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Interleukin-6 and Human Immunodeficiency Virus Load, But Not Plasma Leptin Concentration, Predict Anorexia and Wasting in Adults with Pulmonary Tuberculosis in Malawi

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Background: Wasting is a prominent feature of tuberculosis and may be more severe among individuals with HIV coinfection. It is likely that several biological mechanisms, including the anorexia of infection, are contributing to wasting.

Objective: The purpose of this study was to determine whether leptin concentrations, in relation to the inflammatory cytokine response and level of HIV infection, are contributing to loss of appetite and wasting in adults with pulmonary tuberculosis and HIV infection.

Design: We characterized plasma leptin concentrations in relationship with self-reported loss of appetite, body mass index, fat mass (FM), IL-6, and HIV load in a cross-sectional study of 500 adults who presented with pulmonary tuberculosis in Zomba, Malawi.

Results: Plasma leptin concentrations, associated with FM, signifi-

cantly decreased by increasing tertile of plasma HIV load ($P = 0.0001$). Leptin concentrations were inversely associated with plasma IL-6 concentrations after adjusting for sex, age, FM, and HIV load. Plasma leptin concentrations were associated with neither loss of appetite nor wasting. Inflammation, reflected by increased IL-6 concentrations, was associated with loss of appetite (odds ratio, 3.41; 95% confidence interval, 1.91–6.09), when adjusted for sex, age, FM, leptin concentrations, and HIV load. A high plasma HIV load was associated with severe wasting, defined as body mass index less than 16.0 kg/m² (odds ratio, 2.14; 95% confidence interval, 1.09–4.19) when adjusted for sex, age, IL-6, FM, and leptin concentrations.

Conclusion: This study suggests that the anorexia and wasting seem primarily determined by the level of inflammation and the level of HIV infection in patients with tuberculosis and HIV coinfection. (*J Clin Endocrinol Metab* 90: 4771–4776, 2005)

TUBERCULOSIS HAS REEMERGED with the AIDS pandemic to become the world's leading cause of death from a single infectious agent, accounting for a quarter of the avoidable adult deaths in the developing world (1, 2). Wasting is a prominent feature of tuberculosis and is probably one of the determinants of disease severity and outcome. Coinfection with HIV and tuberculosis may worsen the wasting seen in tuberculosis or HIV infection alone (3). It is likely that several biological mechanisms, including the anorexia of infection, are contributing to wasting. Inflammatory cytokines are principal candidates as mediator of the metabolic changes resulting in tuberculosis-associated wasting. Inflammatory cytokines trigger the host's acute phase response and possibly also the anorexia during infections (4). Several microbial products as well as leptin and cytokines reduce food intake after parental administration, suggesting a role of these substances in the anorexia of infection (4, 5).

The fat-derived hormone leptin is best known as a key mediator of energy metabolism (6). High leptin concentra-

tions signal the presence of sufficient energy stores to the hypothalamus, which respond by reducing appetite and increasing energy expenditure. Leptin concentrations are proportional to fat mass (FM) and are reduced in starvation (7). In addition to playing a role in energy regulation, leptin also regulates endocrine and immune functions and belongs to the same class of cytokines as IL-6 (8). Animal studies have suggested that leptin mediates anorexia in chronic inflammatory states (9). On these bases, leptin may be involved in the cross-regulation between nutritional status and the immune response in tuberculosis.

Leptin concentrations may be low as a result of low body fat in tuberculosis or high as a result of the host inflammatory response. High leptin concentrations in tuberculosis patients could suppress appetite and food intake, which could be one of the contributing factors of weight loss and wasting. Low leptin concentrations may suppress immunity and worsen disease outcome. Two studies from Turkey suggested high leptin concentration in adults with tuberculosis (10, 11), whereas one study from Indonesia found low leptin concentrations in adults with tuberculosis (12).

