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**BACKGROUND**

HIV+ pts are at increased risk of cardiovascular disease (CVD). Carotid intima-media thickness (IMT) is an established marker for subclinical atherosclerosis and is increased in HIV+ pts. Chronic inflammation and endothelial dysfunction may play a key role in the development of CVD, but little data exists in this population.

**OBJECTIVES**

- To assess carotid IMT, inflammatory and endothelial activation biomarkers in HIV+ vs. HIV-
- To correlate inflammatory and endothelial activation biomarkers to carotid IMT in HIV+ vs. HIV-

**METHODS**

- Study design**
- Prospective, single-site, observational cohort study of HIV+ patients and age- and sex-matched uninfected healthy controls
- Inclusion Criteria**
- ≥13 years of age and HIV+
- Exclusion Criteria**
- Known cardiovascular disease, diabetes, or current opportunistic infection or other acute inflammatory condition
- Study Evaluations**
- PE, BP, ht/wt, hip-to-waist ratio, past medical history
  - Carotid ultrasound:
    - Separately measured right and left common carotid artery (CCA) and internal carotid artery (ICA) intima-media thicknesses
  - Blood sampling after ≥ 8 hours fasting
    - Lipoprotein profile, glucose, insulin
    - Inflammatory markers:
      - Tumor necrosis factor-α (TNF-α)
      - Soluble tumor necrosis factor receptors I & II (sTNFR-I, II)
      - Interleukin-6 (IL-6)
      - High sensitivity C-reactive protein (hsCRP)
  - Endothelial activation markers:
    - vonWillebrand's factor (vWF)
    - Soluble intercellular adhesion molecule-1 (sICAM-1)
    - Soluble vascular cell adhesion molecule-1 (sVCAM-1)
  - Established cardiovascular marker:
    - Myeloperoxidase (MPO)
- Data analysis**
- Group comparison done using distributionally appropriate two-sample tests
  - Correlations done using Spearman correlation coefficients

| Patient Characteristics<br>[[Median (Range)] Unless Stated Otherwise |                       |                  |         |
|--|-----------------------|------------------|---------|
|  | HIV-infected (n = 62) | HIV- (n = 32)    | P value |
| Age  | 44 (12-72)            | 38 (13-66)       | 0.02    |
| Males, no. (%)   | 41 (64%)              | 18 (49%)         | 0.13    |
| Race, no. (%)  |                       |                  | 0.63    |
| Black  | 30 (47%)              | 17 (46%)         |         |
| Caucasian  | 26 (40%)              | 19 (49%)         |         |
| Hispanic   | 7 (11%)               | 2 (5%)           |         |
| Asian  | 1 (2%)                | 0 (0%)           |         |
| Body mass index (kg/m <sup>2</sup> )                                 | 26.1 (18.0-40.9)      | 24.9 (15.9-34.0) | 0.027   |
| Waist-to-hip ratio   | 1.31 (0.72-1.9)       | 0.84 (0.69-1.0)  | <0.001  |
| Smoking habits, no. (%)  |                       |                  | 0.009   |
| Current  | 17 (27%)              | 2 (6%)           |         |
| Past   | 10 (15%)              | 3 (8%)           |         |
| Never  | 37 (58%)              | 31 (86%)         |         |
| Systolic BP (mm Hg)  | 120 (90-154)          | 110 (90-126)     | 0.001   |
| Diastolic BP (mm Hg)   | 80 (58-180)           | 70 (50-90)       | <0.001  |
| Total cholesterol (mg/dl)  | 174 (88-336)          | 183 (111-286)    | 0.81    |
| LDL cholesterol (mg/dl)  | 99 (30-228)           | 105 (54-182)     | 0.87    |
| HDL cholesterol (mg/dl)  | 40 (16-93)            | 53 (28-87)       | <0.001  |
| Triglycerides (mg/dl)  | 149 (33-716)          | 65 (17-1138)     | <0.001  |
| Glucose (mg/dl)  | 86 (55-111)           | 81 (67-95)       | 0.017   |
| Insulin (mIU/l)  | 13 (3-70)             | 7 (3-19)         | <0.001  |
| FH of premature CVD  | 5 (8%)                | 4 (11%)          | 0.72    |
| FH of type 2 diabetes  | 15 (25%)              | 4 (11%)          | 0.20    |
| HIV duration (months)  | 153 (3 - 268)         |                  |         |
| Cumulative PI therapy (months)                                       | 38 (0-156)            |                  |         |
| Cumulative NRTI therapy (months)                                     | 88 (0-271)            |                  |         |
| Cumulative NNRTI therapy (months)                                    | 31 (0-94)             |                  |         |
| Current CD4+ cell count  | 652 (152-1718)        |                  |         |
| Nadir CD4+ cell count  | 200 (0-780)           |                  |         |
| HIV-1 RNA <400 copies/ml, no. (%)                                    | 52 (84%)              |                  |         |

LDL = low-density lipoprotein; HDL = high-density lipoprotein; PI = Protease inhibitor; NRTI = nucleoside analogue reverse transcriptase inhibitor; NNRTI = non-nucleoside analogue reverse transcriptase inhibitor

