Vitamin E Supplementation and In Vivo Immune Response in Healthy Elderly Subjects

A Randomized Controlled Trial

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Objective.—To determine whether long-term supplementation with vitamin E enhances in vivo, clinically relevant measures of cell-mediated immunity in healthy elderly subjects.

Design.—Randomized, double-blind, placebo-controlled intervention study.

Setting and Participants.—A total of 88 free-living, healthy subjects at least 65 years of age.

Intervention.—Subjects were randomly assigned to a placebo group or to groups consuming 60, 200, or 800 mg/d of vitamin E for 235 days.

Main Outcome Measures.—Delayed-type hypersensitivity skin response (DTH); antibody response to hepatitis B, tetanus and diphtheria, and pneumococcal vaccines; and autoantibodies to DNA and thyroglobulin were assessed before and after supplementation.

Results.—Supplementation with vitamin E for 4 months improved certain clinically relevant indexes of cell-mediated immunity in healthy elderly. Subjects consuming 200 mg/d of vitamin E had a 65% increase in DTH and a 6-fold increase in antibody titer to hepatitis B compared with placebo (17% and 3-fold, respectively), 60-mg/d (41% and 3-fold, respectively), and 800-mg/d (49% and 2.5-fold, respectively) groups. The 200-mg/d group also had a significant increase in antibody titer to tetanus vaccine. Subjects in the upper tertile of serum α-tocopherol (vitamin E) concentration (>48.4 μmol/L [2.08 mg/dL]) after supplementation had higher antibody response to hepatitis B and DTH. Vitamin E supplementation had no effect on antibody titer to diphtheria and did not affect immunoglobulin levels or levels of T and B cells. No significant effect of vitamin E supplementation on autoantibody levels was observed.

Conclusions.—Our results indicate that a level of vitamin E greater than currently recommended enhances certain clinically relevant in vivo indexes of T-cell-mediated function in healthy elderly persons. No adverse effects were observed with vitamin E supplementation.

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CONSIDERABLE evidence indicates that aging is associated with altered regulation of the immune system, which contributes to the increased incidence of infectious and neoplastic diseases as well as to the prolonged periods of recovery after illness and greater morbidity observed in elderly subjects.1-6 Age-related functional changes have been well defined for both humoral and cell-mediated immune responses. Altered T-cell-mediated immunity is reflected in the inability of many elderly to mount a delayed-type hypersensitivity skin response (DTH).3,4 The decrease in DTH has been shown to be associated with greater mortality.3,6 Wayne et al reported significantly greater mortality rates in healthy older subjects with anergy compared with those with positive DTH response during a 7-year prospective study. Christou et al showed that in 245 preoperative patients (mean age [SD], 64 [12.8] years) DTH was the best predictor of sepsis-related death. In that study, the subjects were divided into 3 groups: anergic, relatively anergic, and reactive. Eighty-seven percent of anergic patients who developed major sepsis died from it compared with 66% in the relatively anergic and 16.7% in the reactive groups. Thus, both relative and total anergy are associated with increased morbidity and mortality outcomes in the elderly. Cohn et al administered DTH tests to elderly residents of a nursing home and documented their
survival over the next 18 months. They showed that survivors had a significantly higher diameter of induration compared with those who died during the observation period. These 2 studies indicate that in addition to anergy, lower DTH response is associated with increased morbidity and mortality in the elderly.

Another important aspect of the age-associated changes in immune function is a decreased antibody response. The decrease in specific antibody production has been observed for both primary and secondary antibody responses. While there is consistent evidence that primary antibody response decreases with age, some studies have reported no change in secondary antibody response with age. In addition, decline in both primary and secondary antibody titer is more rapid in elderly subjects compared with young subjects. Furthermore, this decrease was observed in responses that are both T-cell dependent, such as the response to hepatitis B and influenza vaccines and tetanus toxoid, and T-cell independent, such as response to pneumococcal vaccine. While the antibody response to foreign antigens decreases with age, the level of antibodies against self antigens has been shown to increase with age. Prostaglandin E2 (PGE2) production increases with age and contributes to the age-associated dysregulation of the immune response. Increased production of prostaglandins is associated with age-related inflammatory, neoplastic, and autoimmune diseases. We have previously shown that vitamin E supplementation above the currently recommended level significantly decreases PGE2 production while significantly enhancing DTH, mitogenic response, and interleukin 2 (IL-2) production in old mice.