The roles of leptin and the inflammatory cytokine response in the anorexia and wasting of patients with tuberculosis and HIV infection have not been characterized. The purpose of this study was to characterize plasma leptin concentrations

First Published Online May 31, 2005

Abbreviations: BIA, Bioelectrical impedance analysis; BMI, body mass index; CI, confidence interval; FM, fat mass; OR, odds ratio.

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in HIV-infected and uninfected adults with pulmonary tuberculosis in relation to nutritional status, level of inflammation, and level of HIV infection. Moreover, we aimed to determine whether leptin concentrations, in relation to inflammation and level of HIV infection, are contributing to loss of appetite and wasting.

To address these objectives, we characterized plasma leptin concentrations in relationship with self-reported loss of appetite, body mass index (BMI), FM derived from bioelectrical impedance analysis (BIA), plasma IL-6, and plasma HIV load in a cross-sectional study of 500 adults who presented with pulmonary tuberculosis in Zomba, Malawi.

Subjects and Methods

The study population consisted of 500 adults who presented with new sputum-positive pulmonary tuberculosis in Zomba Central Hospital between July 1999 and September 2001. This cross-sectional sample was drawn from a micronutrient supplementation study. Subjects were offered HIV testing and screened for HIV antibodies after written informed consent. All subjects were given appropriate pre- and posttest HIV counseling. Subjects received standard short course chemotherapy for tuberculosis as per guidelines of the Malawi National Tuberculosis Program (13). Adults with a previous history of treated pulmonary tuberculosis were excluded. Three sputum samples from each subject were examined with Auramine-O dark fluorescent staining method. Sputum-positive pulmonary tuberculosis was considered proven when at least one of three sputum stains showed acid-fast bacilli. HIV infection was diagnosed on the basis of a positive rapid test (Determine 1/2 Rapid test; Abbott Laboratories, Johannesburg, South Africa) and confirmed by a positive ELISA for HIV-1 antibodies (Wellcozyme; Wellcome Diagnostics, Dartford, Kent, UK).

Body weight was determined to the nearest 0.1 kg using an adult balance (Seca 700 balance, Seca Corp., Hanover, MD), and standing height was determined to the nearest centimeter. Wasting was defined as BMI (weight/height²) less than 18.5 kg/m² and severe wasting as BMI less than 16.0 kg/m², in accord with World Health Organization strata for BMI grading for severity of malnutrition (14).

Single-frequency BIA was performed at 50 kHz and 800 μ A (RJA Systems, Inc., Detroit, MI) with standard tetrapolar lead placement. BIA measurements were performed in triplicate for each subject. The reproducibility of repeated BIA measurements was greater than 99%. To calculate FM and body cell mass, equations that were validated in a sample of adults with and without HIV infection were used (15, 16). A standard questionnaire, with closed questions, was used to determine loss of weight and loss of appetite. Loss of appetite was considered positive when the subject gave loss of appetite as a reason for the observed loss of weight in the last month.

Blood samples were obtained by venipuncture (Sarstedt Monovette,

Newton, NC) at initial diagnosis of tuberculosis. Subjects were not asked about prior food intake. Aliquots of plasma were made in trace element-free cryovials, and samples were stored in liquid nitrogen. Plasma samples were kept in liquid nitrogen or at -70°C until the time of laboratory analyses. Plasma HIV load was measured using quantitative HIV-1 RNA PCR (Amplicor monitor, version 1.5; Roche, Branchburg, NJ) with a sensitivity limit of 400 HIV RNA copies per milliliter.

Plasma leptin concentrations were measured by ELISA using human leptin quantikine colorimetric sandwich ELISA kit (R&D Systems, Inc., Minneapolis, MN). Plasma IL-6 concentrations were measured by ELISA (human IL-6; R&D Systems). Quality control was assessed by repeated analysis of pooled human plasma controls run at the beginning and end of each analysis. Standard curves were run periodically using standard reference material 986C (National Institute of Standards and Technology, Gaithersburg, MD). Throughout all analyses, the plasma samples were run in a masked fashion. Due to the unavailability of some sample aliquots, plasma IL-6 and HIV load could not be measured in 1 and 16 samples, respectively.

