Platelet Derived Soluble Glycoprotein VI Decreases Prior to Coronary Event in HIV Positive Patients

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Disclosures

- The authors have no conflicts of interest relevant to this work to declare

HIV+ individuals are at increased risk for cardiovascular disease

- HIV and ART related dyslipidaemia
- HIV driven immune activation and inflammation
- Increased rates of traditional risk factors

Role of platelets in atherosclerosis

- Adapted from Kaplan et al. 2011 Haematology

Platelet receptor function is a key component of the pathogenesis of atherosclerosis

Soluble glycoprotein VI may be an important negative feedback mechanism

- Adapted from: Kaplan et al. 2011 Haematology
Aims

• To determine if sGPVI levels were different in HIV positive individuals compared with HIV negative controls

• To determine if sGPVI levels were predictive of a diagnosis of coronary artery disease in people living with HIV

Methods

• Retrospective case-control study of HIV positive individuals seen at the Alfred Hospital, Melbourne

• January 1996 – December 2009

• Cases were HIV positive individuals with a first diagnosis of coronary artery disease (CAD)

• Defined as:
  • Acute myocardial infarction
  • Positive coronary Angiogram
  • Clinical diagnosis (angina with consistent ECG)

Methods

HIV+ with diagnosis of CAD

HIV+ with no history of CAD

Healthy HIV negative volunteers

Matched 1:2

(n = 24)

Age/Sex

HIV+ Cases

n = 24

Samples 1 and 12 months prior to diagnosis

HIV+ Controls

n = 46

2 samples 12 months apart analysed

Healthy Controls

n = 41

Single sample analysed

Platelet function assessment

• sGPVI levels were determined by ELISA from platelet-poor plasma using standard techniques

   (1)  (2)  (3)

Al-Tamimi et al. Platelets 2009;20(3):143-149

Statistical Methods

• Results are summarized by group, using Fisher’s exact or chi-squared tests for categorical variables and the Mann-Whitney U-Test for continuous data.

• Correlations were determined using Spearman’s correlation co-efficient

• Multiple linear regression was performed to adjust for possible confounders

• Statistical significance defined as p<0.05

• Stata 11.0/IC (College Station, Texas)

Ethics approval

• This project was approved by the Alfred Hospital Ethics Committee (Project Number: 205/09)

• All participants provided written consent to have their plasma stored and used for future research
Participant Characteristics

<table>
<thead>
<tr>
<th></th>
<th>HIV cases (A)</th>
<th>HIV controls (B)</th>
<th>Healthy controls (C)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>24</td>
<td>46</td>
<td>41</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>21 (87.5)</td>
<td>42 (91.3)</td>
<td>37 (90.2)</td>
<td>0.620</td>
</tr>
<tr>
<td>Age, years</td>
<td>52.5 (42-62)</td>
<td>52.0 (42-59)</td>
<td>49.0 (42-56)</td>
<td>0.368</td>
</tr>
<tr>
<td>Current Smokers</td>
<td>12 (50.0)</td>
<td>19 (41.3)</td>
<td>3 (7.3)</td>
<td>0.490</td>
</tr>
<tr>
<td>Diabetes</td>
<td>4 (16.6)</td>
<td>3 (6.5)</td>
<td>0 (0)</td>
<td>0.184</td>
</tr>
<tr>
<td>Hypertension</td>
<td>13 (54.1)</td>
<td>5 (10.0)</td>
<td>7 (17.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Antipatelet treatment</td>
<td>10 (41.6)</td>
<td>1 (2.1)</td>
<td>0 (0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Framingham Risk score, %</td>
<td>50 (8-14.5)</td>
<td>7 (5.5-14.5)</td>
<td>5.9 (3.6-10.1)</td>
<td>0.057</td>
</tr>
</tbody>
</table>

