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Thyroid Function and Depression in HIV-1 Infection

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ABSTRACT

Thyroid abnormalities have been reported in persons with HIV infection, although data have been inconsistent with respect to its frequency and association with specific medications. The purpose of this study was to explore thyroid system response to thyroid releasing hormone stimulation in persons with and without HIV infection and determine the extent to which their response was associated with depression. As part of a larger study of neuroendocrine response persons with HIV-1 infection, control and HIV-1 infected individuals were evaluated. Participants' response to TRH stimulation was evaluated via TSH, total T3, and T4 levels at baseline and 15, 30, 45, and 60 minutes after TRH stimulation. Participants with HIV infection had a more robust response to TRH stimulation as measured by higher levels of TSH, lower levels of T4 and modestly higher levels of T3. Depressed persons had a reduced TSH response to stimulation and lower levels of both T4 and T3, although the effect of depression on T4 was not statistically significant. These results suggest that TSH response to TRH-stimulation may be exaggerated in individuals with HIV infection but reduced in those with depression. They also suggest that the effects of depression and HIV infection may interact, and may provide a partial explanation for observed thyroid abnormalities in HIV-infected individuals. Results thus provide a partial explanation for findings on thyroid and depression in those affected by HIV infection.

Keywords: Thyroid; HIV; Depression

1. Introduction

HIV-1 infection produces a wide range of effects in the human body including devastating effects on the immune system as well as on multiple other organ systems. HIV-1 affects the central nervous [1-3] producing significant cognitive and psychiatric morbidity. Current treatments for HIV infection may themselves result in metabolic dysfunction [4,5]. As treatment of HIV infection has shifted from a focus on helping patients to survive to its management as a chronic disease, the importance of detecting and managing all of its complications has increased.

Thyroid function in HIV-1+ individuals has increasingly been an area of concern due to reports of thyroid function abnormalities such as hypothyroidism in these patients. Data suggest that HIV-1 infection by itself is associated with thyroid abnormalities and that some antiretroviral (ARV) medications may also be related. Thyroid dysfunction may occur as the result of immune system reconstitution [6,7] and are associated with other viral infections in HIV-1+ patients such as hepatitis C [8]. Several studies have found evidence of abnormal thyroid function in persons with HIV-1 infection [9]. These studies show that patients with HIV-1 may have elevated rates of either overt or subclinical hypothyroidism defined as the presence of elevated TSH with reduced or normal levels of T3 and T4 [10-14]. The clinical manifestations of hypothyroidism, such as fatigue, apathy, and depression, have clear clinical significance for patients' quality of life as well as their functional status [15,16].

Various authors have suggested that these abnormalities result from infection-related autoimmune processes or ARV therapy [17-20]. Some studies have suggested that treatment with the ARV medication stavudine is specifically associated with increased risk for hypothyroidism [17,20,21]. It should be noted, however, that other investigations have not found that thyroid dysfunction is associated with ARV therapy generally [18,22] or with specific ARV medications [23]. In a small case control study, hypothyroidism was not associated with ARV treatment [18], and another study found no relation between hypothyroidism and any ARV treatment or, specifically, treatment with stavudine [22].

Thyroid abnormalities have also been reported in persons with HIV-1 infection who have not been treated with ARV medications [10,24]. Bongiovanni [25], in a

longitudinal study of thyroid function in HIV-1+ patients, found substantial rates of subclinical hypothyroidism in both treated and untreated HIV-1+ patients at baseline and the development of new cases of subclinical hypothyroidism in both untreated persons and patients beginning treatment with ARV medications as both groups were followed over 24 months. The overall picture is complicated by results of two studies of thyroid function in nonclinical samples of HIV-1+ individuals found no evidence of thyroid abnormalities [26,27]. The exact relation of thyroid abnormalities to HIV infection and its treatment is thus unclear.

Several possibilities exist to account for abnormal thyroid function in those affected by HIV-1 infection. Immune reconstitution after the initiation of antiretroviral treatment has been associated with autoimmune phenomena, including increases in thyroid antibodies [6,7]. Six patients with subclinical hypothyroidism in the report by Calza *et al.* [14], however, had normal levels of thyroid autoantibodies. As already noted, hypothyroidism may be associated with ARV medication use, although no specific mechanism has been elucidated.

A link between thyroid function mood disorders is well established [28,29]. Since the observations that depression can result from hypothyroidism and that antidepressant efficacy is enhanced through the administration of supplemental thyroid hormone [30-32], investigators and clinicians have been aware of the importance of understanding thyroid function in persons with depression.

