Endocrine and Metabolic Changes in HIV Disease

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Learning Objectives

- Document the metabolic co-morbidities, such as diabetes, obesity and osteoporosis, in men and women with HIV-infection.
- Describe the pathophysiology of metabolic abnormalities in HIV disease.
Faculty Disclosure

- Please see conference program for disclosures.

Off-Label Disclosure

- There will be no off-label discussions in this presentation.
Metabolic Disorders: Outline

- Lipodystrophy
- Hypogonadism
- Glucose disorders
- Bone density
Projected Proportion of those Living With HIV in United States 50+ Years* 2001-2017


Slide Courtesy of Amy Justice, MD, PhD
Significance of Metabolic Disorders in HIV infection

- In the HAART era, HIV has become a chronic disease for many patients.
- Importance of aging-related comorbidities, such as obesity, diabetes, osteoporosis and heart disease, has increased.
- Etiology of obesity, cardiovascular disease and osteoporosis is multifactorial.
Multifactorial Etiology of Abnormalities in Metabolic Abnormalities
Adipose Tissue Changes - Lipodystrophy

- **Lipoatrophy**
  - Diffuse loss of subcutaneous adipose tissue
  - One-third of HAART-treated patients
  - Associated insulin resistance, dyslipidemia and increased inflammation

- **Lipohypertrophy**
  - Excess of abdominal visceral tissue or ectopic deposition in liver, epicardium and muscle
  - Insulin resistance

- **Mixed lipodystrophy**
Regional Body Fat Changes in HIV-infected Patients

Peripheral Fat Wasting  Fat Accumulation

Normal

HIV Lipodystrophy
HIV Lipodystrophy
Less Abdominal, Thigh and Extremity Fat in HIV-infected Men

<table>
<thead>
<tr>
<th></th>
<th>HIV+/HAART</th>
<th>HIV-</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg/m²)</td>
<td>23.9 (2.8)</td>
<td>28.4 (4.6)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Visceral Fat (cm²)</td>
<td>128 (51)</td>
<td>149 (60)</td>
<td>0.11</td>
</tr>
<tr>
<td>Abdominal SQ Fat (cm²)</td>
<td>121 (86)</td>
<td>275 (125)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Thigh SQ Fat (cm²)</td>
<td>46 (52)</td>
<td>130 (61)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Extremity Fat by DXA (g)</td>
<td>4678 (2564)</td>
<td>9436 (3592)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Brown, 15th CROI, 2008
Lipoatrophy – Mechanisms and Risk Factors

- Increased fat break down and inflammation in lipoatrophy
- Mitochondrial dysfunction in adipocytes which leads to adipocyte apoptosis
- Other risks – male sex, older age and more advanced HIV disease and nuclear genetic polymorphisms
- Worsened by NRTIs stavudine, zidovudine, and nelfinavir

Lichtenstein, JAIDS 2003, Jacobson CID 2005, Montes AIDS 2010
Basal Lipolysis is increased in HIV+ Subjects

Hadigan, Metabolism, 2002
Increased Markers of Inflammation and Subcutaneous Fat in HIV Infection

Brown, 15th CROI, 2008
When Good Fat Turns Bad: Adiposopathy: Subcutaneous Fat Biopsy: Macrophages

HIV+ HIV-

Jan, Antiviral Therapy, 2004
Lipoatrophy: Treatment

- Switching from NRTI - Full restoration does not occur
  - Mean weight gain in extremity fat mass was 1.2 kg (loss was 5-6 kg)
- No benefit from rosiglitazone; modest increased fat (0.35 kg) from pioglitazone
- Facial fillers for cosmetic reasons
- Recombinant leptin - may improve insulin resistance

HIV Lipodystrophy
Lipohypertrophy: Mechanisms

- Dysregulation of fatty acid metabolism due to HIV or antiretroviral agents, which lead to selective deposition in the visceral adipose tissue depots

- Increased local cortisol concentration owing to aberrant conversion from cortisone

- Relative growth hormone deficiency

Lipohypertrophy: Treatment

- Switch from protease inhibitor to atazanavir and ritonavir
- Exercise
- Metformin - may worsen lipoatrophy. Use when glucose intolerance
- Testosterone – although correlated clinically, no benefit from treatment
- Growth hormone – lipolytic, reduces abdominal fat by 17-20%, but worsening DM

