Immunodeficiency and other clinical immunology

Elevated IgE level in relationship to nutritional status and immune parameters in early human immunodeficiency virus–1 disease

Gail Shor-Posner, PhD,[a, b] Maria Jose Miguez-Burbano, MD,[a] Ying Lu, PhD,[a] Daniel Feaster, MS,[b] MaryAnn Fletcher, PhD,[b] Howerde Sauberlich, PhD,[c] and Marianna K. Baum, PhD[a, b] *Miami, Fla., and Birmingham, Ala.*

Elevation of IgE has been associated with T-cell dysregulation and with the occurrence of opportunistic infections in patients with acquired immunodeficiency syndrome. The precise cause of IgE overproduction during the early stages of human immunodeficiency virus (HIV)–1 disease, however, has not been established. In light of reports demonstrating that IgE production may be affected by vitamin E levels in an animal model, we evaluated nutritional status in relationship to plasma IgE levels and immune parameters in 100 asymptomatic HIV-1–seropositive and 42 HIV-1–seronegative homosexual men. Approximately 18% of the HIV-1–seropositive population demonstrated biochemical evidence of plasma vitamin E deficiency (<5 μg/ml). Subsequent analysis of available samples indicated a dramatic elevation of IgE levels (308 ± 112 IU/ml) in vitamin E–deficient seropositive subjects (n = *9) as compared with age and CD4-matched HIV-1–seropositive persons with adequate vitamin E levels* (n = *16, 118.1 ± 41.1 IU/ml) and significantly lower levels (59.5 ± 15.7 IU/ml) in HIV-1–seronegative men* (n = *20,* p = *0.01). This effect, which was independent of CD4 cell count, did not appear to be influenced by atopic or gastrointestinal parasitic disease. The low plasma vitamin E levels were related at least in part to dietary intake* (r = *0.552,* p = *0.01), suggesting that supplementation may be warranted in HIV-1–infected persons in whom vitamin E deficiency develops. Analysis of covariance revealed a strong relationship between IgE levels and CD8 cell counts* (p < *0.006), and between IgE level and vitamin E deficiency* (p < *0.039). Although nutritional deficiency is unlikely to be the principal cause of immunoglobulin dysregulation in HIV infection, these results demonstrate that vitamin E deficiency may play a contributory role in IgE elevation during the early stages of disease. (J ALLERGY CLIN IMMUNOL 1995;95:886-92.)*

Key words: *IgE, human immunodeficiency virus–1 infection, vitamin E, nutritional status*

IgE antibodies appear to have an important role in the function of immunohomeostasis.[1, 2] Through interaction with IgE, cells of the immune system produce and release several potent mediator molecules that amplify the immune response. This unusual amplification capability, however, makes the system highly susceptible to perturbations, which may result in overproduction of IgE. Moreover, IgE elevation has been associated with frequent occurrence of hay fever, asthma, and eczema in patients with agammaglobulinemia[3-5] and with various disorders, including the hyper-IgE syndrome, myeloma IgE, congenital and acquired

From the [a]Departments of Epidemiology and Public Health and [b]The Center for the Biopsychosocial Study of AIDS, University of Miami School of Medicine, and the [c]Division of Experimental Nutrition, Department of Nutrition Sciences, University of Alabama at Birmingham.

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Reprint requests: Gail Shor-Posner, Department of Epidemiology and Public Health, University of Miami School of Medicine, P.O. Box 01609 (R-669), Miami, FL 33101.

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Abbreviations used
AIDS: Acquired immunodeficiency syndrome
HIV: Human immunodeficiency virus
PGE_2: Prostaglandin E_2

cellular immunodeficiencies, and some viral infections.[5-9]

Recent investigations[10] have demonstrated a dramatic increase in IgE levels in persons infected with human immunodeficiency virus (HIV)–1, particularly in patients with acquired immunodeficiency syndrome (AIDS) with low CD4 cell counts (<200 cells/mm^3). Although IgE elevation has been associated with T-cell dysregulation, opportunistic infections, and an increase in allergic manifestation in patients with AIDS,[11-16] the precise cause of increased IgE levels in HIV-1–infected persons during the early stages of HIV disease remains unknown. Because IgE production has been shown to be affected by vitamin E status in an animal model,[17] the present study evaluated total serum IgE levels in relationship to nutritional status and immune parameters in HIV-1–seropositive homosexual men during the early stages of HIV-1 infection. Our findings, previously presented in preliminary form,[18] indicate that IgE elevation is prevalent during the early stages of HIV disease, independent of CD4 cell count, and is particularly evident in persons with low plasma levels of vitamin E.