Comparisons of categorical data were made using χ^2 tests. Comparisons between continuous variables were made using t tests. Appropriate variable transformations were made to reduce the skewness of the data, such as \log_{10} transformation for leptin, IL-6, and HIV load. Univariate ANOVA was used to test for linear trends of plasma leptin concentrations across categories of plasma HIV load. Linear regression models were used to explore the relationships between plasma leptin concentrations and FM, IL-6, and HIV load. Univariate and multivariate logistic regression models were used to evaluate determinants of self-reported loss of appetite and associations with severe wasting.

A significance level of $P < 0.05$ was used in this study. Statistical analyses were conducted using software packages SAS 8.01 (SAS Institute, Cary, NC) and SPSS 9.0 (SPSS, Inc., Chicago, IL). The protocol was approved by the institutional review boards of the Johns Hopkins School of Medicine (Baltimore, MD) and the College of Medicine, University of Malawi (Blantyre, Malawi), with final approval by the Office for Protection from Research Risk of the National Institutes of Health (Bethesda, MD).

Results

The study population consisted of 370 HIV-positive and 130 HIV-negative adults with sputum-positive pulmonary tuberculosis. Of all participants, 69% (156 of 227) of men and 78% (214 of 273) of women were HIV positive. Table 1 shows characteristics of study participants by sex and HIV status, such as age, body composition, IL-6, HIV load, and plasma leptin concentrations.

When comparing men and women (data not shown), men were older and had lower FM ($P = 0.0001$), \log_{10} leptin concentrations ($P = 0.0001$) and higher body cell mass ($P =$

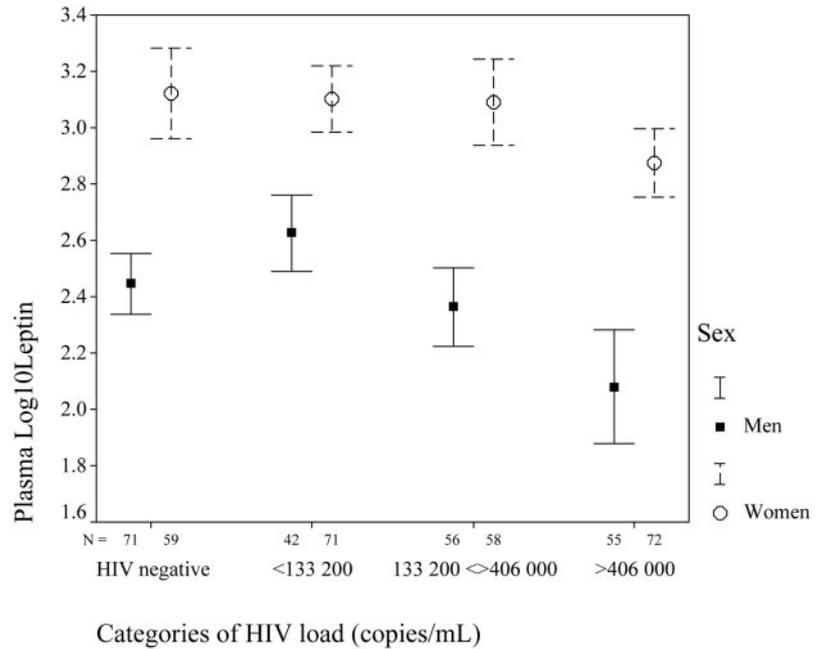
TABLE 1. Characteristics of adults with and without HIV infection presenting with pulmonary tuberculosis in Zomba, Malawi

