Indices of Thyroid Function and Weight Loss in Human Immunodeficiency Virus Infection and the Acquired Immunodeficiency Syndrome

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Abnormalities of thyroid hormone levels have been reported in the acquired immunodeficiency syndrome (AIDS), but there has been debate as to whether they are appropriate for the clinical status of the patients. Inappropriate maintenance of circulating 3,3′,5-triiodothyronine (T_3) levels could contribute to weight loss. Although many patients with AIDS have a history of wasting, recent data indicate that prolonged periods of stable weight occur in AIDS and that short-term weight loss is present in a subset of patients with anorexia, many of whom have active secondary infection (AIDS-SI). Therefore we analyzed thyroid hormone levels in a cohort of subjects that have been characterized in terms of recent weight loss and caloric intake. Asymptomatic patients with human immunodeficiency virus infection (HIV^+) had short-term stable weights, normal caloric intake, and normal serum T_3 levels. In AIDS, average short-term weight was stable, caloric intake was normal, and T_3 levels were decreased by 19%. In AIDS-SI, both short-term weight loss and anorexia were significant, and this group showed a 45% decrease in T_3 levels. The free T_3 (FT_3) index was decreased by 30% in AIDS and by 50% in AIDS-SI. Free thyroxine (FT_4) levels were decreased while thyroxine-binding globulin (TBG) capacity was increased in HIV^+ and AIDS; TBG sialylation was unchanged. Thyrotropin (TSH) levels were slightly increased in AIDS, although levels remained within the normal range. 3,3′,5′-triiodothyronine (rT_3) levels were decreased in HIV^+, AIDS, and AIDS-SI. Thus asymptomatic patients with HIV infection whose weight is stable maintain normal T_3 levels. T_3 and FT_3 levels begin to decrease in AIDS, whereas those patients with secondary infection, anorexia, and weight loss (AIDS-SI) show decreases in T_3 levels consistent with the "euthyroid-sick syndrome."
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SEVERE NONTHYROIDAL ILLNESS is accompanied by disturbances in thyroid hormone metabolism known as the "euthyroid-sick syndrome."[1,2] Such disorders are usually accompanied by a decrease in circulating 3,3′,5-triiodothyronine (T_3) levels and may be accompanied by increases in serum 3,3′,5′-triiodothyronine (rT_3) levels. The decrease in T_3 level is thought to be beneficial in that it may help preserve protein and limit energy expenditure.[1-3] T_3 replacement therapy in the decreased T_3 state of caloric deprivation is not beneficial and may be harmful.[4,5]

The acquired immunodeficiency syndrome (AIDS) is caused by infection with the human immunodeficiency virus (HIV), which depletes T-helper lymphocytes, leading to susceptibility to opportunistic infections and neoplasms.[6] During the course of AIDS, patients show striking weight loss.[7-9] Decreases in serum T_3 levels in AIDS have been reported by some laboratories,[10-12] but not by others,[13-16] and questions have arisen as to the significance of these findings. Some investigators have described the decrease in serum T_3 levels as an appropriate response similar to that seen in other nonthyroidal illnesses.[11] Others have questioned whether the failure to show decreased T_3 level despite advanced AIDS is inappropriate and might contribute to wasting.[10,13]

Although many patients with AIDS have a history of weight loss, long periods of stable weight are common.[17,18] Recently we have noted that short-term weight loss occurs only in a portion of subjects with HIV infection or AIDS.[19] Those subjects showed significant anorexia during an inpatient metabolic ward study and frequently were found to have active secondary infections (AIDS-SI); weight change was highly correlated with food intake.[19] Given the varied results and differing interpretations in studies of thyroid function in AIDS, we now have studied thyroid hormone indices in this well-characterized population. We find that serum T_3 levels are strikingly decreased in AIDS subjects with anorexia, secondary infection, and short-term weight loss.