Depression is common in persons treated for HIV infection [33] and a link between thyroid function mood disorders is well established [28,29]. Estimates of the prevalence of depression in persons with HIV infection vary widely depending on clinical population and method of depression diagnosis, ranging from 0% to as high as 37% [34,35]. Since the observations that depression can result from hypothyroidism and that antidepressant efficacy is enhanced through the administration of supplemental thyroid hormone [30-32], investigators and clinicians have been aware of the importance of understanding thyroid function in persons with depression.

Given the reported incidence of subclinical hypothyroidism in HIV infection and the hypothyroidism to depression, it is possible that thyroid abnormalities may in part account for the prevalence of depression in this population. Most studies of thyroid function in persons with HIV-1 infection have employed a cross-sectional design with measurement of thyroid indices on a single occasion. As reviewed above, studies have yielded conflicting results. Few studies have employed the more sensitive strategy of evaluating individuals' response to thyroid stimulation via thyrotropin releasing hormone (TRH). Beltran *et al.* [17] evaluated thyroid response to TRH stimulation in persons with HIV-1 infection and evidence of thyroid abnormalities. Although this study found some evidence of HIV-1 infection related thyroid abnormalities at baseline related to study selection criteria, no differences in thyroid response to TRH were observed.

The relation of the effects of HIV-1 infection and depression on thyroid function may thus be complex and interacting. HIV-1 infection, as well as other viral infections, can cause thyroid function abnormalities. The association of HIV infection and depression may exist for a number of reasons, ranging from the purely psychological to the neuroendocrinological [33]. A better understanding of how these factors interact might provide a better understanding of thyroid abnormalities and depression in this population. The purpose of this study was thus to investigate the relations of HIV infection, depression, and thyroid function. We hypothesized that both HIV-1 infection and depression would be related to indices of thyroid function.

2. Method

Data reported in this paper are drawn from a larger study that focused on immune and endocrine response in HIV-1 infected individuals, all of whom had a history of injecting drug use, and uninfected individuals with or without a history of injecting drug use (IDU). Preliminary analyses suggested that IDU status was not related to thyroid response but was closely related to mood. Analyses that included both depression and IDU status also showed that they were closely related but that inclusion of IDU status did not provide additional information with respect to thyroid response; in no models was IDU status significantly related to thyroid markers. For clarity's sake, IDU status is thus not included in the analyses reported here. Data on participants' use of specific ARV medications were not available for use in analyses. The occurrence of hepatitis C infection was not evaluated in this study, and the small number of individuals who reported their status on this variable limited its use in analyses. The presence of antithyroid antibodies among participants was not evaluated and thus data on this issue are not reported.

Participants: Men and women aged 18 to 50 years were enrolled for this study. All participants gave informed consent prior to initiation of the study and all participants were paid for their participation. Potential participants were excluded from participation if they reported a history of head injury with loss of consciousness, learning disability or a history of major psychiatric illness such as schizophrenia or bipolar disorder, hypertension or diabetes mellitus. The study was conducted under a protocol approved by the University of Miami Human Subjects Research Office.

HIV-1 *Infection Inclusion and Exclusion Criteria*: HIV-1-positive participants were required to bring evidence of their serostatus to the study. Additionally, their peripheral plasma viral load was determined using the PCR amplicor method (Roche Diagnostics; at the Clinical Immunology Laboratory in the Department of Medicine, the University of Miami School of Medicine). HIV-1-positive participants were free of any AIDS-defining infections at the time of the study. Verification of HIV-1 seronegative status was not done as part of this study.

TRH-Stimulation Challenge: On arrival in the morning, each participant was asked to relax in a sitting position in a chair and an intravenous line was inserted in a vein in their arm for collection of blood. Each patient received 100 μg of TRH (Thyril, obtained commercially) and blood samples were collected at baseline and at 15, 30, 45 and 60 minutes after TRH administration.

Depression: Participants' mood was assessed using the Beck Depression Inventory [36]. The BDI is a widely-used self-report measure of depressive symptoms. Persons were characterized as depressed if they scored 12 or higher on this measure, based on previous studies of the sensitivity and specificity of this or similar cut off scores in other groups of normal and medically ill patients [37,38].

2.1. Laboratory Procedures

Plasma Isolation: Blood was collected in tubes with EDTA added as an anticoagulant. Samples were centrifuged at 1000 g within 30 minutes and stored at −70˚C until analyzed for TSH, total T4 and T3.