Thoni Diabetes Metab 2002; Kohli HIV Med 2007; Wunder Antivir Ther 2007
Lipohypertrophy: Tesmorelin Treatment

- Tesmorelin, a synthetic analogue of growth hormone releasing hormone
- Stimulates synthesis of IGF-1 in the liver, without excess Growth Hormone
- 11-15% reduction in visceral adipose tissue at 6 mos.
- Very mild deterioration in glucose tolerance
- Potential risk of increased IGF-1 and malignancies

Falutz JAIDS 2010, Clayton Nat Rev Endocrinol 2011
Dyslipidemia

- Untreated - Hypertriglyceridemia, low HDL, low LDL and a predominance of small LDL particles

- Treated – “Return to health” – higher LDL

- Ritonavir-boosted protease inhibitors – increased TG and LDL
Dyslipidemia - Treatment

- Safe – Pravastin, fluvastatin, niacin, fenofibrate, gemfibrozil, omega-3 fatty acids
- Use with caution – atovastatin, rosuvastatin
- Not safe – simvastatin, lovastatin

Metabolic Disorders: Outline

- Lipodystrophy
- Hypogonadism
- Glucose disorders
- Bone density
Testosterone: Production and Regulation


Only 2% is free testosterone; 98% is bound.
Age-Adjusted Sex Hormones in Men by HIV-Status in MACS Cohort

- Total Testosterone
  - HIV+: 600
  - HIV-: 600
  - p = 0.68

- Free T
  - HIV+: 100
  - HIV-: 100
  - p = 0.0004

- SHBG
  - HIV+: 60
  - HIV-: 60
  - p < 0.0001

Monroe, HIV Medicine, 2012
Risk Factors Associated with Androgen Deficiency and HIV

- Overall prevalence 20-25%
- Wasting (50% prevalence hypogonadism)
- Weight loss
- CD4 cell count <350 cell/mL
- AIDS
- Aging
- Specific meds – megace, glucocorticoids, ketoconazole, opioids

Mechanism of Primary and Central Hypogonadism in HIV

- **Central effects**
  - Hypothalamically mediated stress and undernutrition
  - Opiate use
  - Invasion by opportunistic infections or malignancies - Toxoplasmosis, CMV, Kaposis sarcoma, Lymphoma

- **Primary testicular effects**
  - Cytokine excess - decreases steroidogenesis
  - TNF decrease the p450-dependent side chain cleavage enzyme
  - IL-1 inhibit the binding of LH to Leydig cells
  - Invasion by toxoplasms, CMV, neoplasms

Sellmeyer, Endocrin Rev 1996; Poretsky, Metabolism 1995; De Paepe, Hum Pathol 1989
Increased Likelihood of Hypogonadism with Drug Use

Dobs, Endocrine Soc 2005
Higher the BMI, the lower the TT in a Population-based Sample

Body Mass Index

NHANES III
N=1460

p=0.0036
HIV-infected Men in the MACS Cohort have a Lower Free T Compared to HIV-uninfected Equivalent to ~ 6-8 yrs of Aging

β HIV status: -0.13, p<0.001; β age: -0.01, p<.0001

Monroe, Endo Soc, 2010
SHBG is Higher in HIV-infected. Both Increase with Age in the MACS Cohort

Monroe, Endo Soc, 2010
Consequences of Hypogonadism HIV Disease

- Reduced muscle mass – sarcopenia, decreased strength, decreased function status
- Low bone density
- Depression
- Decreased sexual function
- Decreased QOL

Grinspoon, JCEM 1996;81:4051-8
Farifield, J Appl Physiol 2001;90:2166-71
Dolan, Arch Int Med 2004;164:897-904
Grinspoon, JCEM 2000;85:60-5
Effects of TE on Body Composition in AIDS Wasting Syndrome


TE – 300 mg i.m. q3 wk
Changes in body composition in testosterone-treated HIV-infected men and women