Cholesterol levels

<table>
<thead>
<tr>
<th></th>
<th>HIV cases (A)</th>
<th>HIV controls (B)</th>
<th>Healthy controls (C)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol</td>
<td>5.0 (4.7-6.3)</td>
<td>5.2 (4.5-5.6)</td>
<td>5.5 (4.4-6.2)</td>
<td>0.706</td>
</tr>
<tr>
<td>LDL-cholesterol</td>
<td>2.9 (2.4-3.5)</td>
<td>2.8 (2.2-3.2)</td>
<td>3.6 (1.4-4.1)</td>
<td>0.803</td>
</tr>
<tr>
<td>HDL-cholesterol</td>
<td>1.0 (0.9-1.2)</td>
<td>1.0 (0.9-1.1)</td>
<td>1.4 (1.1-1.8)</td>
<td>0.459</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>2.0 (1.5-3.2)</td>
<td>1.8 (1.5-2.7)</td>
<td>0.8 (0.7-1.5)</td>
<td>0.199</td>
</tr>
</tbody>
</table>

HIV specific characteristics

<table>
<thead>
<tr>
<th></th>
<th>HIV cases (A)</th>
<th>HIV controls (B)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of HIV infection, years</td>
<td>13.6 (9.3-17.3)</td>
<td>10.8 (5.0-15.5)</td>
<td>0.103</td>
</tr>
<tr>
<td>Receiving ART</td>
<td>24 (100)</td>
<td>41 (89.1)</td>
<td>0.113</td>
</tr>
<tr>
<td>ARV regimen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protease inhibitor</td>
<td>16 (66.6)</td>
<td>24 (52.1)</td>
<td>0.251</td>
</tr>
<tr>
<td>NNRTI</td>
<td>5 (20.8)</td>
<td>19 (41.3)</td>
<td>0.381</td>
</tr>
<tr>
<td>Integrase Inhibitor</td>
<td>2 (8.3)</td>
<td>0 (0)</td>
<td>0.047</td>
</tr>
<tr>
<td>CD4+ cell nadir, cells/µL</td>
<td>129 (70-225)</td>
<td>113 (20-240)</td>
<td>0.421</td>
</tr>
<tr>
<td>CD4+ T-cell count, cells/µL</td>
<td>485.5 (335-699)</td>
<td>411 (287-546)</td>
<td>0.044</td>
</tr>
<tr>
<td>CD8+ T-cell count, cells/µL</td>
<td>1076 (881-1293)</td>
<td>888 (584-1615)</td>
<td>0.404</td>
</tr>
<tr>
<td>Detectable HIV VL‡</td>
<td>11 (45.8)</td>
<td>10 (22.7)</td>
<td>0.059</td>
</tr>
</tbody>
</table>

sGPVI levels are higher in HIV positive individuals

sGPVI levels are lower immediately prior to CAD diagnosis in HIV Positive Patients

Changes remained when those taking antiplatelets were excluded
No significant change in sGPVI across time points for HIV cases or controls

No correlation between sGPVI and HIV measured factors

Weak correlation between sGPVI and cholesterol levels and platelet count

Difference remained significant following adjustment

- Following adjustment for:
  - Smoking status
  - Total and LDL cholesterol
  - Antiplatelet use
  - Platelet count
  - Systolic blood pressure

- Healthy controls continued to have lower sGPVI than HIV positive individuals (p < 0.001)

- At one month prior to event HIV-cases continued to have lower sGPVI compared with HIV-controls (p = 0.033)

Is lower sGPVI a pathological process directly contributing to CVD in HIV?

Limitations

- Small sample size
- Homogeneous patient population
- Single centre
- Retrospective design
- Use of stored samples
Conclusion

• HIV infection is associated with increased sGPVI levels

• Lower sGPVI levels are seen prior to diagnosis of coronary artery disease in HIV positive individuals

• This may reflect a loss of negative-feedback mechanisms and be an important pathological step in the development of symptomatic coronary artery disease

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