Assays: Plasma was assayed using RIA kits obtained commercially (DSL, Webster, Texas) as described by the vendors. The TSH kit used had a sensitivity of 0.04 μIU/ml and its intra- and inter-assay coefficients of variance (CV) were 3.46% and 6.63% respectively. The total T3 assay had a sensitivity of 4.3 ng/dL and intra- and inter-assay CV were 2.2% to 9% and 5.62% to 12.4% respectively. Total T4 assay had a sensitivity of 0.4 μg/dL and its intra- and inter-assay CVs were 1.5% to 8.5% and 2.8% to 17.3% respectively.

2.2. Data Analyses

The overall data analysis strategy was to evaluate the relation of HIV infection and depression to thyroid function over time using repeated measures analysis of covariance (ANCOVA) models. In order to control for possible confounding variables, models included age, gender, and body mass index (BMI). Interactions among the two main factors in these analyses (HIV, depression) were explored to evaluate the extent to which their interactions would be related to thyroid function.

Dependent variables (TSH, T3, and T4) were first natural log transformed to satisfy linearity assumptions underlying ANCOVA. Separate ANCOVA models were created for each outcome (TSH, T4 and T3) across assessments, with all possible two- and three-way interactions explored in preliminary analyses. No significant between-subjects interactions for TSH, T4, or T3 were found, and final models include only main effects for factors and covariates. The within-subjects effect for change over time was significant only for TSH response, as were several of the interactions of factors and covariates with time and are reported. None of the within-subjects effects was statistically significant for T4 or T3 response and are not reported here.

3. Results

Descriptive statistics for the sample are presented in **Table 1** for both categorical and continuous variables. The final ANOVA model for TSH is presented in **Table 2** and graphically in **Figures 1** and **2** (all figures present model-corrected estimated values).

Both HIV-1 infection status and depression were associated with TSH response to TRH stimulation, but in

Table 1. Descriptive statics.

Categorical Variables		
	N	Percent
Gender		
Male	53	59
Female	37	41
HIV Status		
Negative	60	67
Positive	30	33
Race/Ethnicity		
Non-Hispanic White	20	22
Black	53	59
Hispanic	17	19
Depressed		
Not Depressed	51	57
Depressed	30	33
Continuous Variables		
	Mean	SD
Age	38.3	6.6
Years of Education	12.1	1.8
BMI	17.2	7.1

opposite directions. Persons who were HIV-1+ had a greater TSH response to stimulation (**Figure 3**) while those with depression had a reduced response (**Figure 1**) relative to those without either condition. Significant interactions of time course of TSH response with HIV-1 infection status (F = 2.99, df = 4, 296, p = 0.02), gender (F = 3.30, df = 4, 296, p = 0.01), depression (F = 2.79, df = 4, 296, p = 0.03), and age (F = 3.01, df = 4, 296, p = 0.02) were found, suggesting that the pattern of individuals' TSH response over time varied with respect to these variables.

Table 2. Between-subjects effects for TSH.

Source	df	Mean Square	F	Sig.
Intercept	1	15.50	10.53	0.00
Serostatus	1	12.49	8.48	0.01
Gender	1	24.05	16.33	<0.001
Depression	1	8.01	5.44	0.02
BMI	1	2.69	1.82	0.18
Age	1	0.00	0.00	0.99
Error	74	1.47		

The model for T3 is presented in **Table 3** and **Figures 2** and **4**. Significant effects for depression, BMI, and age were found. No significant interaction of time with any variable was found. Depressed participants had lower levels of T3, while those with and without HIV-1 infection did not differ significantly.

Neither HIV status nor depression was significantly related to T4 response (Full model not shown; HIV status F[1,65] = 0.49, p = 0.49; Depression F[1,65] = 1.00, p = 0.32). There was a significant effect for gender (with women having higher levels of T4). No significant interactions of time with other variables were obtained.

Inspection of the plot of T4 response for those with

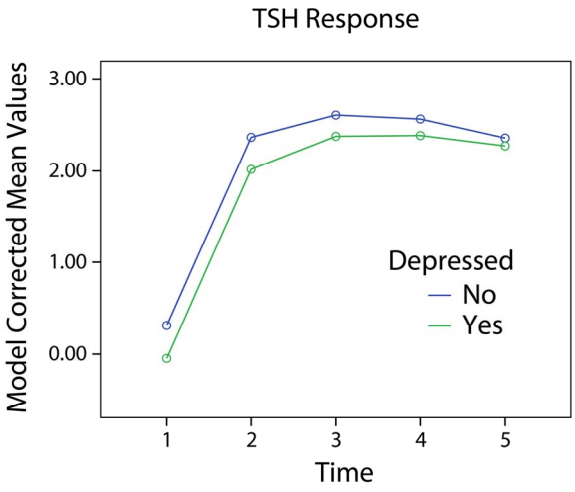

Figure 1. TSH response and depression.