Vicious Circle: Bidirectionality of Low Testosterone and Obesity

- Decreased muscle mass
- Increased fat mass

Low testosterone levels

- Increased aromatase
- Increased estradiol
- Increased inflammatory factors

Visceral obesity
Insulin resistance

### Treatment of Male Hypogonadism In HIV: Testosterone Formulations

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Dosage and Frequency</th>
</tr>
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<tbody>
<tr>
<td><strong>Injectable</strong></td>
<td></td>
</tr>
<tr>
<td>Testosterone cypionate/enanthate</td>
<td>200 mg every 2 wk</td>
</tr>
<tr>
<td><strong>Implantable</strong></td>
<td></td>
</tr>
<tr>
<td>Testosterone pellets</td>
<td>150-450 mg (2-6 pellets) every 3-6 mo</td>
</tr>
<tr>
<td><strong>Transdermal</strong></td>
<td></td>
</tr>
<tr>
<td>Topical gel - AndroGel (1% or 1.62%), Fortesta 2%, Testim 1%</td>
<td>50-70 mg daily</td>
</tr>
<tr>
<td>Axillary solution - Axiron</td>
<td>30-120 mg daily</td>
</tr>
<tr>
<td>Patch system -- Androderm</td>
<td>5 mg daily</td>
</tr>
<tr>
<td><strong>Buccal</strong></td>
<td></td>
</tr>
<tr>
<td>Buccal system - Striant</td>
<td>30 mg every 12 h</td>
</tr>
</tbody>
</table>
Anemia and HIV

- Anemia seen in 63-95% of HIV patients
- Associated with severity of HIV disease
- Mechanism – decreased erythropoietin production, erythropoietic response, and trapping of iron in reticuloendothelial cells
- Low T predicts anemia (adjusted OR 3.27)
- T replacement mechanism – Increased erythropoietin production, leading to increased Hgb synthesis and erythroid precursors

Risky Sexual Behaviors

- Among 1168 HIV + gay and bisexual men in New York and San Francisco
- 19% used Testosterone, 12% viagra
- Users more likely to be white, >45 yrs of age and more educated
- Use was related to unprotected receptive anal intercourse and unprotected insertive oral intercourse with both HIV+ and HIV unknown men

Purcell et al. AIDS 2005 (19): S57-66
Metabolic Disorders: Outline

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- Hypogonadism
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- Bone density
Risk of Incident Diabetes Mellitus in the Multicenter AIDS Cohort Study (1999-2003)

4 fold increased risk of DM in HAART-treated men

Brown, Dobs Arch Int Med, 2005
Mechanisms Explaining the Increased Risk of DM and Insulin-Resistance in HIV-Infection

- Obesity
- Lipodystrophy
- Severe illness
- Reduced testosterone concentrations
- HAART
  - Mitochondrial toxicity
Longitudinal increases in waist circumference are associated with HIV-serostatus, independent of antiretroviral therapy.

Adjusted for exposure to the 3 major ART classes, age, nadir CD4, BMI, and time since baseline visit.

Brown, AIDS, 2007
Decreasing Insulin Sensitivity with Increasing Visceral Adipose Tissue in HIV-infected Patients with Lipodystrophy

Hadigan, Am J Phys Endo and Metabolism, 2006
### Hyperinsulinism Worse in the Usual Risk Factors plus Lower CD4 Counts

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per 5 year increase)</td>
<td>1.09 (1.01, 1.19)</td>
</tr>
<tr>
<td>BMI (per 5 unit increase)</td>
<td>2.82 (2.36, 3.38)</td>
</tr>
<tr>
<td>Nadir CD4 (per 50 cell decrease)</td>
<td>1.06 (1.00, 1.13)</td>
</tr>
<tr>
<td>Hepatitis C +</td>
<td>1.22 (0.65, 2.30)</td>
</tr>
<tr>
<td>Family history of DM</td>
<td>1.27 (0.98, 1.63)</td>
</tr>
<tr>
<td>Non-caucasian</td>
<td>1.53 (1.09, 2.15)</td>
</tr>
</tbody>
</table>

Brown, AIDS, 2005
Lower free T associated with insulin resistance, but not diabetes

<table>
<thead>
<tr>
<th></th>
<th>Outcome: Diabetes</th>
<th>Outcome: HOMA-IR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>β (p-value)</td>
</tr>
<tr>
<td>Log Free T</td>
<td>0.81 (0.47, 1.38)</td>
<td>-0.15 (&lt;0.01)</td>
</tr>
<tr>
<td>HIV-infected/HIV-uninfected</td>
<td>1.88 (1.02, 3.49)</td>
<td>0.22 (&lt;0.0001)</td>
</tr>
</tbody>
</table>