However, few interventions have been successful in enhancing the immune response of older subjects. The present study was conducted to determine the effect of different levels of vitamin E supplementation on in vivo, clinically relevant measures of immunity. Since it has been suggested that stimulation of immune function in the aged might also result in the undesirable effect of increased autoantibody formation, decreased neutrophil killing, or both, we also tested the effect of vitamin E supplementation on serum autoantibody levels against DNA and thyroglobulin as well as on the ability of neutrophils to kill Candida albicans.

METHODS

Subjects were recruited via advertisement and through telephone interviews with an existing group of available subjects (Figure 1). Initially acceptable volunteers—i.e., those with no acute or serious chronic diseases, not receiving prescription medication or nonsteroidal anti-inflammatory drugs on a regular basis, not taking vitamin or mineral supplements for the last 3 months, with serum vitamin E levels less than 27.9 μmol/L (1.2 mg/dL) (10% of subjects screened; normal average for men and women without supplement use is 24 and 27 μmol/L [1.03 and 1.15 mg/dL], respectively), and who had not been vaccinated for hepatitis B and pneumococcal vaccine—were invited to the Jean Mayer USDA Human Nutrition Research Center on Aging (HNRCA) at Tufts University for a day of screening procedures. All subjects had to have a normal physical examination that included a chest radiograph (if one had not been done within the previous year) and a 12-lead electrocardiogram, clinical chemistry profile, complete blood cell and differential counts, and routine urinalysis before being admitted to the study. The study was approved by the Tufts University/New England Medical Center Human Investigation Review Committee. Before screening, each volunteer signed an informed consent document. The experimental design and schedule for DTH, vaccination, and blood collection from subjects are shown in Figure 2.

A randomized, double-blind, placebo-controlled protocol was implemented using free-living subjects of both sexes. Eighty-nine healthy older adults (≥65 years) were enrolled after screening. Subjects were randomly assigned to placebo or to 60, 200, or 800 mg/d of vitamin E using a set of randomized numbers generated by the program Design (SPSS Inc, Chicago, IL). The lowest dose was chosen to represent twice the US recommended daily allowance for vitamin E; the highest dose was chosen based on our previous short-term study; and the middle dose was chosen as an intermediate dosage found in many over-the-counter vitamin E supplements. The treatments were coded, and the order of assignment for each code was prepared by the study statistician. The key to the
codes was kept in a sealed envelope with the recruiter who was not involved in the execution of the protocol. All samples were analyzed without knowledge of the codes. Each group received 2 capsules per day to be ingested with dinner. Vitamin E capsules contained either 30, 100, or 400 mg of dl-a-tocopherol in soybean oil (Hoffmann-LaRoche Inc, Nutley, NJ); the placebo capsules contained soybean oil only but were identical in taste and appearance to the vitamin E capsules. Capsules were provided in calendar-oriented, blister-pack pill dispensers (Modulus III Inc, Redding, Conn). The subjects consumed the capsules daily for 235 days and were asked to continue their typical food intake, dietary habits, and lifestyles. To assure that no substantial change in dietary habits or intake of nutrients with known effects on the immune response had occurred during the study, each subject completed 3-day dietary records, and serum and urinary levels of other nutrients were measured before and after supplementation. Subjects were required to abstain from taking any other vitamin or mineral supplements during the period of study and were to take no other medication without first consulting the investigators. Supplement compliance was monitored by measurement of serum vitamin E level (before, after 30 days, and after 128 days of supplementation) and pill count in the returned packages.

Outcome Measures

Delayed-type hypersensitivity skin response was assessed with Multi-Test CMI (Merieux Institute Inc, Miami, Fla), a single-use, disposable applicator of acrylic resin with 8 heads loaded with a glycerine control and the following 7 recall antigens: tetanus toxoid, diphtheria toxoid, streptococcus (group C), Mycobacterium tuberculosis, C albicans, Trichophyton mentagrophytes, and Proteus mirabilis as previously described. The DTH test was administered on the volar surface of the arms. Subsequent DTH tests were administered on the same site or on the alternate arm.