Characteristic ^a	Male			Female		
	HIV negative (n = 71)	HIV positive (n = 156)	P	HIV negative (n = 59)	HIV positive (n = 214)	P ^b
Age (yr)	33.1 \pm 11.6	36.0 \pm 7.9	0.03	30.5 \pm 11.2	32.2 \pm 8.6	0.18
Loss of appetite (% reported)	22.5	39.7	0.01	28.8	41.1	0.24
Loss of weight (% reported)	74.6	81.4	0.30	81.4	86.9	0.24
BMI (kg/m ²)	18.7 \pm 3.1	18.5 \pm 2.6	0.58	18.6 \pm 2.7	18.3 \pm 2.8	0.40
Wasting, BMI <18.5 (%)	54.9	54.5	0.95	54.2	58.4	0.57
Severe wasting, BMI <16.0 (%)	14.7	12.7	0.84	21.0	10.2	0.06
Body cell mass (% of weight)	41.0 \pm 3.8	39.4 \pm 3.1	0.001	33.6 \pm 3.2	33.2 \pm 3.2	0.39
FM (% of weight)	7.2 \pm 4.8	7.4 \pm 5.2	0.81	19.9 \pm 8.8	19.0 \pm 8.7	0.49
Log ₁₀ IL-6 (pg/ml)	1.28 \pm 0.6	1.32 \pm 0.5	0.54	1.36 \pm 0.5	1.33 \pm 0.5	0.67
Log ₁₀ HIV load		5.32 \pm 0.5			5.22 \pm 0.6	
Log ₁₀ leptin (pg/ml)	2.45 \pm 0.5	2.33 \pm 0.6	0.17	3.12 \pm 0.6	3.02 \pm 0.5	0.20
Leptin, actual range (pg/ml)	13.25–3,678.2	2.30–9,240.6		1.57–13,877.5	52.85–35,269.9	

^a Mean \pm SD for continuous variables.

^b P values assessed by t tests for continuous variables, χ^2 tests for categorical data.

FIG. 1. Log-transformed mean plasma leptin concentrations with 95% CI are depicted by sex and plasma HIV load. Among all participants with pulmonary tuberculosis, men had significantly lower \log_{10} leptin concentrations than women. There was no significant difference in mean \log_{10} leptin concentrations between HIV-negative individuals, compared with HIV-positive individuals in the lowest tertile of HIV load. However, mean \log_{10} leptin concentrations significantly decreased with the increase of plasma HIV load in both men and women ($P = 0.0001$ and $P = 0.01$, respectively). P values assessed by univariate ANOVA to test for linear trends of plasma leptin concentrations across categories of plasma HIV load.



0.0001) than women. There was no difference in BMI or the proportion of individuals with wasting between men and women. There was no difference in mean \log_{10} IL-6 concentrations between men and women and no difference in mean \log_{10} HIV load between male and female HIV-positive adults.

Figure 1 shows plasma leptin concentrations with 95% confidence interval (CI) by sex and categories of plasma HIV load. This figure illustrates that plasma leptin concentrations were not different between HIV-negative subjects and HIV-positive subjects in the lowest tertile of HIV load. However, plasma leptin concentrations significantly decreased by increasing tertile of plasma HIV load.

The linear relationships between plasma leptin concentrations and FM, IL-6, and HIV load are shown in Table 2. To determine an independent association of FM, inflammation, and HIV infection with leptin concentrations, we examined the relationships in multivariate linear models that adjusted sex, age, and all variables in the model. In univariate linear regression analysis, FM ($P = 0.0001$) was positively correlated with \log_{10} leptin concentrations, whereas \log_{10} IL-6 ($P = 0.0001$) and \log_{10} HIV load ($P = 0.0001$) were inversely correlated with \log_{10} leptin concentrations. In multivariate linear regression that adjusted for sex, age, and all other variables in the model, \log_{10} leptin concentrations remained independently associated with FM ($P = 0.0001$) and inversely with \log_{10} IL-6 concentrations ($P = 0.02$). The adjusted regression coefficient J for a linear association with \log_{10} leptin

concentrations was 4.18 (95% CI, 3.57–4.80) for FM and -0.10 (95% CI, -0.18 to -0.01). for \log_{10} IL-6 concentrations. The association between \log_{10} HIV load and \log_{10} leptin concentrations did not reach significance in multivariate analysis ($P = 0.06$).

