ABSTRACT

Background. Renal disease is a leading cause of morbidity in HIV-infected adults in the HAART era. Cystatin C has been proposed as a more sensitive marker of renal function, but it may be affected by ongoing inflammation. We aimed to study Cystatin C levels in a cohort of HIV-infected pediatric patients at 3 Spanish centers.

Methods. Multicenter cross-sectional observational study. Renal function was assessed by means of first morning urine protein/creatinine and albumin/creatinine ratios and creatinine-estimated glomerular filtration rates (GFR), together with the following inflammation markers: Cystatin C, reactive C protein, beta-2-microglobulin and 25(OH)-vitamin D levels. A control group of healthy children and adolescents was used.

Results. Eighty-three patients (51 females, mean age 12.7 years) and 44 controls were included. The mean creatinine level was 66.8 micromol/L (25–105 micromol/L) in the HIV-infected patients and 63.6 micromol/L (25–99 micromol/L) in the control group. No differences in Cystatin C levels were observed between the two groups.

In HIV-infected patients, Cystatin C levels correlated with GFR (r=0.27; p=0.015), age at first HAART (r=0.31; p=0.01), and beta-2-microglobulin (r=0.56; p=0.001). In multivariate analysis, lower GFR (p=0.014) and higher beta-2-microglobulin levels (p=0.001) remained as independent risk factors for higher Cystatin C values.

Conclusions. Cystatin C values were associated with GFR and beta-2-microglobulin. Cystatin C may be a marker of renal function in HIV-infected pediatric patients, independently of ongoing inflammation or viremia.

Introduction

• Renal disease has become an important cause of morbidity in HIV-infected children in the HAART era.

• Cystatin C has been proposed as a more sensitive marker of renal function.

• Some studies conducted in HIV-infected adults suggest that Cystatin C is an inflammation marker. This could represent a bias when using Cystatin C in the evaluation of renal function in uncontrolled patients.

• Data on Cystatin C in HIV-infected pediatric patients are scarce.

Study objectives

• To determine Cystatin C levels in a cohort of HIV-infected children and adolescents and a group of healthy controls to evaluate how Cystatin C correlates with epidemiologic and renal function variables.

• To associated Cystatin C with HIV infection variables, and renal function and inflammation markers in the HIV-infected cohort.

Conclusions

• Neither infected children nor healthy controls presented abnormal levels of Cystatin C.

• In our cohort of well controlled HIV infected children, Cystatin C remained as a good renal marker independently of ongoing inflammation.

Abbreviations: GFR, glomerular filtration rate; HAART, highly active antiretroviral therapy; BMI, body mass index; CD4%, CD4+ T cell percentage; CMR, creatinine; C, cystatin C; 25(OH)D, 25-hydroxyvitamin D; BMI, body mass index; CMR, creatinine; C, cystatin C; 25(OH)D, 25-hydroxyvitamin D; UACR, urine albumin/creatinine ratio; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides; HbA1c, hemoglobin A1c; RNA, retroviral RNA; PI, protease inhibitor; HAART, highly active antiretroviral therapy; n, number; %, percentage; SD, standard deviation; IQR, interquartile range; CI, confidence interval; p, probability; OR, odds ratio; aOR, adjusted odds ratio; r, correlation coefficient; p, probability; p<0.05, statistically significant; 95% CI, 95% confidence interval.

Patients and Methods

Multicenter cross-sectional study

Inclusion criteria:
- HIV-infected children and adolescents aged up to 18 years.

Exclusion criteria:
- Previous renal disease.
- Previous thyroid disease or corticoid therapy.

Epidemiologic and medical history data were collected from medical charts.

Laboratory methods:
- Blood sample was used to determine CD4+ cells count, HIV-RNA viremia, creatinine, reactive C protein, beta-2-microglobuline and Cystatin C.
- A urine sample to determine albumin/creatinine ratio and protein/creatinine ratio was collected too.
- Glomerular filtration rate was estimated from creatinine levels using Schwartz formula in patients aged up to 11y, and according to Cockroft-Gault formula in patients > 12y.

Study design

PHASE 1

- Infected population
- Healthy population

DESCRIPTIVE STUDY
- Patients characteristics
- Renal function
- Cystatin C

PHASE 2

- Infected population

COMPARATIVE STUDY
- Cystatin C vs Patients characteristics

PHASE 1

- Infected population
- Healthy population

COMPARATIVE STUDY
- Cystatin C vs Patients characteristics

PHASE 2

- Infected population

COMPARATIVE STUDY
- Infection variables

Results

• Main characteristics of infected and healthy patients

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>HIV-infected patients N=83</th>
<th>Controls N=44</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female gender, n (%)</td>
<td>51 (61.4)</td>
<td>34 (77.3)</td>
<td>0.452</td>
</tr>
<tr>
<td>Black ethnicity, n (%)</td>
<td>11 (13.4)</td>
<td>2 (4.5)</td>
<td>0.125</td>
</tr>
<tr>
<td>Age (years); median (IQR)</td>
<td>13.4 (10.1–16.4)</td>
<td>11.5 (7.3–14.5)</td>
<td>0.615</td>
</tr>
<tr>
<td>BMI; z-score; median (IQR)</td>
<td>-0.2 (0.8 to 0.5)</td>
<td>0.5 (8.0 to 3.2)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

• Renal function variables

| Abnormal albumin/creatinine ratio | 7 (10–9) | 5 (1–13) | 0.787 |
| Abnormal protein/creatinine ratio | 13 (20–30) | 4 (5–15) | 0.207 |
| GFR; median (IQR) | 137 (128–150) | 125 (119–145) | 0.036 |
| GFR < 90 ml/min/1.73 m² | 2 (2.4) | 0 (0) | 0.295 |
| Cystatin C; mg/L; mean (SD) | 0.87 (0.15) | 0.88 (0.12) | 0.881 |

• Descriptive analysis of HIV infected cohort

Comparative analysis: cystatin C vs HIV infection variables

- None of the patients in either groups presented abnormal levels of Cystatin C.
- Among HIV-infected patients, higher Cystatin C levels were observed: naïve (0.95 vs 0.87; p=0.019).
- HAART regimen based in IP (0.88 vs 0.82; P=0.06)

Comparative analysis: cystatin C vs renal function

- A negative correlation with glomerular filtration was observed (r=-0.27; p=0.013).
- No relation between Cystatin C and albuminuria or proteinuria was observed.

Comparative analysis: cystatin C vs inflammation activity

- A strong positive correlation between beta-2-microglobuline and Cystatin C was observed (r=0.56; p=0.001).
- No other relations were observed.

Multivariate analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Beta coefficient</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAART regimen including a PI</td>
<td>0.032</td>
<td>-0.031 to 0.096</td>
<td>0.317</td>
</tr>
<tr>
<td>Age at first HAART (years)</td>
<td>0.062</td>
<td>-0.056 to 0.180</td>
<td>0.395</td>
</tr>
<tr>
<td>Underactive TSH values</td>
<td>-0.012</td>
<td>-0.056 to 0.032</td>
<td>0.752</td>
</tr>
<tr>
<td>Estimated glomerular filtration rate</td>
<td>-0.011</td>
<td>-0.038 to 0.015</td>
<td>0.527</td>
</tr>
<tr>
<td>Beta-2-microglobuline levels</td>
<td>0.159</td>
<td>0.044 to 0.210</td>
<td>0.001</td>
</tr>
</tbody>
</table>

In the multivariate analyses, Cystatin C remained significantly associated with An beta-2-microglobuline levels and GFR values.