METHODS

Population and sample collection

Our recent HIV studies have evaluated the nutritional status of 100 HIV-1–seropositive (Centers for Disease Control stages II and III) and 42 HIV-1–seronegative homosexual men, 20 to 55 years old, who were free of other risk factors for transmission of HIV-1 infection.[19] Subjects were excluded if they were taking a medication or had a medical history significant for any condition known to influence nutritional status. No subjects were taking any systemic antiretroviral chemotherapeutic agents. The two groups of subjects were of similar age and ethnic background (white or Hispanic) and were of middle-class socioeconomic status with a similar mean education level (completion of twelfth grade). All studies were performed in accordance with the human subject policies of the University of Miami School of Medicine and the National Institutes of Health, Bethesda, Md.

As described previously, specific nutrient abnormalities are prevalent in asymptomatic HIV-1–infected[19] and seronegative homosexual men.[20] Biochemical evidence of vitamin E deficiency was observed in approximately 18% of the seropositive subjects; all the seronegative participants, however, had adequate plasma vitamin E levels.

The present study determined immunoglobulin levels in all the vitamin E–deficient HIV-1–seropositive subjects with available frozen serum (n = 9). Control subjects were randomly selected from age-matched HIV-1–seropositive men with adequate vitamin E levels and similar CD4 cell counts (n = 16) and HIV-1–seronegative participants (n = 20). All samples were blinded to investigators, and processed and analyzed identically.

Clinical procedures

All subjects were questioned as to medical history, including history of allergic diseases, and were given a general physical examination, whereby any signs or symptoms consistent with HIV-1 infection were documented.

Laboratory immunology

The IgE levels were assessed with the Microplate Total IgE, a two-site immunoradiometric technique, supplied by Kallestad (Chasica, Minn.). IgG, IgA, and IgM were measured in all participants with the QM300 system (Kallestad), which is an automated, random access–rate nephelometer with the capability of providing sensitive, accurate measurement of biologic fluids.

Lymphocyte surface markers (CD4 and CD8) were detected by flow cytometry, with two-color direct immunofluorescence with monoclonal antibodies conjugated to phycoerythrin to measure the CD4 population or to fluorescein isothiocyanate to measure the CD8 cell population. Both monoclonal antibodies were obtained from Coulter Immunology (Miami, Fla.).

The RAST was performed in all subjects with the Allercoat Microplate enzyme assay sorbent test modified assay procedure of Pasteur Inc. (Chasica, Minn.). All participants were tested with disks of ES1 (mixture of different environmental antigens including dog and cat epithelium, *Dermatophagoides farinae,* and house dust mite), GS1 (mixture of different grasses, including perennial ryegrass and sweet vernal, Timothy, Johnson, and Bermuda grasses), and MS1 *(Penicillin notatum, Cladosporium herbarium, Aspergillus fumigatus,* and *Alternaria tenius).*

Nutritional status

Measurements of serum albumin (by Sequential Multiple Analyses Computer–26) were analyzed by a commercial laboratory. Total plasma vitamin E level was determined by high-performance liquid chromatography.[21] The normal range used for vitamin E was 5 to 15 μg/ml, with levels less than 5 μg/ml considered biochemically deficient.

As described previously,[19] all subjects were questioned with respect to their dietary intake by a semi-

TABLE I. Immunoglobulin profile

	HIV-1 status	
	Seropositive	**Seronegative**
IgE (IU/ml)	187.6 ± 50.2*	59.5 ± 15.7
IgG (mg/dl)	1551.8 ± 147.7†	1095.0 ± 69.3
IgA (mg/dl)	184.5 ± 18.9	238.9 ± 26.8
IgM (mg/dl)	118.9 ± 10.1	112.8 ± 7.58

Immunoglobulin levels (mean ± SEM) are indicated for HIV-1–seropositive men ($n = 25$) and HIV-1–seronegative control subjects ($n = 20$).
*Significant differences in IgE levels between groups demonstrated at $p = 0.004$.
†Statistical tendency ($p = 0.06$).

quantitative food frequency questionnaire, an instrument standardized for nutritional epidemiologic studies.