Figure 2 shows that plasma leptin concentration increases proportionally with percentage of body fat. In univariate analysis, the fitted regression lines for men and women were \log_{10} leptin = $1.86 + 0.07 * FM$ and \log_{10} leptin = $2.26 + 0.04 * FM$, respectively, with a difference in the slope of the regression lines between \log_{10} plasma leptin and FM among men and women ($P = 0.001$).

Determinants of appetite and wasting

The relationships between self-reported loss of appetite and plasma leptin concentrations, IL-6, and HIV load are shown in Table 3. To determine which factors contribute to loss of appetite, we examined the relationships in multivariate logistic regression models that adjusted for sex, age, FM, and all other variables in the model. This table shows that plasma leptin concentrations were not associated with loss of appetite. In a univariate logistic regression analysis, \log_{10} IL-6 ($P = 0.0001$) and \log_{10} HIV load ($P = 0.03$) were associated with loss of appetite. In multivariate logistic regression analysis, only higher \log_{10} IL-6 ($P = 0.0001$) remained associated with loss of appetite. The adjusted odds ratio (OR)

TABLE 2. Factors associated with plasma leptin concentrations in adults with pulmonary tuberculosis

Variable	Regression coefficient, β univariate ^a	95% CI	P	Regression coefficient, β multivariate ^a	95% CI	P
FM (% of weight)	5.00	4.57 to 5.43	0.0001	4.18	3.57 to 4.80	0.0001
\log_{10} IL-6 (pg/ml)	-0.34	-0.45 to -0.23	0.0001	-0.10	-0.18 to -0.01	0.02
\log_{10} HIV load	-0.28	-0.39 to 0.17	0.0001	-0.08	-0.17 to 0.01	0.06

^a Univariate and multivariate linear regression; adjusted for sex, age, and all other variables in the model.

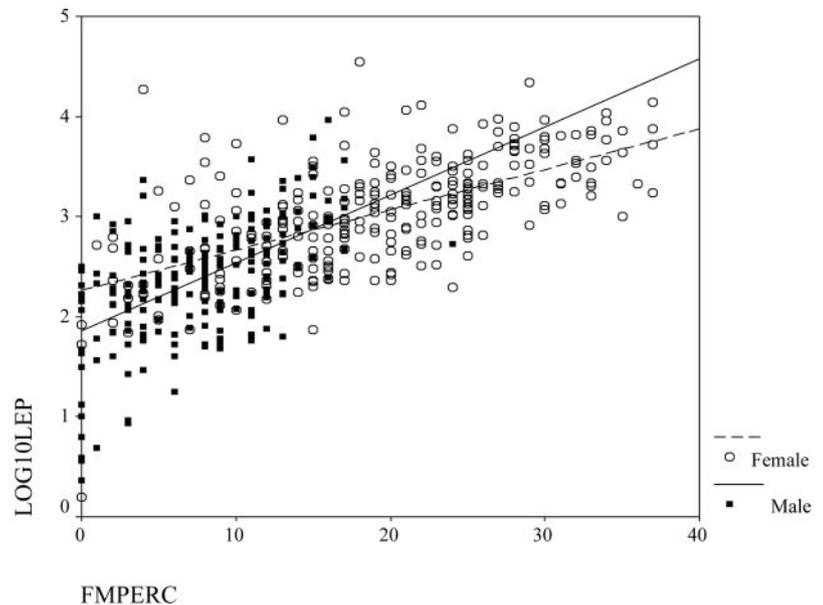


FIG. 2. Relationship between \log_{10} plasma leptin and percentage of body fat among men (squares, solid line) and women (circles, broken line) with pulmonary tuberculosis. The fitted regression lines were \log_{10} leptin = $1.86 + 0.07 *FM$ and \log_{10} leptin = $2.26 + 0.04 *FM$, respectively, with a difference in the slope of the regression lines between \log_{10} plasma leptin and FM among men and women ($P = 0.001$).

for an independent association of \log_{10} IL-6 with loss of appetite was 3.41 (95% CI, 1.91–6.09).