SUBJECTS AND METHODS

Patient Population

This study was approved by the Committee on Human Research of the University of California, San Francisco. The patient population has been described in detail in an earlier publication.*[19] A subset of 15 patients with AIDS as defined by the revised criteria of the Centers for Disease Control[20] were studied; none had active secondary infections at the time of study (AIDS group). A second group of nine subjects was studied during the course of secondary infections (AIDS-SI group). *Pneumocystis carinii* was found in four, one of whom also had systemic cytomegalovirus infection, three had bacterial sinusitis, and one had bacteremia due to a urinary tract infection. Fourteen subjects with HIV infection who had not yet developed an AIDS-defining illness were also studied (HIV^+ group). Subjects were excluded for dementia, severe diarrhea,

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Submitted July 11, 1992; accepted December 8, 1992.

Supported by grants from the National Institutes of Health (DK40990), the AIDS Clinical Research Center of UCSF (University-wide Task Force on AIDS 91RCC86-SF), the Jewish Community Endowment Fund, and the Department of Veterans Affairs.

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*The subjects in this study of thyroid hormone indices include all but one of the subjects whose resting energy expenditure, caloric intake, and weight trends were previously reported.[19] There were no longer sufficient quantities of serum for study on the subject that was excluded.

significant oral lesions, or known prior endocrinological disease. In addition, we simultaneously studied 15 healthy controls whose plasma was negative for antibody against HIV. All subjects were males and the groups were age-matched.

Diet

Subjects were admitted to a metabolic ward, the Special Diagnostic and Treatment Unit at the San Francisco Veterans Administration Medical Center, and offered an unrestricted hospital diet consisting of 15% protein, 45% carbohydrate, and 40% fat, as described previously.[19] Food was tailored to each subject's food preferences. Calorie counts were performed for a 24-hour period during the hospital stay using the energy/nutrient analysis program of the Department of Veterans Affairs, a centralized hospital computer program that uses U.S. Department of Agriculture Handbooks 8 and 456, and information from the food manufacturers. Serum samples were drawn the morning after an overnight fast, once during each inpatient study.

Weight Trends

Although 71% of the HIV$^+$ and all of the AIDS and AIDS-SI subjects had a history of weight loss during the course of their illness, many were not losing weight at the time of study; some were actively gaining weight.[19] Therefore we analyzed the short-term change in weight during a 28-day period surrounding the inpatient study by assessing weights obtained in the clinic 14 days before and 14 days after the study.[19] When clinic weights were not available exactly on those days, the mathematical average of the weight for the two nearest surrounding clinic days was used, as described in detail previously.[19] Control subjects were not analyzed for weight change.

Resting Energy Expenditure

During an inpatient admission, resting energy expenditure (REE) was measured in the fasting state 14 hours after the evening meal.[19] REE was determined by indirect calorimetry using a Horizon metabolic cart MMR in the canopy mode (SensorMedics, Anaheim, CA).

Thyroid Hormone Levels

Total T_3, T_3 uptake, total thyroxine (T_4), and free T_4 (FT_4) levels were measured with Clinical Assays Gammacoat radioimmunoassay (RIA) kits from Baxter Health Care (Cambridge, MA). The Gammacoat RIA FT_4 (two-step) assay has been extensively studied in nonthyroidal illness and gives results that correlate highly with equilibrium dialysis.[21,22] rT_3 level was measured by RIA with reagents from Serono-Baker Diagnostics (Allentown, PA). Serum thyrotropin (TSH) level was measured by assay with the MAGIC mab TSH IRMA from Ciba Corning Diagnostic (Medfield, MA). Interassay coefficients of variation are as follows: Total T_3, 4.8%; T_3 uptake, 2.3%; total T_4, 5.2%; FT_4, 4.9%; rT_3, 7.9%; and TSH, 2.2%. Thyroxine-binding globulin (TBG) capacity was estimated using the inverse of the T_3 uptake ($100/T_3$ uptake).† The free T_3 index was computed as (total T_3) × (T_3 uptake/100). Total urinary nitrogen was determined by the Kjeldahl method.