Adjusted for age, race, BMI, and HCV status

Brown, AIDS, 2005
Insulin Resistance Worsens with HAART Exposure

Brown, AIDS, 2005
Odds Ratios for Incident Diabetes by Quartile of Week 48: sTNFR1

- Q1: 1.0
- Q2: 5.36 (0.77, 37.5)
- Q3: 14.0 (1.37, 143)
- Q4: 39.4 (2.17, 716)

Adjusted for baseline marker level, age, CD4 < 200 cells/mm³ at week 48, 48 wk BMI, and IDV use

p-value, test for trend=0.01

Brown, Diabetes Care, 2010
Mitochondrial Toxicity induced by NRTIs

- Nucleoside inhibition of DNA polymerase-γ
  ⇒ Depletion of mitochondrial DNA (mtDNA)
  - abnormal fat oxidation
  - Adipocyte apoptosis
  - Fat biopsies show abnormal mitochondria

Benbrick, J NeurolSci 1997; Agarwall, Mutat Res 1997, Masini, 1999
Indinavir inhibits Glucose Transport (GLUT 4) into the Cell

Murata, AIDS, 2002
Improvement with Metformin in HIV Patients with Insulin Resistance and Lipodystrophy

Change in Insulin AUC

<table>
<thead>
<tr>
<th>Change in Insulin AUC</th>
<th>Placebo</th>
<th>Metformin</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>500</td>
<td></td>
</tr>
<tr>
<td>1000</td>
<td>1500</td>
<td></td>
</tr>
<tr>
<td>2000</td>
<td>2500</td>
<td></td>
</tr>
<tr>
<td>3000</td>
<td></td>
<td></td>
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</tbody>
</table>

Change in Waist Circumference

<table>
<thead>
<tr>
<th>Change in Waist Circumference</th>
<th>Placebo</th>
<th>Metformin</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1.5</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>-1.0</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>-1.5</td>
<td></td>
</tr>
</tbody>
</table>

n=26 Metformin 500 mg bid

Glucose Dysregulation in HIV: Treatment

- Lifestyle modification – Diet, exercise
- Metformin – especially in patients < 60 years of age and BMI > 35
- Pilglitazone – if Type 2 DM and lipoatrophy
- HbA1c may be inaccurate in HIV-infected individuals - ? High MCV
- Cardiovascular disease - unclear

Kim Diabetes Care 2009; Hadigan JCEM 2002
Metabolic Changes in HIV-Infections: Outline

- Lipodystrophy
- Hypogonadism
- Glucose disorders
- Bone density
Increased Risk of Osteopenia and Osteoporosis in HIV-infection

Prevalence of Reduced Bone Mineral Density by HIV Status

<table>
<thead>
<tr>
<th>HIV Positive on HAART</th>
<th>HIV Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteoporosis (T-score &lt; -2.5)</td>
<td>8</td>
</tr>
<tr>
<td>Osteopenia (T-score = -1.0 - -2.5)</td>
<td>55</td>
</tr>
<tr>
<td>Osteopenia (T-score = -1.0 - -2.5)</td>
<td>32</td>
</tr>
</tbody>
</table>

p = 0.02

Brown, Dobs, J Clin Endocrinol Metab 89:1200-6, 2004
HIV and Low Bone Mass

- Meta-analysis found that osteoporosis was 3-4 times more common in HIV-infected persons.
- Fracture was 60% higher in HIV-infected men and women.
- Prevalence of osteopenia to be 33-65% and osteoporosis to be 6-16%.
  - In the general population, 55% of people age 50+ have osteoporosis.

HIV and Decreased Bone Mass: Mechanism

- In untreated HIV, bone resorption and bone formation are uncoupled
- Elevated markers of resorption
- With initiation of ART, bone resorption markers increase sooner and to a greater degree than markers of bone formation
- Creates a catabolic window that promotes bone loss: 2-6% loss with 48-96 weeks of ART
Multifactorial Etiology of Abnormalities in Metabolic Abnormalities
Conclusions

- HIV-infected patients are living longer
- Metabolic disturbances include lipodystrophy, dyslipidemias, diabetes mellitus and insulin resistance, hypogonadism and osteoporosis
- Antiretroviral medications are playing a decreasing role in the pathogenesis of glucose abnormalities
- Chronic inflammation likely leads to many of these co-morbid conditions
- Treatment should first address life style and established treatment options.
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