Statistical methods

The relationship between IgE level and nutritional status (e.g., albumin, plasma vitamin E level) was evaluated with Spearman correlation procedures, as were the relationships between IgE and immune parameters, and dietary intake and plasma vitamin E levels, with a p value less than 0.05 considered statistically significant for all results.

The effect of vitamin E deficiency on IgE levels was examined by analysis of covariance with the natural log of IgE, and with HIV status and laboratory measures of disease progression (CD4 and CD8 cell counts), included as covariates. In post hoc analyses the effects of HIV status were further evaluated by fully interacting HIV status with all other model predictors; the effect of vitamin E deficiency in HIV-negative subjects could not be estimated because none of the HIV-negative subjects was vitamin E deficient. All analyses used type III sums of squares, where the effect of all other variables in the model are held constant.

The Wilcoxon rank test was used in the RAST analysis, and Spearman correlation procedures were used to determine the relationship between IgE level and allergic response. Significant differences between means were compared with Duncan's new multiple range test or with independent Student t test procedures, with results expressed as means and SEM measurements.

RESULTS

Clinical evaluation

No clinical evidence of AIDS or AIDS-related conditions (i.e., signs or symptoms that would have placed the subjects in any Centers for Disease Control stage IV category) was observed in the HIV-1–infected participants. No significant influence of ethnic background, socioeconomic status, or educational level on measures of nutritional status was established.

Immunoglobulin profile

Table I indicates mean and SEM measurements of the IgE, IgA, IgG, and IgM levels for the HIV-1–seropositive and –seronegative men. IgE levels were significantly higher in the HIV-1–infected men (187.6 ± 50.3 IU/ml) compared with those of the seronegative control subjects (59.4 ± 15.7 IU/ml, $p = 0.03$). Levels of IgA and IgM were similar in both groups, although IgG levels tended to be higher in the infected men ($p = 0.06$). No significant relationships among the immunoglobulins were detected.

Immune status

The HIV-1–infected men had significantly lower mean CD4 (611.0 ± 63.9 cells/mm^3) and higher CD8 (918.3 ± 120.7 cells/mm^3) cell counts relative to the control group, whose mean CD4 cell count was 834.3 ± 56.6 cells/mm^3 ($p = 0.02$) and CD8 cell count was 568.9 ± 37.6 cells/mm^3 ($p = 0.035$). No significant relationships were demonstrated between IgE and CD4 cell count in either the HIV-1–seropositive ($r = 0.149$) or the seronegative men ($r = 0.29$). A negative relationship between IgE and CD8 cell count was observed in both the infected men ($r = -0.39$) and the control subjects ($r = -0.09$) but did not reach statistical significance.

Atopic disease

A RAST to grasses, environmental allergens, and molds was performed for all patients. Overall, very little response was demonstrated in the two groups. Only six of the HIV-1–infected men and four of the HIV-1–seronegative subjects had a detectable response. No response greater than grade II (absent to low response) was observed in either group. No significant differences in IgE level were revealed between persons who had a response between 0 and 1 and participants who had a response higher than 1 ($p = 0.130$).

Nutritional status

Physical examination did not reveal any clinical evidence of nutritional deficiencies or excesses. Serum albumin values were within the range considered to be normal for all the HIV-1–seropositive (mean, 4.2 ± 0.06 gm/dl) and HIV-1–seronegative subjects (4.3 ± 0.05 gm/dl) (Table II).

Vitamin E level and immune status

The vitamin E–deficient subjects and matched vitamin E–adequate HIV-1–seropositive subjects had similar CD4 cell counts: 604.9 ± 99.4 cells/m^3 in the deficient group and 614.7 ± 85.7 cells/m^3 in