Sialylation of TBG

The nondenaturing isoelectric focusing method of Takamatsu et al[23] was used to assess sialylation of TBG. Serum (10 μL) was incubated with 10 μCi ^{125}I-L-thyroxine (1,250 μCi/μg, Dupont-NEN Research Products, Boston, MA) for 1 hour at room temperature. Isoelectric focusing was then performed on a prefocused vertical polyacrylamide gel containing 5% acrylamide, 8% glycerol, and 2.5% Pharmalyte (pH 4.2-4.9) ampholines (Pharmacia, Piscataway, NJ) using 1 mol/L glycine as the catholyte and 0.1 mol/L phosphoric acid as the anolyte. Gels were focused at a maximum power of 20W for 3,600 V × hours, after which the gels were immediately dried. After exposure of the gel on XAR5 film (Eastman Kodak, Rochester, NY), the bands were excised and counted in a gamma scintillation counter. As a control, serum from one subject in the third trimester of pregnancy was run on each gel.

Statistics

Because many of the values in HIV$^+$ and AIDS were not normally distributed, ANOVA was performed using the Kruskal-Wallis test for nonparametric statistics and correlations were performed using the Spearman Rank Correlation Coefficient, using the Crunch Statistical Program (Oakland, CA). Data in tables and text are presented as the mean ± standard error; data in figures are presented as the mean ± 2 standard deviations.

RESULTS

HIV$^+$, AIDS, and AIDS-SI subjects had CD4 counts below the normal range (<450), consistent with their disease status (Table 1). Most of these subjects with HIV disease had a prior history of weight loss,[19] but similar to what was described previously, average weight was stable in HIV$^+$ and AIDS. In contrast, short-term weight loss was striking in AIDS-SI, with an average decrease of almost 5% of body weight in 28 days. Eight of nine AIDS-SI subjects showed weight loss. There was a trend toward decreased body mass index in AIDS and AIDS-SI. Similar to what was found previously,[19] REE was increased by 11% in HIV$^+$, 23% in AIDS, and 29% in AIDS-SI. Caloric intake during the metabolic ward study was similar in control, HIV$^+$, and AIDS; however, caloric intake was decreased by 34% in AIDS-SI (Table 1).

There were no significant differences in total urinary nitrogen excretion among the groups (Table 1). Thus in AIDS-SI, despite decreased caloric (and protein) intake, urinary nitrogen loss was the equivalent of that in controls, indicating negative nitrogen balance.

Results of thyroid function tests in this population are presented in Table 2 and Figs 1 through 4. There were no significant differences in total T_4 concentrations among the groups (Table 2 and Fig 1). Measured FT_4 concentrations (Table 2 and Fig 2) were slightly but significantly decreased in HIV$^+$ ($P < .01$ *v* control) and AIDS ($P < .001$ *v* control). Total T_3 concentrations (Table 2 and Fig 3) were normal in HIV$^+$, but slightly decreased (19%) in AIDS ($P < .02$ *v* control); more important, T_3 level was decreased by 45% in AIDS-SI ($P = .0001$ *v* control).

T_3 uptake was decreased in HIV$^+$ and AIDS (Table 2). Using T_3 uptake, TBG capacity was calculated to be increased (HIV$^+$, $P < .001$; AIDS, $P = .0001$ [*v* control]). Increases in TBG levels have also been previously reported in AIDS.[10,15] As a consequence of the small decreases in both total T_3 level and T_3 uptake, the FT_3 index (Table 2 and Fig 4) was decreased by 30% in AIDS ($P < .0001$ *v*

†TBG capacity can be estimated from T_3 uptake because total T_4 level was not significantly altered among the four study groups (see text).

Table 1. Metabolic Characteristics

	Control (n = 15)	HIV⁻ (n = 14)	AIDS (n = 15)	AIDS-SI (n = 9)
CD4 cell count*	ND	184 ± 45.8†	52.8 ± 24.5	32.6 ± 11.8
Short-term weight change (%BW/28 d)*	ND	0.33 ± .62	−0.42 ± .82	−4.96 ± 1.44‡
BMI (kg/m²)*	24.2 ± .75 (100)	23.7 ± .66 (95.5)	22.4 ± .90 (92.6)§	22.1 ± 1.0 (91.3)§
REE (kcal/kg BW)*	20.9 ± 0.49 (100)	23.1 ± 0.67 (111)‖	25.7 ± .89 (123)¶	26.9 ± 1.22 (129)¶
Caloric intake (kcal/kg BW)*	35.4 ± 3.07 (100)	34.9 ± 1.53 (98.3)	34.7 ± 3.03 (97.9)	22.6 ± 3.35 (63.7)#
Total urinary nitrogen (g/24 h)**	14.1 ± 0.95 (100)	13.9 ± 1.08 (98.6)	13.3 ± 0.91 (94.3)	13.2 ± 1.16 (93.6)

