Intact Parathyroid Hormone predicts intima media thickness in HIV infected subjects

Antonio Bellasi¹,², Antonella Lattanzi³, Rosario Rossi³, Chiara Stentarelli³ Stefano Zona³, Vincenzo Rochira³, Antonella Santoro³, Cristina Mussini³, Paolo Raggi⁴ and Giovanni Guaraldi³

¹Nephrology and Dialysis Unit, Azienda Ospedaliera S. Anna, Como, Italy
²Department of Health Sciences, University of Milan, Italy
³Metabolic Clinic, Infectious and Tropical Diseases Unit, Department of Medicine, Azienda Ospedaliera Universitaria Polidinico di Modena, Modena, Italy
⁴Mazankowski Alberta Heart Institute, University of Alberta, Canada
Physiological Actions of PTH

1998
TIP 39
PTH-R2
- Pain perception
- Somatostatin
- Growth hormone
- Pancreas
- Renin

1923
PTH
PTH-R1
- Ca-P regulation
- Calcitriol synthesis
- Bone formation/resorption

1987
PTHrP
PTH-R3
- Keratinocytes
- Transplacental transport of Ca-P
- Others
Plasma Parathyroid Hormone and the Risk of Cardiovascular Mortality in the Community

_Hagstrom et_ Circulation 2009; 119: 2765-2771

Upsala Longitudinal Study of Men (ULSAM)

Community-based study of elderly men (mean age 71, N=958)

Median follow-up 9.7 years

117 deaths due to CV disease

HR for 1 SD increase in PTH: 1.38 (95%CI: 1.18-1.60)

Elevated plasma PTH (>5.27 pmol/l) accounted for 20% (95%CI:10-26%) of the _attributable risk proportion_ for CV mortality
Pathways linking PTH to CVD

Cardiac calcification

Vascular calcification/remodelling

Left ventricular hypertrophy

Renal dysfunction

Inflammation biomarkers

Association with established CVD risk factors
Rationale of the study

Some evidence exists that intact parathyroid hormone (iPTH) and bone mineral abnormalities may contribute to the development of vascular disease and are linked to reduced survival in the general population.

Whether iPTH is associated with atherosclerosis in HIV-infected individuals has not been elucidated.
Methods and materials

• We utilized the patient's records from subjects referred to Clinica Metabolica at the University of Modena and Reggio Emilia

• Study design: Retrospective, cross-sectional study

• All tests were carried out between 2010 and 2013

We identified 472 consecutive male and female HIV-infected subjects who underwent an Intima-Media Thickness (IMT) and intact PTH assessment
Methods and materials

Intact-PTH was assessed via chemioilluminescence DXI Beckmann (range 15-88 pg/mL)

Intima media thickness: assessed via GE Vivid S5 cardiovascular ultrasound system with a high-resolution (≥7.5 MHz) linear array ultrasound transducer

• Patients were divided in 2 groups based on the mean thickness of IMT measured in the common, internal and external carotids. High IMT was defined as a mean IMT above the 75th percentile of the study cohort distribution.

STATISTICAL PLAN
• Parametric and non-parametric tests as well as logistic regression analysis were used to compare patients’ characteristics between low- and high-IMT and to test the association between high IMT and iPTH.
• Variables significantly associated with IMT on univariable analyses and variables known to be associated with either iPTH or IMT were entered into the final multivariable adjusted model. The most parsimonious model was selected via a stepwise approach.
Results