The relationships between severe wasting and plasma leptin concentrations, IL-6, and HIV load are shown in Table 4. To determine which factors contribute to severe wasting, we examined the relationships in multivariate logistic regression models with severe wasting, defined as BMI less than 16 kg/m², as the outcome variable. In univariate analyses, \log_{10} leptin ($P = 0.0001$), \log_{10} IL-6 ($P = 0.0001$), and \log_{10} HIV load ($P = 0.0006$) were associated with severe wasting. In multivariate analysis that adjusted for sex, age, the interaction between leptin and FM, and all other variables in the model, only higher HIV load ($P = 0.03$) remained associated with severe wasting. The adjusted OR for an independent association of \log_{10} HIV load with severe wasting was 2.14 (95% CI, 1.09–4.19).

Discussion

This study demonstrates that plasma leptin concentrations are associated with FM and the inflammatory cytokine (IL-6) response. Leptin reflected the percentage of FM and decreased with the increase of HIV load. Inflammation, characterized by IL-6 concentrations, was associated with loss of appetite, and level of HIV-replication, characterized by plasma HIV load, was associated with severe wasting. This study suggests that leptin does not seem to account for the anorexia and weight loss in tuberculosis. The anorexia and wasting in patients with tuberculosis and HIV coinfection seem primarily determined by the level of inflammation and the level of HIV infection.

The role of leptin in tuberculosis has been limited to adults without tuberculosis and HIV coinfection (10–12, 17). In 30 patients with tuberculosis in Turkey, higher leptin concentrations were described among those with active tuberculosis, compared with controls (10). Similar results were reported in another study from Turkey involving 25 patients with tuberculosis (11). However, these differences were significant only among women but not among men in the first study (10) and only among men but not among women in the second study (11) from Turkey.

One study from Indonesia found lower leptin concentrations in 60 HIV-negative patients with active tuberculosis, compared with 30 healthy controls (12). And in effect, leptin concentrations in the untreated tuberculosis patients from Indonesia were similarly low as those in our study. In the present study, plasma leptin concentrations were not different between HIV-negative subjects and HIV-positive subjects in the lowest tertile of HIV load. However, plasma leptin concentrations significantly decreased by increasing tertile of plasma HIV load. The lower leptin concentrations in tuberculosis patients with high plasma HIV load may simply be attributed to further deprived nutritional status because body fat is the most important determinant of plasma leptin concentrations. This is consistent with the observation that the nutritional status in patients with pulmonary tuberculosis in Malawi significantly decreases by increasing HIV load (18).

We demonstrated that leptin concentrations reflected the percentage of FM, but although leptin concentrations were higher among female than among male patients, the regres-

TABLE 3. Factors associated with self-reported loss of appetite in adults with pulmonary tuberculosis

Risk factor	Univariate OR (95% CI)	P	Multivariate OR (95% CI) ^a	P
\log_{10} leptin (pg/ml)	0.82 (0.62–1.09)	0.17	1.06 (0.65–1.72)	0.81
\log_{10} IL-6	2.60 ± 1.73 –3.91)	0.0001	3.41 (1.91–6.09)	0.0001
\log_{10} HIV load	1.52 (1.04–2.23)	0.03	1.38 (0.90–2.12)	0.14

^a Univariate and multivariate logistic analysis; adjusted for sex, age, FM, and all other variables in the model.

TABLE 4. Factors associated with severe wasting (BMI <16.0 kg/m²) in adults with pulmonary tuberculosis

Risk factor	Univariate OR (95% CI)	P	Multivariate OR (95% CI) ^a	P
Log ₁₀ leptin (pg/ml)	0.40 (0.28–0.59)	0.0001	1.00 (0.47–2.15)	0.99
Log ₁₀ IL-6	3.71 (2.09–6.59)	0.0001	2.03 (0.93–4.42)	0.07
Log ₁₀ HIV load	3.03 (1.61–5.72)	0.0006	2.14 (1.09–4.19)	0.03

^a Univariate and multivariate logistic analysis; adjusted for sex, age, the interaction between FM and leptin, and all other variables in the model.

sion lines for the two genders intersect, with a steeper slope for men than women. Similar data in human populations and experimental animals generally show regression lines that remain parallel across a wide range of body fat. This is to our knowledge the first study that demonstrates this unusual feature, which may be specific for chronic disease, but further research is needed to gain insight into this characteristic.

