Association of markers of gut microbial translocation and inflammation with insulin resistance in HIV-infected persons

Michael Reid1, Yifei Ma2, Rebecca Scherer1,2, Jennifer C. Price1, Audrey French3, Michael Plankey4, Phyllis C. Tien1,2

1Department of Medicine, University of California, San Francisco, CA; 2Medical Service, Department of Veteran Affairs Medical Center, San Francisco; 3Department of Medicine, John H. Stroger, Jr. Hospital of Cook County, Chicago, IL; 4Department of Medicine, Georgetown University Medical Center, Washington, DC

Abstract

Background- Microbial translocation has been proposed as an important driver of immune activation and inflammation in virologically suppressed HIV-infected adults. It is hypothesized that microbial translocation may alter concentrations of cytokines that lead to insulin resistance, even after controlling for other traditional determinants of diabetes.

Methods- This was a cross sectional study of 377 HIV-infected patients on highly active antiretroviral therapy (HAART) and 241 HIV-uninfected controls. Cytokine plasma was assayed for the gut barrier marker intestinal fatty binding protein (iFABP), a surrogate of microbial translocation, as well as sCD14 and sCD163, both markers of monocyte activation, and interleukin (IL)-6, an inflammatory cytokines. Association between these markers and insulin resistance, quantified by Homeostasis Model Assessment (HOMA) and by fully-adjusted multivariate regression analysis, was evaluated using multiple imputation after controlling for traditional and HIV-related factors.

Results- Mean iFABP levels were significantly higher in HIV-infected persons compared with controls (543 vs. 353 pg/mL; p<0.001). Mean concentrations of sCD14 (2.17 vs. 1.59 mg/L, p=0.033), sCD163 (244 vs. 178 pg/mL, p<0.001) and IL-6 (167 vs. 129 pg/mL, p<0.001) were also higher in HIV-infected participants. Among HIV-infected patients, those in the highest tertile of iFABP levels had significantly lower CD4 nadir (p=0.027) and were more likely to have a history of opportunistic infections (p=0.044) and active Hepatitis C infection than those in other tertiles. In unadjusted linear regression, increasing sCD163 levels were associated with increased insulin resistance. While traditional determinants, including body mass index and gingival circumference were also predictive of insulin resistance, neither sCD14 levels nor sCD163 levels were associated with increased insulin resistance in adjusted multivariate models.

Conclusions- Gut epithelial barrier dysfunction, immune activation and inflammation were higher in HIV-infected persons compared to controls. While increased epithelial dysfunction was seen in HIV-infected patients, iFABP was not predictive of insulin resistance. By contrast, sCD163 levels were independently associated with insulin resistance in multivariable models. Possible mechanisms are sought to better elucidate the role of sCD163 in the pathogenesis of diabetes.

Table 1. Demographics and clinical characteristics stratified by HIV and hepatitis C virus infection status

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>sCD14 Adjusted* (Median ± IQR)</th>
<th>sCD163 Adjusted* (Median ± IQR)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>sCD14 adjusted</td>
<td>1.96 (1.51, 2.54)</td>
<td>1.49 (1.17, 1.87)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>sCD163 adjusted</td>
<td>1.20 (1.10, 1.30)</td>
<td>1.17 (1.16, 1.37)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Table 2. Association of HIV, HCV, and HIV/HCV with HOMA-IR compared to controls after adjustment of demographic, lifestyle, and metabolic factors plus adjustment for iFABP, sCD163, sCD14, and IL-6. HIV/HCV coinfected had significantly greater HOMA-IR than controls after adjustment for demographic, lifestyle, and metabolic factors; the association weakened after additional adjustment for sCD163, but not with iFABP, sCD14, or IL-6.

<table>
<thead>
<tr>
<th>Infection Status</th>
<th>Adjusted* (Estimate (95%CI))</th>
<th>Adjusted+ (Estimate (95%CI))</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV mononucleosis</td>
<td>0.97 (0.91, 1.03)</td>
<td>1.05 (0.94, 1.16)</td>
</tr>
<tr>
<td>HIV/HCV coinfected</td>
<td>1.37 (1.24, 1.52)</td>
<td>1.18 (1.10, 1.27)</td>
</tr>
<tr>
<td>HCV mononucleosis</td>
<td>1.12 (1.03, 1.22)</td>
<td>1.19 (1.10, 1.30)</td>
</tr>
<tr>
<td>HCV/HIV coinfected</td>
<td>1.36 (1.24, 1.50)</td>
<td>1.47 (1.32, 1.64)</td>
</tr>
</tbody>
</table>

Table 3. Association of markers of microbial translocation and inflammation with HCV and HCV status. sCD163 was independently associated with greater HOMA-IR in all four groups.