- Not normally distributed
- Median (IQR): 0.07 (0.06-0.08)
- High IMT > 0.08

4 (0.8%) patients with a mean IMT > 1.2 mm
<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (n=472)</th>
<th>Low IMT (n=342)</th>
<th>High IMT (n=130)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>49.2 (7.6)[472]</td>
<td>48 (7)[342]</td>
<td>52.2 (8.4)[130]</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Male Sex % [n]</td>
<td>66.7% [315]</td>
<td>62.9% [215]</td>
<td>76.9% [100]</td>
<td>0.005</td>
</tr>
<tr>
<td><strong>Clinical Characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic Kidney Disease %[n]</td>
<td>12.92% [61]</td>
<td>13.74% [47]</td>
<td>10.77% [14]</td>
<td>0.48</td>
</tr>
<tr>
<td>Metabolic Syndrome %[n]</td>
<td>23.94% [113]</td>
<td>23.39% [80]</td>
<td>25.38% [33]</td>
<td>0.739</td>
</tr>
<tr>
<td>Averaged IMT (mm)</td>
<td>0.19 (2.08)[472]</td>
<td>0.07 (0.01)[342]</td>
<td>0.51 (3.95)[130]</td>
<td>0.206</td>
</tr>
<tr>
<td><strong>Laboratory characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White Blood Cell Count (10^3/ ml)</td>
<td>12.86 (120.9)[472]</td>
<td>13.52 (137.03)[342]</td>
<td>11.14 (61.09)[130]</td>
<td>0.795</td>
</tr>
<tr>
<td>Total limphocytes count (10^3/ ml)</td>
<td>2021 (688.8)[472]</td>
<td>2031.5 (694.2)[342]</td>
<td>1993.5 (676.1)[130]</td>
<td>0.589</td>
</tr>
<tr>
<td>Total CD4 lymphocytes count (/ ml)</td>
<td>621.6 (234.1)[472]</td>
<td>629 (238.6)[342]</td>
<td>602.2 (221.4)[130]</td>
<td>0.252</td>
</tr>
<tr>
<td>Total CD8 lymphocytes count (/ ml)</td>
<td>875.4 (403.9)[472]</td>
<td>860.8 (391.7)[342]</td>
<td>914 (433.4)[130]</td>
<td>0.222</td>
</tr>
<tr>
<td>C-reactive protein (mg/ dl)</td>
<td>0.4 (2.7)[472]</td>
<td>0.4 (3.2)[342]</td>
<td>0.3 (0.6)[130]</td>
<td>0.445</td>
</tr>
<tr>
<td>Glucose (mg/dl)</td>
<td>97.7 (20.9)[472]</td>
<td>96.4 (19)[342]</td>
<td>101.1 (25.1)[130]</td>
<td>0.052</td>
</tr>
<tr>
<td>Total cholesterol (mg/ dl)</td>
<td>197.7 (40.8)[472]</td>
<td>195.6 (39.5)[342]</td>
<td>203.4 (43.6)[130]</td>
<td>0.078</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>151.4 (84.8)[472]</td>
<td>146.4 (79.8)[342]</td>
<td>164.7 (95.9)[130]</td>
<td>0.053</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dl)</td>
<td>50.2 (16)[472]</td>
<td>51.5 (16.3)[342]</td>
<td>46.6 (14.5)[130]</td>
<td>0.002</td>
</tr>
<tr>
<td>LDL cholesterol (mg/ dl)</td>
<td>117.3 (31.6)[472]</td>
<td>115.9 (31.4)[342]</td>
<td>121.1 (32.1)[130]</td>
<td>0.117</td>
</tr>
<tr>
<td>APO1 lipoprotein (mg/ dl)</td>
<td>146.4 (28)[472]</td>
<td>147.8 (27.3)[342]</td>
<td>142.5 (29.7)[130]</td>
<td>0.078</td>
</tr>
<tr>
<td>APOB lipoprotein (mg/dl)</td>
<td>91.9 (23.5)[472]</td>
<td>89.8 (22.6)[342]</td>
<td>97.6 (24.7)[130]</td>
<td>0.002</td>
</tr>
<tr>
<td>eGFR (ml/ min/ 1.73m2)</td>
<td>92.9 (20.6)[472]</td>
<td>92 (20)[342]</td>
<td>95 (22)[130]</td>
<td>0.172</td>
</tr>
<tr>
<td>Proteinuria (g/ mg)</td>
<td>16.1 (60.3)[472]</td>
<td>14.2 (37.5)[342]</td>
<td>21.2 (97.6)[130]</td>
<td>0.428</td>
</tr>
<tr>
<td>Calcium (mg/ dl)</td>
<td>4.76 (0.23)[472]</td>
<td>4.77 (0.23)[342]</td>
<td>4.73 (0.22)[130]</td>
<td>0.067</td>
</tr>
<tr>
<td>Phosphorous (mg/ dl)</td>
<td>3.21 (0.52)[472]</td>
<td>3.22 (0.52)[342]</td>
<td>3.17 (0.53)[130]</td>
<td>0.388</td>
</tr>
<tr>
<td>intact PTH (pg/ml)</td>
<td>43.4 (25.4)[472]</td>
<td>41.8 (25.5)[342]</td>
<td>47.6 (24.7)[130]</td>
<td>0.027</td>
</tr>
<tr>
<td>Magnesium (mg/dl)</td>
<td>2.01 (0.14)[472]</td>
<td>2.02 (0.14)[342]</td>
<td>1.97 (0.14)[130]</td>
<td>0.002</td>
</tr>
</tbody>
</table>
Results