NOTE. Values are means ± SE; values in parentheses are percentages of control values.
Abbreviations: BW, body weight; ND, not determined; BMI, body mass index.
*Values for some of these subjects were included in reference 19.
†$P = .0025$ *v* AIDS; $P < .0025$ *v* AIDS-SI.
‡$P < .002$ *v* HIV⁺; $P < .05$ *v* AIDS.
§$P < .1$ *v* control.
‖$P < .025$ *v* control.
¶$P < .0001$ *v* control.
#$P < .01$ *v* control and HIV⁺, $P < .02$ *v* AIDS.
**n = 14 for AIDS; n = 8 for AIDS-SI.

control) and by 50% in AIDS-SI ($P < .0001$ *v* control; $P < .05$ *v* HIV⁺). There was a significant correlation between FT_3 index and weight loss using the Spearman Rank Correlation Coefficient ($R_s = .444, P < .01$).

No subject was clearly hypothyroid, as all TSH levels were within the normal range; however, there was a small but significant increase in TSH levels in AIDS (Table 2; $P < .0005$ *v* control, $P < .01$ *v* HIV⁺), and there was a trend toward an increase in TSH levels in AIDS-SI ($P < .1$) compared with controls. rT_3 levels (Table 2) were significantly decreased in HIV⁺, AIDS, and AIDS-SI (all $P < .0001$ *v* control), as reported by others previously.[10,15]

There was no increase in sialylation of TBG in AIDS. Examples of TBG isoforms from four controls and four AIDS patients along with an example from a pregnant woman are shown in Fig 5. A shift in the prevalence of isoforms migrating toward the anode is seen in serum from the pregnant woman, where the fourth band down from the cathode accounts for 24% of total, as compared with controls (n = 16) where the fourth band represents 12.1% ± 0.5% of total. The fourth band was 10.5% ± 0.55% in HIV⁺ (n = 15), 12.0% ± 1.01% in AIDS (n = 15), and 8.8% ± 1.07% in AIDS-SI (n = 8). A more sensitive estimate of sialylation is the ratio of band 4 to band 1, which is 2.7 in the pregnant woman but only 0.50 ± 0.03 in controls. The ratios in HIV⁺ (0.39 ± 0.03), AIDS (0.51 ± .07), and AIDS-SI (0.32 ± 0.02) were not different from those in controls. There was no significant correlation between the amount of sialylation of TBG and levels of TBG in AIDS and HIV⁺ (data not shown).

DISCUSSION

We studied indices of thyroid function in cohorts of patients with HIV infection that have been carefully characterized with regard to recent weight loss and caloric intake. Both infection and caloric intake are known to influence thyroid hormone levels,[1-5] although some data suggest that even during infection the changes in some of these indices may be predominantly due to decreased food intake.[24]