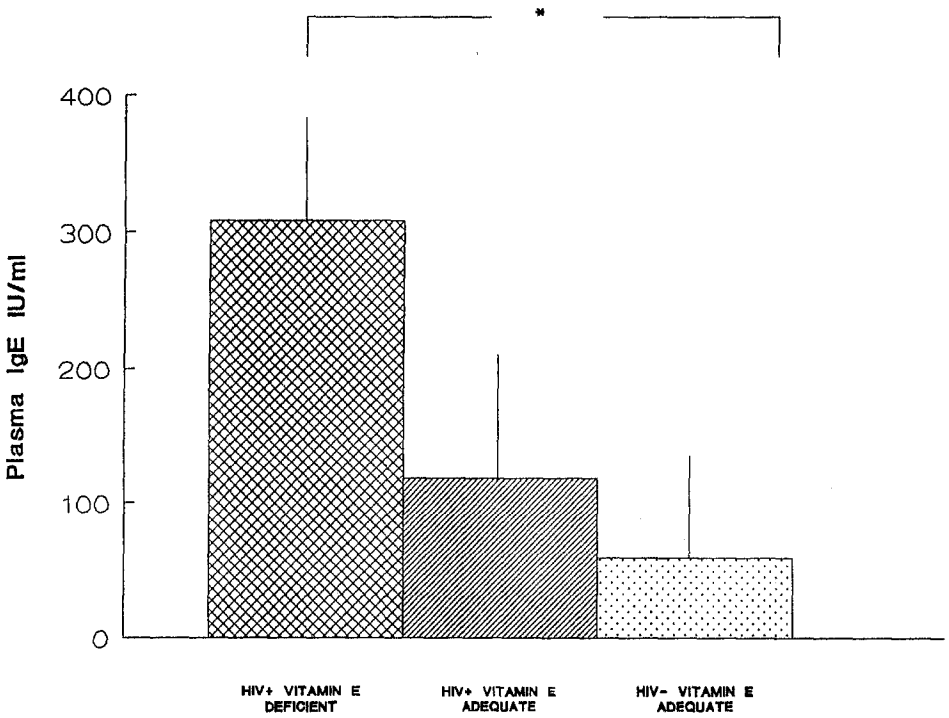

FIG. 1. IgE levels are significantly elevated in HIV-1–seropositive men with biochemical deficiency of vitamin E (n = 9) relative to nondeficient seronegative control subjects (n = 20). *Asterisk*, p = 0.01.

TABLE II. Nutritional status

	HIV-seropositive men		Nondeficient HIV-seronegative men
	Vitamin E–deficient	Nondeficient	
Albumin (gm/dl)	4.1 ± 0.09	4.2 ± 0.08	4.3 ± 0.05
Plasma vitamin E (μg/ml)	4.1 ± 0.2	11.9 ± 1.5	10.7 ± 1.1
Dietary vitamin E intake (mg/day)	63.6 ± 46.7*	442.9 ± 105.3*	92.9 ± 48.3

*HIV-1–infected men with deficient plasma vitamin E status (n = 9) consumed significantly less vitamin E per day relative to vitamin E–adequate HIV-seropositive men (n = 16, $p < 0.02$).

the vitamin E–adequate group. In addition, CD8 cell counts were not significantly different in the vitamin E–deficient (681.6 ± 45.0 cells/mm^3) and vitamin E–adequate HIV-1–seropositive men (910.0 ± 124.1 cells/mm^3).

Vitamin E level and IgE status

As illustrated in Fig. 1, the HIV-1–seropositive subjects with biochemical deficiency of vitamin E exhibited elevated IgE levels (307.8 ± 112.0 IU/ml) as compared with the seronegative control subjects (59.4 ± 15.7 IU/ml, p = 0.01). The IgE levels of the HIV-1–seropositive vitamin E–adequate participants (118.1 ± 41.1 IU/ml) tended to be lower as compared with the HIV-1–seropositive men with vitamin E deficiency (p = 0.10) and were not significantly different from those of the control subjects.

The results of the analysis of covariance revealed a significant relationship between vitamin E deficiency and IgE level ($p < 0.038$) (Table III). A prominent and significant association was also found between CD8 cell count and IgE level ($p <$ 0.006). No relationship between CD4 cell count

TABLE III. Analysis of covariance: Predicting natural log (IgE) levels

Independent variables	Total (n = 46)*		HIV$^+$ subjects (n = 26)†		HIV$^-$ subjects (n = 20)	
	F	p	F	p	F	p
Vitamin E deficiency	4.62	0.038	4.84	0.034	—	—
HIV status	3.04	0.089	—	—	—	—
CD4 cell count	2.12	0.153	0.18	0.679	3.50	0.069
CD8 cell count	8.54	0.006	6.86	0.013	0.81	0.374
Full model	4.24	0.006	3.06			0.015

*R^2 = 0.29.
†R^2 = 0.32.

and IgE level, however, was observed. As indicated in Table III, the overall model was significant at the 0.006 level. In post hoc analyses the effect of vitamin E deficiency and CD8 cell counts on IgE level was confirmed in HIV-1–infected subjects.