The study from Indonesia reported a negative association between C-reactive protein and leptin, whereas our study demonstrates a negative association between the inflammatory cytokine (IL-6) response and leptin concentrations in adults with pulmonary tuberculosis (with and without HIV infection). Experimental and animal studies have shown that inflammatory mediators are able to increase leptin production (4, 10, 19, 20). However, the acute inflammatory response is different from the more chronic inflammatory response in tuberculosis. The results from this study support the hypothesis of van Crevel *et al.* (12) that the prolonged inflammatory response in tuberculosis may deplete or exhaust leptin production.

Theoretically, decreased leptin concentrations could impair protective cellular immunity to *Mycobacterium tuberculosis* (12) because leptin is necessary for an effective cell-mediated immune response (21). For instance, CD4 T lymphocyte activities are suboptimal in the absence of leptin (7, 21). The present study suggests that the inflammatory response may deplete leptin production, which theoretically suppresses immunity. Low leptin levels, as a result of poor nutritional status and chronic inflammatory response, may be a contributing factor in suppressing the immune function and worsening the outcome of tuberculosis. Further studies are needed to clarify whether this hypothesis is true.

Conversely, in theory, low plasma leptin concentrations should increase appetite and decrease energy expenditure. However, the present study shows that leptin was not associated with loss of appetite, after adjusting for other factors, and this finding reinforces the conclusion of Schwenk *et al.* (17) that leptin does not account for the weight loss and anorexia in tuberculosis.

We demonstrated that leptin concentrations were not, but IL-6 was, associated with loss of appetite. Experimental studies showed that parenteral administration of cytokines (including IL-6) reduce food intake, suggesting a role in the anorexia during infection (4, 5). Earlier studies also suggested a role of cytokines (including IL-6) in the development of wasting in the pre-era of highly active antiretroviral therapy (22, 23). Further research is needed into the role of cytokines in the physiological control of eating and energy balance during acute and chronic infection.

The present study suggests a correlation between plasma leptin concentrations and HIV load, for which two hypo-

thetical mechanisms can be drawn. First, HIV infection *per se* (through nonleptin- and non-IL-6-mediated mechanism) results in wasting and loss of body fat. Furthermore, decreased leptin concentrations as a result of loss of body fat occur mainly with higher concentrations of HIV load (perhaps suggesting that these changes happen only with more severe or longer duration of HIV infection, which may be of relevance regarding the pathophysiology lipodystrophy syndrome in HIV-infected patients on HAART). Second, increased IL-6 concentrations (either directly or through other mechanisms of chronic inflammation) results in blunting of appetite, which aggravates weight loss, fat loss, and subsequently a decrease in leptin production.

A limitation of this study is that blood samples were not uniformly collected in a fasted state, which would have increased the confidence of our conclusions.

This study suggests that leptin does not play a role in the anorexia and wasting in tuberculosis but that it may play a role as a mediator between nutritional status and host defense, which could explain thin people's susceptibility to tuberculosis or the link between malnutrition and disease outcome. In addition, IL-6 production was associated with loss of appetite. Current knowledge (4) on the different mechanisms involved in the anorexia of infection suggests some therapeutic options for treatment, including substances that antagonize cytokine action in combination with nutritional support.

Acknowledgments

We thank Dana Totin Moncrief, Barbara Dancheck, Amanda Ray, and Michelle Ricks for their contributions to laboratory and data analyses.

Received December 27, 2004. Accepted May 20, 2005.

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Reprints will not be available from the author.

This work was supported in part by the National Institutes of Health (Grant AI41956), the Fogarty International Center, the Wageningen Agricultural University, and the Radboud University Nijmegen Medical Centre.

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