Subclinical hypothyroidism in HIV-infected subjects

Marco Bongiovanni¹*, Fulvio Adorni², Maddalena Casana¹, Federica Tordato¹, Camilla Tincati¹, Paola Cicconi¹, Teresa Bini¹ and Antonella d’Arminio Monforte¹

¹Clinic of Infectious Diseases, San Paolo Hospital, University of Milan, Milan, Italy; ²National Research Council, Milan, Italy

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Objectives: The correlation between subclinical hypothyroidism [thyroid stimulating hormone (TSH) >4 mIU/L with normal free triiodothyroxine and free thyroxine levels], HIV infection and HAART is still unclear.

Patients and methods: To evaluate the predictive factors of subclinical hypothyroidism in an HIV-infected population, we identified three groups of subjects: G1, subjects on stable highly active antiretroviral therapy (HAART) (for at least 1 year) at baseline and at month 24 (n = 97); G2, subjects naive at both baseline and month 24 (n = 47); G3, subjects starting HAART at baseline (n = 46).

Results: The three groups were comparable with respect to age, gender, body weight and prevalence of HCV infection. At baseline, subclinical hypothyroidism was detected in 14 subjects in G1 (14.4%), 5 in G2 (10.6%) and 4 in G3 (8.7%) (P = 0.18) and these were excluded from the analysis. At month 24, 15 subjects had developed subclinical hypothyroidism: 4 in G1 (4.8%), 3 in G2 (7.1%) and 8 in G3 (19.0%). In the multivariable analysis, the higher increase in total cholesterol was predictive of subclinical hypothyroidism (RR: 1.53 for each additional 10 mg/dL, 95% CI 1.23–1.90; P < 0.01); other variables, which were statistically significant in the univariate analysis, such as G3 group, body weight and higher increase in CD4+ cell count and in triglyceride serum levels were not confirmed to be associated with TSH alterations.

Conclusions: The occurrence of subclinical hypothyroidism in HIV-positive patients seems to be related to the increase in total cholesterol serum levels occurring after HAART initiation. Thyroid function should be monitored in all HIV-infected subjects, especially in those starting HAART.

Keywords: thyroid, HAART, HIV

Introduction

The use of highly active antiretroviral therapy (HAART) in current clinical practice has been associated with benefits in the management of HIV infection, with a dramatic reduction in HIV-related morbidity and mortality.¹,² Several and at times unexpected side effects, which may limit long-term HAART tolerability and efficacy, have been described: abnormalities of lipid, glucose and bone metabolism are increasingly being recognized, including hyperlipidaemia, hyperinsulinaemia, impaired glucose tolerance, diabetes mellitus, lipodystrophy syndrome and reduced bone mineral density.³,⁴ In the past few years, several cases of thyroid, adrenal and gonadal dysfunction have been observed, suggesting a possible effect of HIV and/or antiretroviral drugs on the endocrine system.⁵,⁶ With regard to thyroid function, a higher prevalence of subclinical hypothyroidism compared with the general population has been described,⁷ but the pathogenic role of HAART and of HIV infection itself are still undetermined and, to date, conflicting results have been published.⁸–¹⁰ In particular, no study has yet evaluated the occurrence of this abnormality in HIV-infected subjects starting HAART.

Patients and methods

A total of 190 consecutive HIV-infected subjects followed at our Institute were included in the study. Data on age, gender, weight, lipodystrophy (defined as body fat abnormalities consistent with lipoatrophy, lipoaccumulation, or both, clinically evident for both the patient and the physician), duration of known HIV infection, CDC stage and HCV infection were collected at baseline and at month 24. Clinical examination and routine haematological, biochemical, immunological and virological tests were collected at baseline,
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at month 24 and whenever available. Baseline tests were performed for all patients from January 2003 to December 2003. Subjects with known thyroid or endocrine dysfunction were excluded from the study. Thyroid function was evaluated at baseline and after 24 months by determination of serum free triiodothyronine (FT3) levels [measured by an RIA kit (Cis Bio)] and free thyroxine (FT4) and thyroid stimulating hormone (TSH) levels [both measured by an immunoradiometric assay kit (Beckam Coulter)]. Subclinical hypothyroidism was defined as TSH levels \( > 4 \text{ mIU/L} \) with normal FT3 (range 3.1–6.5 pmol/L) and FT4 (range 0.8–1.9 ng/dL) levels in accordance with other reports on HIV-infected populations.\(^9\) Thyroid auto-antibodies tests were not available for all the patients included.

