr>
<tr>
<td>BMI</td>
<td>-0.90</td>
<td>.367</td>
<td>4.25</td>
<td>.0001</td>
<td>-4.10</td>
</tr>
<tr>
<td>BMI (m)</td>
<td>-0.90</td>
<td>.368</td>
<td>3.76</td>
<td>.0002</td>
<td>-4.16</td>
</tr>
<tr>
<td>HDL-C</td>
<td>0.20</td>
<td>.838</td>
<td>-1.61</td>
<td>.109</td>
<td>-1.31</td>
</tr>
<tr>
<td>HDL-C (m)</td>
<td>-0.21</td>
<td>.830</td>
<td>-1.50</td>
<td>.136</td>
<td>-1.68</td>
</tr>
<tr>
<td>LDL-C</td>
<td>-0.15</td>
<td>.878</td>
<td>2.54</td>
<td>.012</td>
<td>-1.33</td>
</tr>
<tr>
<td>LDL-C (m)</td>
<td>-0.09</td>
<td>.930</td>
<td>1.67</td>
<td>.096</td>
<td>-0.44</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>0.11</td>
<td>.914</td>
<td>1.26</td>
<td>.210</td>
<td>-2.26</td>
</tr>
<tr>
<td>Glucose</td>
<td>2.71</td>
<td>.007</td>
<td>-0.27</td>
<td>.789</td>
<td>-0.02</td>
</tr>
<tr>
<td>Glucose (m)</td>
<td>1.91</td>
<td>.058</td>
<td>0.06</td>
<td>.951</td>
<td>-0.01</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.33</td>
<td>.021</td>
<td>1.13</td>
<td>.258</td>
<td>-0.68</td>
</tr>
<tr>
<td>Diabetes (m)</td>
<td>1.39</td>
<td>.168</td>
<td>1.72</td>
<td>.086</td>
<td>-0.87</td>
</tr>
</tbody>
</table>

Control variables include scanner, age, ethnicity, CD4 nadir, and cranial vault.
Multi-metabolic model (m) includes BMI, HDL-C, LDL-C, Glucose, Diabetes.
Results: Univariate analysis

Examining each metabolic variable separately to predict brain volumes

1. Greater BMI was associated with smaller cortex and larger white matter
2. Hyperglycemia or diabetes was associated with abnormal white matter
3. Blood pressure was not related to any of the brain volume or density measures.
Results: Multivariate Analysis

Examining combined effects of metabolic variables found:
1. similar correlations to the univariate analysis suggesting these effects have distinct mechanisms
2. CD4 change over 6 months (? reflecting IRIS) was not associated with metabolic variables
Summary

1) Elevated BMI, total cholesterol, glucose, and diabetes correlated with altered gray and white matter volumes in HIV-infected patients on HAART.

2) Glucose dysregulation (hyperglycemia and diabetes) was associated with white matter enlargement and more abnormal signal suggesting edema in white matter.

3) Presumed WM edema could be caused by several mechanisms:
   1) Cerebral macro- or micro-vascular disease
   2) Hyperglycemia or insulin resistance
   3) Neural toxicity of ART
Conclusions and Implications

Clarification of the causal mechanisms of the combined effects of HIV and metabolic variables on brain structure could lead to targeted interventions.

We hypothesized that pro-inflammatory cytokines generated in inflamed central fat could mediate the brain damage that causes NCI.
Mechanisms: Obesity and Inflammation

- Central obesity leads to invasion of the deep subcutaneous and visceral adipose tissues by activated macrophages that form “crown-like structures” (CLS) around adipocytes.

- Fred Sattler (USC), Scott Letendre (UCSD), and I have measured selected cytokines in 130 CHARTER patients and found that interleukin 6 (IL-6), a pro-inflammatory cytokine appeared to mediate the relationship of central obesity to NCI.
Obesity and adipose tissue inflammation

Normal Fat    Inflamed fat with crown-like structures CLS = M1

M2: “Alternatively Activated”
Anti-inflammatory
(IL-4, IL-13, PPARγ and PPARα)

M1: “Classically Activated”
Pro-inflammatory
(LPS, IFNγ, FFA stimulation TLR4)

Apovian 2008; Lumeng, 2008
Both waist circumference and IL-6 increase with higher GDS (NCI)

<table>
<thead>
<tr>
<th></th>
<th>rho</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>WC with n=152</td>
<td>0.21</td>
<td>0.009</td>
</tr>
<tr>
<td>WC w/o GDS=0</td>
<td>0.31</td>
<td>0.0006</td>
</tr>
<tr>
<td>IL-6 with n=152</td>
<td>0.17</td>
<td>0.04</td>
</tr>
<tr>
<td>IL-6 w/o GDS=0</td>
<td>0.18</td>
<td>0.055</td>
</tr>
</tbody>
</table>

* Square root of Global Deficit Score
WC correlates with GDS only in those with the highest tertile (1/3) of blood IL-6 levels.

- High IL-6 tertile: Rho = .39, p = .0005
- Low IL-6 tertile (including GDS=0): Rho = .07, P = .65
Proposed mechanism for effects of central obesity on NCI

Central Obesity → Cytokines (IL-6) → Insulin resistance, diabetes and / or atherosclerosis → Brain damage and NCI
Overall Conclusions

- HIV+ populations have elevated levels of NCI and aging will expose them to added risk from diabetes and obesity.
- Thus, combined effects of these 3 common, global, epidemic diseases (HIV, obesity, and diabetes) will contribute to an increasing prevalence of HAND and its consequences.
- Therapy for this mechanism of HAND might target:
  - Reducing generalized and central obesity (eg, exercise, tesamorlin (growth hormone releasing factor agonist), or bariatric surgery), or
  - Anti-inflammatory drugs (eg, NSAIDs)
Supported by NIH contracts N01 MH22005, HHSN271201000027C and HHSN271201000030C (CHARTER; PI: I. Grant)) and by NIH grant MH79752 (PI: T. Jernigan).