Standard doses of pneumococcal vaccine, polyvalent vaccine (PNU-Immune 23, Lederle Laboratories, Pearl River, NY), hepatitis B vaccine (Recombivax HB, gift from Merck, Westport, Pa), and tetanus and diphtheria vaccine (provided by the Massachusetts Public Health Biologic Laboratories, Boston) were administered on day 156 of the study. Two additional hepatitis B booster doses were administered on days 186 and 216 of the study. Blood was collected before vaccination, 1 month after vaccination (day 186), and 1 month after the second and third hepatitis B booster administrations (days 216 and 246) for measurement of antibodies. The vaccines were chosen to represent primary (hepatitis B) and secondary (tetanus/diphtheria) T-cell-dependent antibody response and T-cell-independent (pneumococcal) antibody responses.

Immunoglobulin G (IgG) antibodies to pneumococcal capsular polysaccharide and to diphtheria and tetanus toxoid were measured by enzyme-linked immunosorbent assay (ELISA) as previously described. Antibodies to hepatitis B surface antigen were measured by radioimmunoassay (Ausb, Abbott Laboratories, North Chicago, Ill) according to the manufacturer's instructions and are reported in units per milliliter.

Total serum IgG, IgM, and IgA were measured by an immunoturbidimetric method using a Cobas Para Centrifugal Analyzer (Roche Diagnostic System, Montclair, NJ) and antibodies from Atlantic Antibodies, Inc (Searborough, Me). Autoantibodies to DNA and thyroglobulin were measured by ELISA using microplates according to the method of Zouali and Stollar. Wells were coated with 2 µg/mL of calf thymus double-stranded DNA and single-stranded DNA (Pharmacia Molecular Biological, Piscataway, NJ) or 100 µL of 1-mg/mL human thyroglobulin (Dako Corp, Carpenteria, Calif) in phosphate-buffered saline (PBS) containing 15-mmol/L sodium azide (NaNO3). The absorption at 410 nm was measured with MultiScan MR 600-microplate reader (Dynatech, Alexandria, Va).

Whole blood was examined with a Baker 9000 Hematology Analyzer for red blood cell (RBC) and white blood cell (WBC) counts, and a blood smear was used to estimate WBC differentials. In addition, the percentage of B cells, T cells, or T helper and T-cytotoxic lymphocytes was determined as previously described.

Serum tocopherol was analyzed from serum samples saved under nitrogen at −70°C using a modified high-performance liquid chromatography method of Bieri et al as previously described.

Nutritional and Safety Assessment

Nutritional status of subjects was assessed before and after supplementation with vitamin E by evaluating dietary intake using 3-day diet records and the GRAND database, as well as blood and/or urinary indicators of different nutrients. To evaluate any adverse effect of long-term supplementation with vitamin E, complete blood cell counts, plasma total protein, albumin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, lactate dehydrogenase, urinary creatinine, thyroid hormones, and plasma lipid profile levels were measured before and after supplementation, as previously described. In addition, the ability of neutrophils to kill C albicans was compared in the different groups after 128 days of supplementation.

Statistical Analysis

Our previous data on DTH was used to calculate the number of subjects per group needed to achieve a 30% increase (a conservative estimate of expected change with vitamin E supplementation) with α=.05 and β=.80. Data were analyzed by repeated-measures analysis of variance (ANOVA) for the effect of time. Differences in dose response were tested as group-by-time interaction in the repeated-measures ANOVA. Data within each group were analyzed by paired Student t test (for variables with normal distribution) or paired Wilcoxon signed-rank test (for variables not having normal distribution). Percent change in DTH and increase in autoantibody titer were compared using Kruskal-Wallis ANOVA (nonparametric). Adjustment for multiple comparisons was made by placing Bonferroni bounds on P values by multiplying the unadjusted P value by the number of comparisons. The antibody titer values were log transformed prior to sta-
tistical analysis. Data are reported as mean (SD) and, if not normally distributed, as median with upper and lower quartile noted. Pearson goodness-of-fit statistics for homogeneity of proportions were used to test if the probability of becoming seropositive in response to hepatitis B (antibody titer of ≥8 IU/mL after the third hepatitis B booster) changes with the tertile of serum vitamin E level. Logistic regression was used to test whether the probability of becoming seropositive (anti–hepatitis B antibody of ≥8 IU/mL) changed by serum vitamin E level.