Every 10 pg/ml increase in PTH

- **Model 1:** Unadjusted
  - O.R.: 1.09
  - 95%CI: 1.01-1.18
  - P=0.02

- **Model 2:** Age and Sex adjusted
  - O.R.: 1.09
  - 95%CI: 1.01-1.18
  - P=0.01

- **Model 3:** Age and Sex + Case Mix
  - O.R.: 1.09
  - 95%CI: 1.02-1.19
  - P=0.01

- **Model 4:** Model 3 + Labs
  - O.R.: 1.10
  - 95%CI: 1.01-1.19
  - P=0.01

- **Model 5:** Model 4 + tenofovir
  - O.R.: 1.10
  - 95%CI: 1.00-1.19
  - P=0.04

- **Model 6:** Model 5 + Mineral Metabolism

**Case mix:** Cardiovascular disease, Diabetes, Metabolic syndrome, eGFR (via MDRD equation)

**Labs:** triglycerides, ApoB lipoprotein, Magnesium, C-reactive protein

**Mineral Metabolism:** 25 OH vitamin D, Serum Phosphorous, Serum Calcium
## Results

Most parsimonious model to predict IMT greater than 75° of the study cohort (stepwise selection)

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio</th>
<th>95% Lower CI</th>
<th>95% Upper CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intact PTH (per 10 pg/ml increase)</td>
<td>1.088</td>
<td>1.005</td>
<td>1.178</td>
<td>0.038</td>
</tr>
<tr>
<td>Age (years)</td>
<td>1.067</td>
<td>1.036</td>
<td>1.098</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.573</td>
<td>0.929</td>
<td>2.663</td>
<td>0.092</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>0.997</td>
<td>0.994</td>
<td>1.001</td>
<td>0.103</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dl)</td>
<td>0.98</td>
<td>0.963</td>
<td>0.998</td>
<td>0.026</td>
</tr>
<tr>
<td>APOB lipoprotein (mg/dl)</td>
<td>1.017</td>
<td>1.006</td>
<td>1.027</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Magnesium (mg/dl)</td>
<td>0.09</td>
<td>0.019</td>
<td>0.416</td>
<td>0.002</td>
</tr>
<tr>
<td>eGFR (ml/min/1.73 m2)</td>
<td>0.126</td>
<td>0.027</td>
<td>0.592</td>
<td>0.008</td>
</tr>
</tbody>
</table>

Legend: CI: Confidence interval; PTH: parathyroid hormone; HDL: high density lipoprotein; eGFR: estimated glomerular filtration rate via the MDRD equation
Results

****Fully adjusted models****

External Right carotid (N=259): OR (95%CI): 1.14 (0.99-1.30)

Internal Right carotid (N=431): OR (95%CI): 1.01 (0.91-1.13)

Common Right carotid (N=470): OR (95%CI): 1.00 (0.91-1.09)

External Left carotid (N=218): OR (95%CI): 0.99 (0.87-1.12)

Internal Left carotid (N=425): OR (95%CI): 1.16 (1.05-1.28)

Common Left carotid (N=470): OR (95%CI): 1.00 (0.91-1.11)

Overall, a trend toward increase IMT associated with iPTH is noted in all carotid artery sites
Limitations and strengths

Retrospective cross-sectional nature does not allow for causal inference

Potential for residual confounding

Relatively large study cohort allowed us to control for numerous factors either associated with IMT or PTH
Conclusions

Mineral bone disorders, such as elevated iPTH is associated with atherosclerosis in HIV-infected subjects.

Notably, this association is statistically significant even for iPTH values within the range of normality.

Future works is needed to confirm this association and the causal relationship between increased iPTH and atherosclerosis.