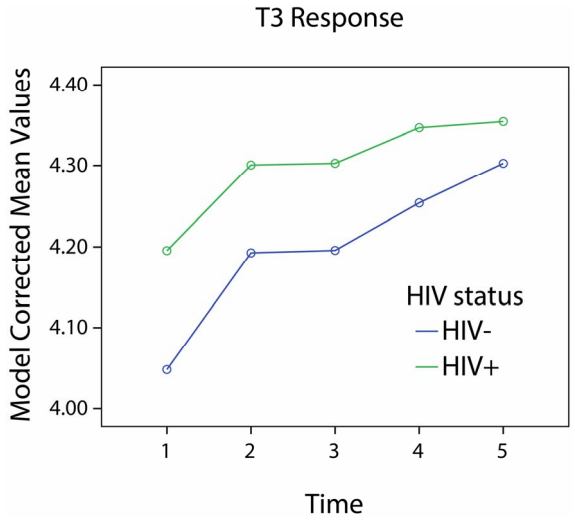

Figure 2. T3 response and HIV status.

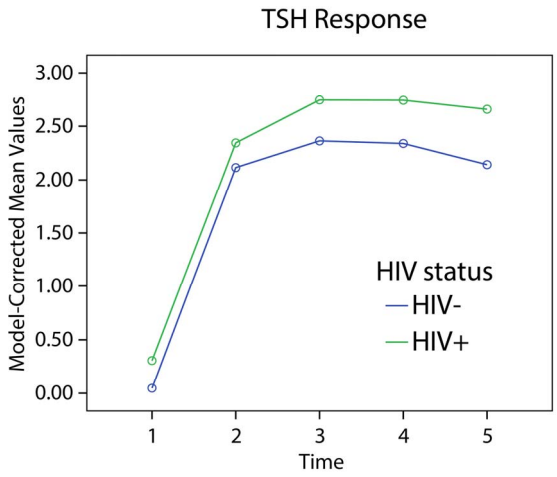

Figure 3. TSH response and HIV status.

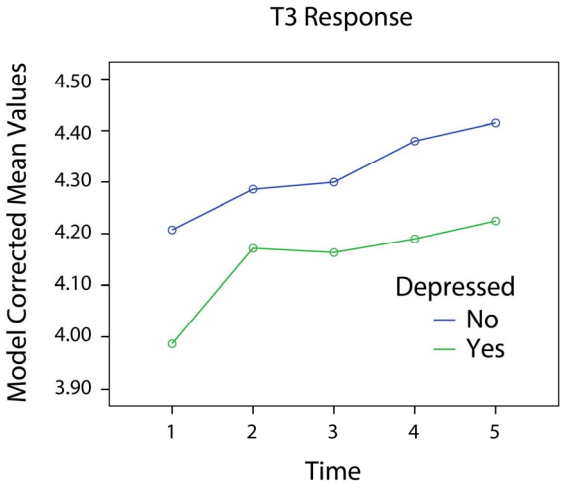

Figure 4. T3 response and depression.

and without depression suggested that depressed participants had lower levels of T4 across times (**Figure 5**). The plot of T4 response in relation to HIV status was similar. These observations raise the possibility that the failure to find statistical significance might have been the result of low power due to our sample size.

4. Discussion

The purpose of this study was to evaluate the effects of HIV-1 infection and depression on thyroid function in a clinically relevant population. Our results show that both HIV-1 infection and depression may have significant but contrasting impacts on thyroid function. These results are summarized in **Table 4**.

These findings present the possibility that two independent processes affect thyroid response to stimulation among persons with HIV-1 infection. The infection itself is associated with a pattern of thyroid function consistent with increased level of T3 but a reduced production of T4 in response to stimulation (an increased response of TSH to TRH stimulation with reduced T4 response). This pattern would be consistent with intact increases in T3 in response to TSH stimulation but reduced effectiveness of conversion of T4 to T3 in the periphery. In contrast, in this study depression was associated with a reduced TSH response to stimulation and lower levels of both T3 and T4. These findings might be consistent with a central effect for depression and a peripheral effect of HIV infection on T4 conversion. This might reflect the direct action of HIV infection of peripheral tissues and the hypothesized link between the hypothalamic-pituitary (HPA) axis and thyroid function, possibly via an autoimmune process [39,40]. This interpretation must be advanced tentatively, as several of the observed effects were not statistically significant.