RESULTS

Six subjects were found to be non-compliant based on their serum vitamin E levels, pill count, and/or significant changes in their levels of other nutrients with known effects on the immune response. These subjects (2 in the placebo, 2 in the 60-mg/d, 1 in the 200-mg/d, and 1 in the 800-mg/d groups) were excluded prior to data analysis; exclusion did not alter the results. Compliance was otherwise excellent, with 10 subjects missing supplement intake for 1 to 4 days out of the 246-day study period.

There was no difference in average age, body mass index (BMI), or distribution of race (all white) or sex among the groups (Table 1). All subjects maintained body weight.

The serum vitamin E concentrations before supplementation were similar in all 4 groups (Table 2). Although no change in serum vitamin E levels was observed in the placebo group, the concentrations in vitamin E–treated groups increased in a dose-dependent manner (P<.001 in each group).

Subjects in all groups had normal values for the laboratory variables measured as part of the safety assessment. Supplementation with vitamin E did not change these variables (data not shown). White blood cell and differential counts of the subjects were within normal range and did not change significantly during the study in any of the groups. Similarly, no effect of vitamin E supplementation was observed on the percentage of T cells, B cells, or T-helper or T-cytotoxic cells (data not shown).

Table 3 shows the results of DTH tests. All 3 vitamin E–supplemented groups showed a significant increase in diameter of induration after 128 days of supplementation compared with baseline; the placebo group showed no change. When DTH was expressed as median percent change, subjects in the 200-mg/d group had a 65% increase, significantly greater (P=.04) than that of the placebo group (17%). Although the median percent changes in the 60-mg/d and 800-mg/d groups (41% and 49%, respectively) were similar to the change in the 200-mg/d group (65%), these changes were not statistically different from the placebo group.

There was no significant change in the total number of positive responses (SD) in any of the groups (3.5 [1.4] vs 4.2 [1.7] in the placebo, 3.6 [1.5] vs 5.1 [1.7] in the 60-mg/d group, 3.6 [1.6] vs 4.3 [1.9] in the 200-mg/d group, and 3.2 [1.3] vs 5.4 [1.6] in the 800-mg/d group before and after supplementation, respectively). Whereas the number of positive antigens is a reflection of both the previous history of antigen exposure and the current status of cell-mediated immunity, the diameter of induration is representative of the current status of cell-mediated immunity and, therefore, might better reflect the change in cell-mediated immunity during an intervention of this length.

Since there was considerable overlap in the serum vitamin E level achieved during supplementation in the 3 different groups, subjects in the middle (34.8–48.4 mmol/L [1.5–2.1 mg/dL]) and upper (≥48.4 mmol/L [≥2.1 mg/dL]) tertiles of serum vitamin E levels after supplementation were compared with those in the lowest (<34.8 mmol/L [<1.5 mg/dL]) tertile of serum vitamin E levels after supplementation. Subjects in the middle and upper tertile of serum vitamin E level had a greater median percent change in DTH (64% and 49%, respectively) than those in the lower tertile (17%) of serum vitamin E level (P=.05 and .11, respectively, Kruskal-Wallis 1-way ANOVA followed by Bonferroni correction), although changes varied widely within tertiles.