Table 2. Thyroid Hormone Indices

	Control (n = 15)	HIV⁺ (n = 14)	AIDS (n = 15)	AIDS-SI (n = 9)
T_4 (μg/dL)	7.4 ± 0.40 (100)	7.5 ± 0.32 (101)	7.1 ± 0.56 (96)	6.8 ± 0.58 (92)
FT_4 (ng/dL)	1.39 ± 0.060 (100)	1.18 ± 0.036 (85)*	1.12 ± 0.058 (80)†	1.35 ± 0.085 (97)
T_3 (ng/dL)	108 ± 6.3 (100)	126 ± 6.0 (116)	88 ± 8.0 (81)‡	59 ± 8.4 (55)§
T_3 uptake (%)	34 ± 0.5 (100)	31 ± 0.7 (91)†	30 ± 0.9 (88)§	32 ± 1.0 (94)
TBG‖	3.0 ± 0.05 (100)	3.3 ± 0.07 (110)†	3.4 ± 0.12 (115)§	3.2 ± 0.11 (107)
FT^3 index	.36 ± 0.018 (100)	.38 ± 0.017 (106)	.25 ± 0.018 (70)¶	.18 ± 0.022 (50)¶#
TSH (μIU/mL)	.90 ± 0.12 (100)	1.28 ± 0.24 (142)	2.77 ± 0.56 (307)**	1.98 ± 0.59 (220)
rT_3 (ng/dL)	26 ± 1.9 (100)	13 ± 1.2 (48)¶	15 ± 1.2 (57)¶	13 ± 1.6 (50)¶

NOTE. Values are means ± SE; values in parentheses are percentages of control values.
*$P < .01$ *v* control.
†$P < .001$ *v* control.
‡$P < .02$ *v* control.
§$P = .0001$ *v* control.
‖TBG capacity defined as $100/T_3$ uptake.
¶$P < .0001$ *v* control.
#$P < .05$ *v* HIV⁺.
**$P < .0005$ *v* control; $P < .01$ *v* HIV⁺.

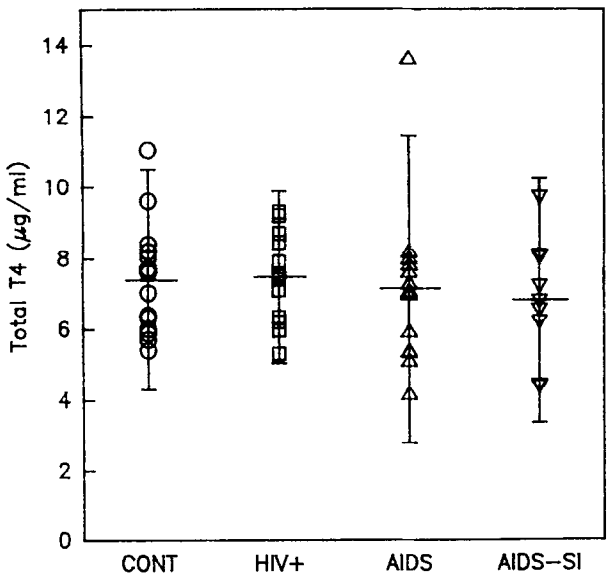

Fig 1. Total T_4 values assayed using the Clinical Assays Gammacoat RIA (see Methods). Means ± 2 SD are shown for each group.

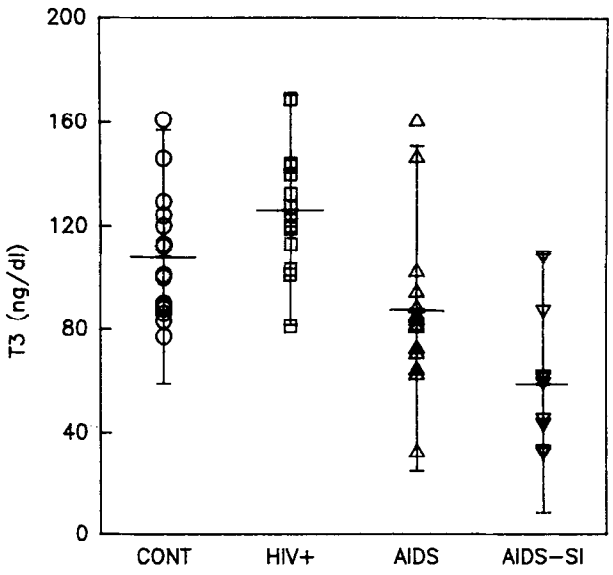

Fig 3. Total T_3 values assayed using the Clinical Assays Gammacoat T_3 RIA (see Methods). Means ± 2 SD are shown for each group.