<table>
<thead>
<tr>
<th>Infection Status</th>
<th>Unadjusted* (Estimate (95%CI))</th>
<th>Adjusted* (Estimate (95%CI))</th>
<th>Fully adjusted* (Estimate (95%CI))</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV mononucleosis</td>
<td>1.04 (0.97, 1.11)</td>
<td>1.05 (0.98, 1.12)</td>
<td>1.02 (0.95, 1.09)</td>
</tr>
<tr>
<td>HIV/HCV coinfected</td>
<td>1.43 (1.32, 1.55)</td>
<td>1.40 (1.29, 1.51)</td>
<td>1.29 (1.18, 1.42)</td>
</tr>
<tr>
<td>HCV mononucleosis</td>
<td>1.00 (0.94, 1.06)</td>
<td>1.01 (0.95, 1.08)</td>
<td>1.02 (0.95, 1.09)</td>
</tr>
<tr>
<td>HCV/HIV coinfected</td>
<td>1.03 (0.97, 1.11)</td>
<td>1.04 (0.98, 1.11)</td>
<td>1.05 (0.99, 1.11)</td>
</tr>
</tbody>
</table>

Introduction

Background- The WIHS was funded primarily by the National Institute of Allergy and Infectious Diseases (U01 AI103401, U01 AI103408, U01 AI03384, U01 AI03384, U01 AI03384, U01 AI03384, and U01 AI03384), with additional co-funding from the European Kingdon Shriver National Institute of Child Health and Human Development (NICHD), the National Cancer Institute (NCI), the National Institute on Drug Abuse (NIDA), and the National Institute on Mental Health (NIMH). The WIHS is funded by R01 AI18713 (PC), which was administered by the National Institute for Research in Care and Education and with resources of the Veterans Affairs Medical Center, San Francisco, CA. The study was also supported by the UCSF Liver Center (P30 DK087453), K24 AI 108156 (PC), and the UO1 Global Food Initiative Fellowship Program.

Acknowledgements

Conclusions

- HIV/HCV coinfected adults have greater HOMA-IR than controls, even after controlling for traditional risk factors for diabetes mellitus
- We found that higher levels of sCD163 may partly explain the association of HIV and HCV with HOMA-IR. However, neither sCD14 nor sCD163 were associated with greater HOMA-IR
- Intergender, regardless of infection status, higher sCD163 was associated with greater HOMA-IR, suggesting that the association is independent of the HIV-associated cascade of microbial translocation, immune activation, and inflammation. 
- Prospective studies are warranted to elucidate the role of CD163 in the pathogenesis of disorders of glucose metabolism, and whether increasing levels of CD163 could impact DM risk.

Methods

Participants of the WIHS at three study sites were included in this cross-sectional analysis.

Study Population

Participants of the Women's Interagency HIV Study (WHI) and the Study of Visceral Adiposity, HIV, and HCV: Biologic Mediators of Steatosis (VAHH) were included in cross-sectional analysis. WHI is a multicenter prospective study established in 1994 to investigate the progression of HIV in women and at risk for HIV. Women enrolled in a Liver Steatosis substudy and a Fibromyositis Substudy, and at WHS sites (San Francisco, DC, and Louisville, KY) were included.

The WHS enrolled 224 participants (89% men) with HIV mononucleosis (n=64), HIV/HCV coinfecion (n=57), HIV mononucleosis (n=55), and neither HIV nor HCV infection (n=78) between October 2010 and June 2014 from the San Francisco Veterans Affairs Medical Center.

After exclusion of participant with diabetes mellitus, WHS and VAHH data were pooled in order to examine the relationship of markers of microbial translocation, monocyte activation, and inflammation with insulin resistance in HIV-infected and uninfected women and men.

Measures

Primary Endpoint

- Intestinal Fatty Binding Protein (iFABP), a marker of enteral and degradative capacity and coregulation of cytokines.
- sCD14 and sCD163, markers of monocyte activation.
- interleukin (IL)-6, a marker of systemic inflammation

Secondary Predictors

Infection status (HIV infection, Hepatitis C virus (HCV) infection), demographic (age at index visit, race/ethnicity, gender), behavioral (cigarette use and alcohol use), anthropometric measurements (body mass index (BMI), waist circumference, hip circumference, metabolic profile, estimated glomerular filtration rate), HIV-related measures (current CD4 cell count, CD4 cell count nadir, current HIV RNA level, history of clinical antidepressants and current use of HAART).

Outcome

Insulin resistance estimated using the Homeostasis Model Assessment (HOMA-IR) defined as fasting insulin (μIU/mL) × glucose (mg/dL)/405.

Statistical Analysis

Multivariable linear mixed models were used to assess the associations of HOMA-IR status and each of the assayed inflammatory markers in unadjusted, demographic adjusted and fully adjusted multivariate models. In models with missing cases, multiple imputation using the chained Equations method was used to impute missing covariates with ten replications.

Figure 1. Marginal age, race, and gender-adjusted means for HOMA-IR stratified by infection status

HIV-coinfected and HCV mono-infected adults had greater HOMA-IR than HIV-monoinfected and controls (demographic-adjusted mean [95% CI]: 1.96 [1.51, 2.54] and 1.56 [1.22, 2.24] vs. 1.41 [1.16, 1.77] and 1.14 [1.17, 1.75], respectively).

Corresponding Author: Dr. Michael Reid 1050 Perimeter Avenue, University of California, San Francisco, CA 94134 Phone: (415) 235-4830, ext 2577 E-mail: mreid@uw.hsc.washington.edu