**RESULTS**

| Carotid IMT and Biomarkers [[Median (Range)] |                       |                              |         |
|--|-----------------------|------------------------------|---------|
|  | HIV-infected (n = 62) | Uninfected Controls (n = 32) | P value |
| Right ICA IMT (mm)                           | 0.93 (0.5-3.5)        | 0.75 (0.4-3.6)               | 0.022   |
| Right CCA IMT (mm)                           | 1.00 (0.7-3.55)       | 0.90 (0.7-1.4)               | 0.041   |
| Left ICA IMT (mm)                            | 1.00 (0.5-4.2)        | 0.80 (0.4-3.6)               | 0.004   |
| Left CCA IMT (mm)                            | 1.10 (0.7-3.0)        | 1.00 (0.7-1.3)               | 0.004   |
| TNF-α (pg/ml)                                | 4.7 (0.4-4.7)         | 1.4 (0.4-85.6)               | 0.058   |
| sTNFR-I(pg/ml)                               | 657.4 (353-1,312)     | 622.4 (265-1,365)            | 0.25    |
| sTNFR-II(pg/ml)                              | 277.8 (56.1-1,247.1)  | 381.4 (75.6-1,070)           | 0.008   |
| hsCRP (mg/ml)                                | 3.63 (3.05-8.46)      | 1.06 (1.59-2.44)             | <0.001  |
| IL-6 (pg/ml)                                 | 3.2 (0.8-71.0)        | 2.2 (0.6-8.2)                | 0.048   |
| MPO (pg/ml)                                  | 5,630 (1,022-27,935)  | 2935 (1,124-10,865)          | 0.005   |
| sICAM-1 (ng/ml)                              | 395 (72.8-2,818)      | 317 (63.3-577.1)             | 0.037   |
| sVCAM-1 (ng/ml)                              | 468 (187.7-2,308)     | 510 (65.5-1,808)             | 0.68    |
| vWF (U/ml)                                   | 15.8 (2.2-417)        | 13.2 (6.4-200)               | 0.34    |

| Correlations Among Biomarkers for HIV+ (R value / P value) |                       |            |             |             |      |             |         |         |     |
|--|-----------------------|------------|-------------|-------------|------|-------------|---------|---------|-----|
|  | HIV-infected (n = 62) |            |             |             |      |             |         |         |     |
|  | TNF-α                 | sTNFR I    | sTNFR II    | hsCRP       | IL-6 | MPO         | sICAM-1 | sVCAM-1 | vWF |
| TNF-α  |                       |            |             |             |      |             |         |         |     |
| sTNFR I  |                       |            |             |             |      |             |         |         |     |
| sTNFR II   |                       |            |             |             |      |             |         |         |     |
| IL-6   |                       |            |             |             |      |             |         |         |     |
| MPO  |                       |            |             |             |      |             |         |         |     |
| sVCAM-1  | 0.58 <0.001           | 0.30 <0.02 | 0.45 <0.001 | 0.58 <0.001 |      | 0.46 <0.001 |         |         |     |
| vWF  |                       |            |             |             |      |             |         |         |     |

| Significant Correlations Between Carotid IMT and Biomarkers (R value / P value) |                       |             |             |              |                              |              |              |              |
|---|-----------------------|-------------|-------------|--------------|------------------------------|--------------|--------------|--------------|
|   | HIV-infected (n = 62) |             |             |              | Uninfected Controls (n = 32) |              |              |              |
|   | R ICA                 | R CCA       | L ICA       | L CCA        | R ICA                        | R CCA        | L ICA        | L CCA        |
| TNF-α   | 0.29 <0.02            |             |             |              |                              | 0.46 <0.009  |              | 0.43 <0.015  |
| sTNFR I   |                       |             |             |              |                              |              |              |              |
| sTNFR II  |                       |             |             | -0.27 <0.037 |                              |              |              |              |
| hsCRP   |                       |             | 0.26 <0.05  |              |                              |              |              |              |
| IL-6  | 0.29 <0.02            |             |             |              |                              |              |              |              |
| MPO   | -0.30 <0.011          |             |             | -0.32 <0.012 | -0.62 <0.001                 | -0.53 <0.002 | -0.59 <0.001 | -0.50 <0.005 |
| sICAM-1   |                       |             |             |              |                              |              |              |              |
| sVCAM-1   |                       |             |             | -0.29 <0.023 |                              |              |              | -0.55 <0.001 |
| vWF   |                       |             |             |              |                              |              |              |              |
| TC  | 0.33 <0.011           |             | 0.31 <0.017 |              | 0.61 <0.001                  | 0.38 <0.026  | 0.56 <0.001  | 0.47 <0.005  |
| HDL   |                       |             |             |              | -0.34 <0.05                  |              |              |              |
| TG  | 0.44 <0.001           | 0.35 <0.006 | 0.38 <0.003 |              | 0.54 <0.001                  | 0.59 <0.001  | 0.50 <0.002  | 0.65 <0.001  |
| Glucose   |                       |             |             |              |                              |              |              |              |
| Insulin   |                       |             |             |              |                              |              |              |              |

**CONCLUSIONS**

- Carotid IMT is higher in HIV+ vs. uninfected healthy controls
- Endothelial activation and inflammation are enhanced in HIV+ patients
- Inflammatory markers correlated with the endothelial activation marker, sVCAM-1
- Support further investigations into the role of inflammation in endothelial dysfunction and CVD in HIV

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