HIV+ subjects showed stable mean weight and normal caloric intake. AIDS subjects showed no significant change in mean weight, although there was more of a tendency toward weight loss. In AIDS-SI subjects, weight loss and decreased caloric intake were striking. All three groups showed hypermetabolism as evidenced by increased REE.[19]

In HIV+ subjects, we found normal T_4, T_3, and FT_3 index, decreased FT_4 and rT_3, and increased TBG levels. In AIDS subjects, we found small but significant decreases in FT_4, T_3, FT_3 index, and rT_3, a normal T_4, and a small increase in TBG capacity and TSH levels. In AIDS-SI subjects, we found a striking decrease in T_3, FT_3 index, and rT_3, normal T_4, FT_4, and TBG, and a trend toward an increase in TSH levels. These findings are suggestive of a progressive defect in the conversion of T_4 to T_3 as the severity of HIV infection progresses and caloric intake decreases secondary to anorexia; however, kinetic studies are needed to prove this hypothesis. Unlike fasting and some other illnesses,[1-3] the presumed decrease in T_4 to T_3 conversion seen here is accompanied by an increase in the pituitary output of TSH (see AIDS and AIDS-SI groups); however, this increase in TSH levels may not be sufficient to restore T_3 levels to normal. There are several nonthyroidal illnesses in which TSH level increases slightly in the face of decreased T_3 level.[25]

TBG levels are increased early in the course of HIV infection, but decreases toward normal levels during second-

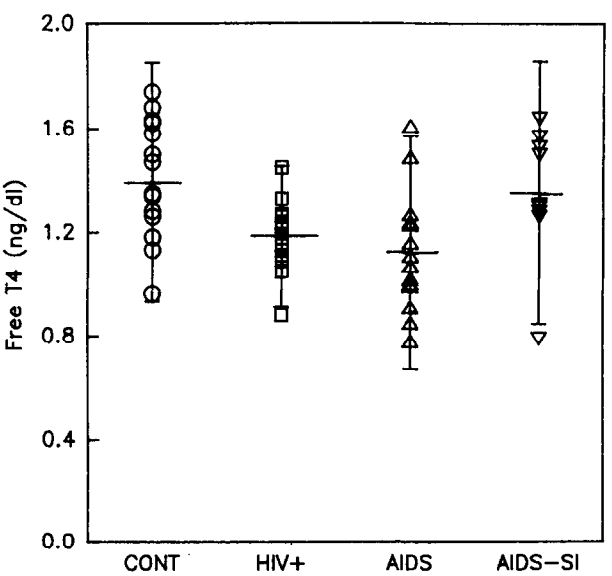

Fig 2. T_4 values assayed using the Clinical Assays Gammacoat FT_4 (two-step) RIA (see Methods). Means ± 2 SD are shown for each group.

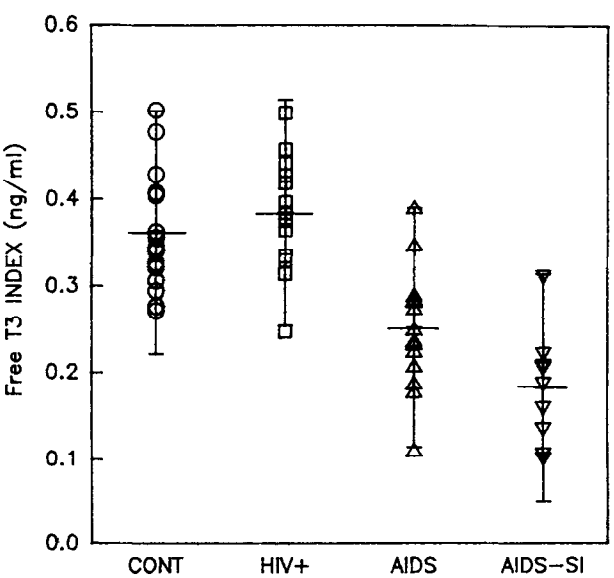

Fig 4. FT_3 index calculated as (total T_3) × (T_3 uptake / 100). Means ± 2 SD are shown for each group.