There was no difference in total nonspecific immunoglobulin levels (IgA, IgM, IgG) between groups at baseline, and it was not affected by vitamin E supplementation (data not shown). However, antibody titer against hepatitis B (primary T-cell–dependent) vaccine increased significantly in the groups consuming 200 mg/d and 800 mg/d of vitamin E (Table 4). The total number who became seropositive after the third hepatitis B injection was higher in the supplementation groups than in the placebo.
Table 4.—Effect of Vitamin E Supplementation on Antibody Titer to Hepatitis B in Elderly Subjects

<table>
<thead>
<tr>
<th>Group (No. of Subjects)</th>
<th>Geometric Mean, U/mL</th>
<th>% With Detectable Hepatitis B Titer$</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (16)</td>
<td>4.0</td>
<td>20</td>
<td>.20</td>
</tr>
<tr>
<td>Vitamin E</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60 mg (18)</td>
<td>4.0</td>
<td>20</td>
<td>.20</td>
</tr>
<tr>
<td>200 mg (18)</td>
<td>4.0</td>
<td>20</td>
<td>.20</td>
</tr>
<tr>
<td>800 mg (18)</td>
<td>4.0</td>
<td>20</td>
<td>.20</td>
</tr>
</tbody>
</table>

* A standard dose of hepatitis B vaccine was administered on day 156 of the study. Two additional hepatitis B booster doses were administered on days 186 and 216 of the study. Blood for serum antibody level measurement was collected before vaccination, 1 month after vaccination (post 1), and 1 month following the second (post 2) and third (post 3) hepatitis B booster administrations. Serum samples with undetectable levels were assigned 4 IU/mL for the purpose of calculating geometric means.
† Post 3 compared with baseline using Wilcoxon signed rank test followed by Bonferroni correction for multiple comparisons.
$ Detectable level set at 8 IU/mL or more as detected by radioimmunoassay after third hepatitis B vaccine booster.

There was no significant effect of vitamin E on antibody response to diphtheria vaccine (1.7-fold increase in the placebo, 60-mg/d, and 200-mg/d groups and a 1.5-fold increase in the 800-mg/d group). There was also no significant increase in the geometric mean of antibody titer in response to tetanus toxoid in the placebo (29.5 µg/mL before vs 45.4 µg/mL after; 1.5-fold increase), 60-mg/d (19.8 µg/mL before vs 32.0 µg/mL after; 1.6-fold increase), or 800-mg/d (17.8 µg/mL before vs 21.1 µg/mL after; 1.2-fold increase) groups. However, a significant increase was observed in the 200-mg/d group (221.1 µg/mL before vs 38.7 µg/mL after; 1.7-fold increase, P=.04). At baseline, all except 5 subjects (distributed among different groups) had more than protective levels (0.01 U/mL) of antibody against tetanus, which precluded testing the effect of vitamin E on protective levels. However, since the elderly have a more rapid drop-off time in response to tetanus vaccine than do younger subjects, it is possible that the significant increase in antibody titer in the 200-mg/d group would produce greater antibody levels for a longer period of time after vaccination. Although all groups had a significant increase in response to the 3 different types of pneumococci measured (PN 6, PN 14, and PN 19), the group receiving 200 mg/d of vitamin E tended to have a greater increase to PN 14 and PN 19 (Table 5). No significant correlation between tertiles of serum vitamin E level and antibody response to tetanus, diphtheria, or pneumococcal vaccine was found.

Table 6 shows the effect of vitamin E supplementation on the levels of 2 autoantibodies: anti-DNA and antityroglobulin. Vitamin E supplementation did not increase the level of either autoantibody. Furthermore, no effect of vitamin E supplementation on the ability of neutrophils to kill C albicans was observed (percent killing after 60 minutes' incubation with opsonized pathogen were 48±7.2% [placebo group], 38±8.8% [60-mg/d group], 50±7.2% [200-mg/d group], and 54±9.6% [800-mg/d group]).

COMMENT

Few interventions have been successful in changing the age-associated decline of the immune response. In the present study, we demonstrate that supplementation of healthy elderly with vitamin E, an antioxidant vitamin that inhibits PGE$_2$ production, significantly improves clinical cell-mediated immune response without an adverse effect in this population.

We have previously shown that short-term (1-month) supplementation with high levels of vitamin E significantly improves DTH, mitogenic response, and IL-2 production in aged mice and healthy older subjects. The present study was designed to determine if levels less than 800 mg/d of vitamin E consumed over a longer period of time would improve clinically relevant indexes of immune response and if levels of vitamin E greater than the RDA should be recommended to older adults.