Three groups of subjects were identified: G1, subjects on stable HAART (for at least 1 year) at baseline and at month 24 \((n = 97)\); G2, subjects naïve at both baseline and month 24 \((n = 47)\); G3, subjects starting HAART at baseline \((n = 46)\).

For statistical analysis, Fisher’s exact test, Pearson test, \(\chi^2\) test and Student’s \(t\)-test were used whenever appropriate. A multivariable logistic regression analysis was used to find predictive factors of developing subclinical hypothyroidism. Variables included in the model were age, gender, risk factors for HIV infection, CDC stage, body weight, HCV infection, lipodystrophy, increase in CD4+ cell count, triglycerides and total cholesterol serum levels, HIV-RNA reduction and group. Variables for which \(P\) was \(< 0.10\) in the univariate analysis were included in the multivariable model. Finally, the same analyses were repeated considering only G3 individuals, adjusting also for months of exposure to thymidine analogues and protease inhibitors (PIs). Subjects with TSH \( > 4 \text{ mIU/L} \) at baseline were excluded from both univariate and multivariable analyses.

The study was conducted in adherence with local drug regulations, guidelines on ‘Good Clinical Practice’, and the principles of the Declaration of Helsinki and the participants gave their consent to the study.

**Results**

The three groups were comparable with respect to age, gender, body weight and prevalence of HCV infection (Table 1). G1 patients had a longer duration of HIV infection, and higher triglycerides and total cholesterol serum levels than G2 and G3 individuals. As expected, G3 subjects had a lower CD4+ cell count and higher HIV-RNA serum levels compared with G1 and G2 subjects. At month 24, G3 subjects had a mean exposure to thymidine analogues of 21.3 months (3–24) and to PIs of 17.4 months (0–24).

At baseline, subclinical hypothyroidism was detected in 14 subjects in G1 (14.4%), 5 in G2 (10.6%) and 4 in G3 (8.7%) \((P = 0.18)\). At month 24, all these patients maintained TSH levels higher than normal, including two of them who started a thyroid replacement therapy at month 18 and 21, respectively. At month 24, 15 subjects had a new diagnosis of subclinical hypothyroidism: 4 in G1 (4.8%), 3 in G2 (7.1%) and 8 in G3 (19.0%). No patient developed a clinical thyroid dysfunction during follow-up.

Table 1. Demographic and clinical characteristics of the three groups at baseline

<table>
<thead>
<tr>
<th></th>
<th>G1 ((n = 97))</th>
<th>G2 ((n = 47))</th>
<th>G3 ((n = 46))</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males (%)</td>
<td>61 (62.9)</td>
<td>30 (63.8)</td>
<td>32 (69.6)</td>
<td>0.42</td>
</tr>
<tr>
<td>Age, years, mean (range)</td>
<td>38 (29–66)</td>
<td>38 (24–51)</td>
<td>39 (23–64)</td>
<td>0.64</td>
</tr>
<tr>
<td>Weight, kg, mean (range)</td>
<td>67 (44–93)</td>
<td>68 (44–94)</td>
<td>66 (52–89)</td>
<td>0.52</td>
</tr>
<tr>
<td>HCV-positive (%)</td>
<td>36 (37.1)</td>
<td>12 (25.5)</td>
<td>11 (23.9)</td>
<td>0.16</td>
</tr>
<tr>
<td>HIV infection duration, months, mean (range)</td>
<td>75 (23–228)</td>
<td>32 (1–208)</td>
<td>18 (1–245)</td>
<td>0.03</td>
</tr>
<tr>
<td>Triglycerides, mg/dL, mean (range)</td>
<td>194 (146–518)</td>
<td>117 (72–207)</td>
<td>139 (85–264)</td>
<td>0.04</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL, mean (range)</td>
<td>201 (133–291)</td>
<td>165 (124–248)</td>
<td>166 (128–227)</td>
<td>0.03</td>
</tr>
<tr>
<td>CD4+, cells/mm(^3), mean (range)</td>
<td>461 (210–664)</td>
<td>513 (341–928)</td>
<td>163 (4–282)</td>
<td>(&lt; 0.01)</td>
</tr>
<tr>
<td>HIV-RNA, log(_{10}) copies/mL, median (range)</td>
<td>1 (1–1)</td>
<td>4.09 (2.82–5.7)</td>
<td>4.83 (2.61–5.7)</td>
<td>0.02</td>
</tr>
<tr>
<td>Months of HAART, mean (range)</td>
<td>40 (12–81)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Months of thymidine analogues, mean (range)</td>
<td>32 (0–66)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Months of protease inhibitors, mean (range)</td>
<td>34 (12–62)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

G1, HAART-treated subjects at baseline and at month 24; G2, naïve subjects at baseline and at month 24; G3, subjects starting HAART at baseline.