Vitamin E level and dietary intake

As shown in Table II, the mean plasma level of vitamin E was 8.85 ± 1.2 μg/ml in the HIV-1–seropositive and 10.66 ± 1.1 μg/ml in the HIV-1–seronegative subjects. Dietary intake of vitamin E was significantly correlated with plasma vitamin E level in the HIV-1–seropositive men (r = 0.552, p = 0.01) and tended to be positively associated with plasma vitamin E levels in the seronegative men (r = 0.466, p = 0.10). Levels of dietary vitamin E intake were considerably greater than the recommended dietary allowance of 10 mg/day. The HIV-1–seropositive men consumed significantly more vitamin E (306.3 ± 78.1 mg/day) relative to the HIV-1–seronegative men, whose intake was 92.9 ± 48.3 mg/day (p = 0.05). Dietary intake of vitamin E in the HIV-1–seropositive vitamin E–deficient subjects, however, was significantly lower (63.6 ± 46.7 mg/day) than the level recorded for the vitamin E–adequate HIV-1–infected subjects (442.9 ± 109.3 mg/day, p = 0.02).

DISCUSSION

The present study, consistent with other investigations,[10, 11] demonstrates elevated IgE levels in HIV-1–infected persons and extends these reports to indicate that nutritional status may be an important factor in the IgE elevation observed during the early stages of HIV-1 disease. Plasma IgE levels were strikingly elevated in HIV-1–infected subjects with deficient plasma vitamin E status and somewhat more elevated in seropositive men with adequate vitamin E levels than in seronegative control subjects. This effect did not appear to be influenced by CD4 cell counts, atopic disease, or opportunistic infections. In accord with previous evidence demonstrating suppressor T-cell regulation of ongoing IgE antibody formation,[22] our findings revealed a significant influence of CD8 cell count on IgE level. As in other studies, IgE elevation was not significantly correlated with IgA, IgG, or IgM, supporting the suggestion that regulation of IgE synthesis is independent of that of the other immunoglobulin isotopes.[10, 11]

The low plasma vitamin E levels observed in asymptomatic HIV-1–infected persons appear to be related at least in part to nutritional intake, because dietary intake was correlated with plasma vitamin E levels, suggesting that normalization may be achieved through dietary supplementation. High levels of vitamin E consumption appear to be necessary to achieve adequate plasma vitamin E status in HIV-1 disease,[23] indicating that additional factors may be involved, possibly including oxidative stress, malabsorption, increased catabolism, or altered nutrient excretion.[24-26]

The prevalence of vitamin E deficiency in early HIV-1 infection is of particular concern because vitamin E has been shown to stimulate several aspects of host resistance, involving delayed cutaneous hypersensitivity reaction, helper T lymphocytes, antibody response, and the reticuloendothelial system.[27] Moreover, vitamin E provides stability for membranes containing polyunsaturated fatty acids and is a powerful antioxidant and inhibitor of lipid peroxidation.[28]

Vitamin E status may influence IgE levels through the synthesis of prostaglandin E_2 (PGE_2) and interleukins. Substantial evidence indicates that secretion of these substances, which are involved in IgE production, is significantly affected by dietary vitamin E supplementation.[29-32] Furthermore, an apparent vitamin E–induced decrease in the immunosuppressor PGE_2 and/or other lipid

peroxidation products has been associated with improved immune responsiveness in healthy elderly persons.[33, 34] In other studies vitamin E supplementation has been associated with greater effectiveness of zidovudine therapy[35] and an improvement in clinical status in patients with recurrent infections.[36] Because enhanced production of PGE_2 has been detected in HIV-infected monocyte cultures,[37-39] vitamin E normalization may be of particular importance in HIV-1 disease. Critical studies are clearly needed to determine whether restoration of adequate vitamin E levels can be associated with improved immune function and slower HIV-1 disease progression.

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