These findings are consistent with the only other readily-identifiable study of stimulated thyroid function in persons with HIV-1 infection [17]. In this study, Beltran and colleagues found high TSH combined with low T4 levels in some patients with HIV-1 infection, but her results were based only on participants preselected as having either subclinical hypothyroidism or normal TSH levels with low T4 compared with a euthyroid control group. This study, however, did not show significant differences in thyroid response. Due to their small sample size, Beltran *et al.* used a nonparametric statistical analysis strategy that did not allow them to control for potential confounding variables such as gender and BMI, as done in our study.

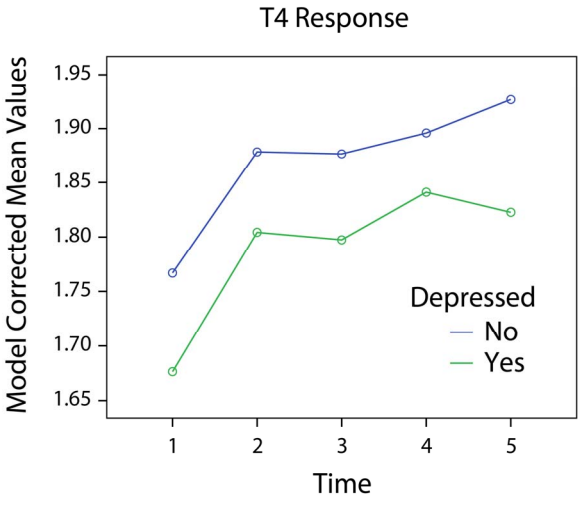

Figure 5. T4 response and depression.

Table 4. Summary of findings.

Effect	TSH	T3	T4
HIV-1 Infection	↑[a]	↑[b]	↓[b]
Depression	↓[a]	↓[a]	↓[b]

[a]Statistically significant (**Figures 1**, **3**, and **4**); [b]Not statistically significant but figures suggest that and effect may be present (**Figures 2** and **5**).

Our results provide a possible explanation for conflicting findings in cross sectional studies of thyroid function in HIV-1 infected individuals. This study's statistical design allowed us to control for several possible confounders, including age, gender, and BMI as well as to take the effects of depression into account while evaluating the effects of HIV-1 infection on thyroid function. These results show that factors such as BMI and gender may have a significant impact on indices of thyroid function and should be considered in future studies. Further, the significant and contrasting effects of HIV-1 infection and depression on thyroid function show that mood may be an important confounder in studies of thyroid function in persons with HIV-1 infection.

Limitations of this study include our inability to evaluate the effects of specific ARV medications on thyroid status, the complex nature of our sample that included persons with and without a history of IDU, and the small number of persons with data on hepatitis C infection that limited our ability to take this factor into account. Further, as with IDU status, hepatitis C infection was closely tied to whether participants were depressed (data not presented), raising the possibility that all of these factors are interrelated. Our sample size was not sufficient to permit us to statistically disentangle the effects of each of these factors.

Another limitation is our lack of data on the presence of antithyroid antibodies in participants. Increased occurrence of antithyroid antibodies has been linked both to depression and HIV-1 infection [41,42] and thus might account in part for the current findings. Increased frequency of antithyroid antibodies has been found in several samples of HIV-1 infected individuals [6,7] as

part of immune reconstitution. On the other hand, Beltran and her colleagues [17] in her sample found no evidence of antithyroid antibodies in her sample of HIV-1 infected persons with either subclinical hypothyroidism or low T4 levels. The possible role of antithyroid antibodies in HIV-related thyroid dysfunction is thus unclear.

In summary, results of this study suggest that both HIV infection and depression may be related to indices of thyroid function in persons with HIV-1 infection but perhaps by difference mechanisms. Analyses also indicate that several other variables, including gender, age, and body mass index may be important in understanding the relations among these variables. These results thus confirm others' observations of a relation of thyroid function to HIV-1 infection and the well-established relation of thyroid function to depression. Our findings emphasize the importance of thyroid function in HIV-1 infection and highlight the possibly complex interaction between the infection and depression.

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