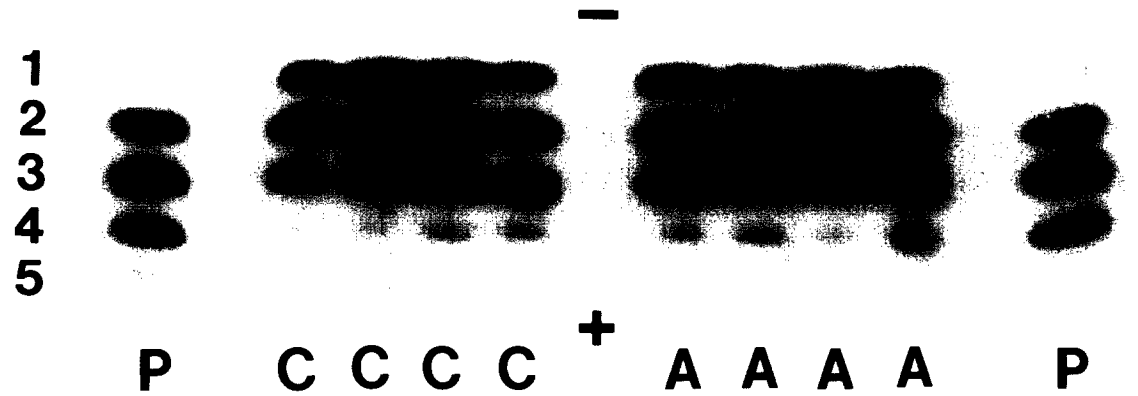

Fig 5. Sialylation of TSH determined using the nondenaturing isoelectric focusing method of Takamatsu et al[23] as described in Methods. Cathode (−) and anode (+) sides are labeled; (C) control; (A) AIDS; (P) pregnancy.

ary infection; the reason for increased TBG levels in HIV infection has not been established. The sialylation state of TBG increases during pregnancy, which is the likely cause of increased TBG levels in pregnancy, as the higher sialylated forms are cleared more slowly from the plasma.[26] We have previously reported that another serum protein (apo E) shows increased sialylation in AIDS.[27] However, here we show that the sialylation of TBG is not increased in AIDS.

All three HIV-infected groups showed decreased rT_3 levels, as has been previously reported.[11,12,14,15] In many nonthyroidal illnesses, when T_3 levels are decreased (due to a presumed decreased conversion of T_4 to T_3), rT_3 levels are usually but not always increased. However, in patients with nephrotic syndrome or hyperparathyroidism, rT_3 levels are often decreased in the presence of low T_3 concentrations.[1-3] In HIV infection, the decrease in rT_3 levels occurs before T_3 levels decrease (Table 2, Figs 3 and 4). Changes in rT_3 distribution and metabolism may occur early in HIV infection. Others have shown that rT_3 levels increase in severely ill AIDS patients who do not survive.[10]

The results of thyroid function tests reported here and elsewhere for subjects with HIV infection[10-16] appear on initial examination to be discordant. However, on careful examination a consistent pattern appears; T_3 and FT_3 concentrations decrease in proportion to severity of illness. We found the most striking decrease in T_3 and FT_3 levels in AIDS-SI subjects who were both actively losing weight as outpatients and anorectic during an inpatient study (AIDS-SI). Weight-stable patients showed normal or slightly decreased T_3 and FT_3 levels. Studies of patients with AIDS and HIV infection do not always show decreases in T_3 levels that are characteristic of the euthyroid-sick syndrome.[13-16] In one of those studies, T_3 levels were within normal limits, but showed a small but significant decrease.[14] However, in other reports, T_3 levels were found to be normal in outpatients, but decreased in those patients hospitalized with *Pneumocystis carinii* pneumonia.[10,12] In another study where mean T_3 levels were not decreased even in CDC stage IV AIDS, T_3 levels were decreased in acutely hospitalized CDC stage IV patients.[15] Likewise, one group found decreased T_3 levels in AIDS patients with secondary infection and signs of serious systemic illness such as decreases in serum sodium and albumin levels.[11] AIDS patients who die during hospitalization also have low T_3 levels.[10,11,14] Thus T_3 levels can reflect the seriousness of the illness and can serve as a prognostic indicator.[10,11,14] The severity of illness also affects TBG, T_4, and FT_4 concentrations. Because TBG levels are increased in many of these patients, the FT_3 levels are decreased even more than the total serum T_3 concentration.