**Discussion**

HIV infection is a chronic, systemic disease possibly leading to multi-organ involvement and affecting the endocrine system as well. Some reports described multiple endocrine imbalances in...
HIV-infected subjects; endocrine function may be altered in these cases because of the possible relationship between the immune and the endocrine system, or through the direct involvement of glands by HIV itself, opportunistic infections or malignancies. Thyroid dysfunction in HIV-positive individuals can result from gland destruction mediated by opportunistic pathogens (Pneumocystis jiroveci or cytomegalovirus) or tumorigenic diseases (Kaposi’s sarcoma). In patients with AIDS, a high prevalence of sick euthyroid syndrome has been reported, probably due to a hypothalamic-pituitary deficit related to the progression of immunodeficiency and cachexia. Subclinical hypothyroidism has often been recognized in the past few years in the HIV-infected population, with a higher prevalence compared with HIV-negative individuals. In two cross-sectional studies, Grappin et al. showed that the cumulative daily dose of both stavudine and lamivudine was significantly related to the presence of hypothyroidism, and Beltran et al. found that the use of stavudine and the lower CD4+ cell count were associated with subclinical hypothyroidism. In a more recent report including a larger population, Quirino et al. reported a similar prevalence of this abnormality in both naïve and HAART-treated subjects. Beltran et al. more recently reported that lower FT4 levels were associated with stavudine use and with a greater didanosine cumulative dose; in this report, no factor was found to be associated with subclinical hypothyroidism in the HIV population except the antiretroviral treatment. The role of HAART was also confirmed by a more recent report, which found that HAART interruption was associated with a normalization of thyroid tests. In this report thyroid dysfunction was not correlated with lipid disorders and no multivariate analysis was presented to confirm the descriptive results reported, explaining the possible differences with our findings.

The present study evaluated the potential relationships among subclinical hypothyroidism, HAART initiation and thymidine analogues exposure. Due to the absence of any statistically significant correlation between these variables, other pathogenic hypotheses than antiretroviral drugs should be considered. Though most of the reports currently available found a correlation between antiretroviral exposure (especially to stavudine, didanosine and ritonavir) and the presence of subclinical hypothyroidism, at the moment, prospective data on this issue are lacking and the possible correlation with lipid alterations has not yet been clearly evaluated.

Our findings demonstrated that the prevalence of subclinical hypothyroidism in HIV-positive individuals was similar in naïve and HAART-treated subjects. During 24 months of follow-up, 15 subjects (9.0%) developed this abnormality, and this finding was more frequent in patients starting HAART compared with the others. As a consequence, a possible acute effect of HAART on thyroid function can be suggested. The role of specific antiretroviral drugs has not been evaluated in the current study, but between antiretroviral exposure (especially to stavudine, didanosine and ritonavir) and the presence of subclinical hypothyroidism might be considered. Though most of the reports currently available found a correlation between antiretroviral exposure (especially to stavudine, didanosine and ritonavir) and the presence of subclinical hypothyroidism, at the moment, prospective data on this issue are lacking and the possible correlation with lipid alterations has not yet been clearly evaluated.

Furthermore, the correlation between the immune reconstitution (evaluated by increase in CD4 cells) and the occurrence of subclinical hypothyroidism might be considered. Although the occurrence of subclinical hypothyroidism in our study was more frequent in subjects starting HAART and was associated with a higher CD4+ cell recovery in the univariate analysis, when adjusting for the other variables this relationship was not confirmed.

The presence of subclinical hypothyroidism seems irreversible; the 14 subjects diagnosed with this abnormality at baseline did not show any significant reduction in TSH levels during follow-up. Nevertheless, these patients did not develop clinical symptoms and only two of them started a substitutive treatment, so that the clinical consequences of this alteration remain uncertain.
One possible limitation of our study is the lack of availability of thyroid auto-antibodies for all the patients at baseline and during follow-up. In addition, due to the small number of subjects developing subclinical hypothyroidism, the role of single antiretroviral drugs has not been evaluated in the study. Larger and more prolonged trials are needed to better assess the clinical impact of subclinical hypothyroidism in HIV-positive subjects.

Our results suggest that thyroid function has to be monitored in all HIV-infected subjects, especially in those starting HAART.

Transparency declarations

None to declare.

References