Thus on careful review of the existing data, there is agreement that the most seriously ill patients with AIDS show decreases in T_3 and FT_3 levels consistent with decreased conversion of T_4 to T_3, presumably a protective change seen in the "euthyroid-sick syndrome" as demonstrated here and in previous reports.[10,12,15] However, the appropriateness of that protective response has been questioned. Despite the inclusion of outpatients with advanced AIDS, Dobs et al[13] found it "surprising" that a decreased T_3 level was not found in their patients; they speculated that decreases in T_3 levels would be found in "acutely-ill hospitalized HIV-infected patients." LoPresti et al[10] have suggested that in patients with AIDS, the "maintenance of normal serum T_3 levels may play a significant role in facilitating weight loss." The concern has been raised that the failure to decrease serum T_3 and FT_3 levels may contribute to inappropriate metabolic rates, weight loss, and protein breakdown in HIV infection.[10] However, none of the patients in previous studies were described with regard to recent weight loss. In addition, fasting or significant caloric restriction decreases serum T_3 levels,[1-3] but caloric intake was not characterized in previous patients. Decreases in serum T_3 levels in fasting patients may contribute to decreased protein catabolism.[4,5]

In our patient population, those subjects with recent weight loss, anorexia, and secondary infection (AIDS-SI) did show appropriate reductions in serum T_3 and FT_3 index levels. In contrast, T_3 levels were maintained in HIV^+ and only slightly decreased in AIDS, conditions where, on average, significant weight loss did not occur and caloric intake was not decreased. The AIDS subject with the lowest T_3 and FT_3 index levels (Figs 3 and 4) was studied 7 weeks after a secondary infection; it is not known how long it takes

for T_3 levels to normalize after secondary infection. It is possible that other AIDS subjects with relatively low FT_3 index levels had undiagnosed infections. There was a significant correlation between weight loss and the decrease in FT_3 index levels. However, it remains to be determined whether the secondary infection, decrease in caloric intake, weight loss, or a combination of these factors are the cause of decreased T_3 levels in HIV disease.

Infection is often accompanied by hypermetabolism; increases in REE have been described in AIDS and HIV infection.[16,19,28,29] It is of note that we found no further increase in REE with the onset of secondary infection in AIDS (AIDS-SI). The failure to see a further increase in REE in this group might be due in part to the decrease in their serum T_3 levels, a change that could provide a compensating decrease in metabolic rate.[1-3,30,31] However, factors other than T_3 levels contribute to the changes in REE seen even in simple starvation.[32] Hence it is possible that the failure to increase REE further in AIDS-SI may be secondary to decreased caloric intake per se.[19] In addition, it is likely that cytokines and other factors regulate REE during infection with HIV.[7]

However, it should be noted that urinary nitrogen loss was not decreased in AIDS-SI, despite decreases in both caloric intake and T_3 levels. Thus in the face of infection with both HIV itself and secondary opportunistic infections, the decrease in T_3 level was not enough to preserve nitrogen balance, as is found in other more controlled situations such as caloric restriction.[4,5] Critically ill intensive care unit patients also show decreased T_3 levels, but have increased urinary nitrogen loss.[1-3]

In summary, weight-stable patients with HIV infection and AIDS are likely to maintain their serum T_3 levels. When anorexia and weight loss occur (which frequently indicates secondary infection), T_3 levels decrease appropriately, consistent with the "euthyroid-sick syndrome."

ACKNOWLEDGMENT

We thank P. Herranz and M. Cho for editorial assistance. The cooperation and support of our patients and the staff of the Infectious Disease Clinic and the Special Diagnostic and Treatment Unit are greatly appreciated. Measurement of total urinary nitrogen was performed in the laboratory of Dr Janet King, University of California, Berkeley, as part of the Pregnancy Emphasis Research Center Program project grant (HD22224).

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