We report here that long-term vitamin E supplementation improves some clinically relevant indexes of cell-mediated immunity in healthy elderly already consuming what have been considered adequate levels of tocopherol as determined by serum vitamin E levels. It should, however, be kept in mind that the current recommended levels are based on studies in young subjects. Of the groups in this experiment given 1 of the 3 doses of vitamin E (60, 200, and 800 mg/d), subjects consuming 200 mg/d of vitamin E had the greatest percent increase in DTH and antibody titer to hepatitis B compared with the placebo, 60-mg/d, and 800-mg/d vitamin E groups. In addition, the 200-mg/d group had a significant increase in antibody response to tetanus and tended to have a greater increase in response to pneumococcal vaccine. The percent change in DTH of the 200-mg/d group was significantly greater than that of the placebo group. Also, while the increase in antibody titer against hepatitis B did not reach statistical significance in the placebo or the 60-mg/d vitamin E groups, a significant increase in antibody titer was observed in the 200-mg/d and 800-mg/d groups. Subjects in the 200-mg/d group developed greater antibody titers compared with subjects in the placebo and other vitamin E–treated groups. These data suggest that while supplementation with 60 mg/d of vitamin E might enhance DTH, it was not adequate to cause a significant increase in antibody titer against hepatitis B or tetanus toxoid. Supplementation with 200 mg/d of vitamin E, however, caused a significant increase in DTH and antibody response, and the magnitude of response for both indexes was greater than that of the other 2 vitamin E groups. Thus, we conclude that in the elderly subjects with serum vitamin E levels of 27.9 µmol/L (1.2 mg/dL) or less who con-
sumed the 3 doses tested, 200 mg/d represents the optimal level of vitamin E for the immune response. The observation that the optimal response was detected in the 200-mg/d group suggests that there might be a threshold level for the immunostimulatory effect of vitamin E. Further studies are needed to determine the upper level of the effect of vitamin E on the immune response.

An alternative approach to determining the optimal level of vitamin E is to establish the serum level above which significant enhancement in immune response is observed. In this study, subjects in the middle and upper tertiles of serum vitamin E after supplementation (>34.8 µmol/L [>1.5 mg/dL]) had a greater percent change in DTH compared with those in the lower tertile of serum vitamin E level, and subjects in the upper tertile of serum vitamin E (>48.4 µmol/L [>2.1 mg/dL]) had a significant increase in antibody titer to hepatitis B compared with those in the lower tertile (<34.8 µmol/L [<1.5 mg/dL]). Therefore, intakes of vitamin E that augment serum vitamin E levels to 48.4 µmol/L (2.1 mg/dL) were sufficient to significantly improve DTH and T-cell-dependent antibody response. After 4.5 months of supplementation, none of the subjects in the placebo or 60-mg/d group had serum vitamin E levels greater than 48.4 µmol/L (2.1 mg/dL), while 55% of subjects in the 200-mg/d group and 84% of subjects in the 600-mg/d group had serum levels above 48.4 µmol/L (2.1 mg/dL). The fact that a greater percentage of subjects in the 600-mg/d group achieved levels above 48.4 µmol/L (2.1 mg/dL), but did not exhibit the greatest percent increase in the indexes measured, provides additional evidence of a threshold level for the immunostimulatory effect of vitamin E.

While our study was too small and not designed to measure change in number of infections, subjects were asked to report all infections in a calendar during the study. When the 3 vitamin E–treated groups were combined, their incidence of self-reported infections (0.53 per person per study period) was 30% lower than that of the placebo group (0.74 per person per study period)(P = .10 by Pearson χ² analysis). In addition, results from animal and epidemiologic studies indicate that the observed immunostimulatory effect of vitamin E might be of clinical significance to the elderly.⁴³⁻⁴⁶

Epidemiologic studies have shown a lower incidence of infectious disease in elderly subjects with high plasma vitamin E concentrations.⁴⁷⁻⁴⁸ Several animal studies have shown that the immunostimulatory effect of vitamin E is associated with increased resistance to infection, such as Escherichia coli and Pneumococcus pneumonia type I.⁴² Of particular interest is our recent observation that old mice supplemented with 500 ppm of vitamin E and infected with influenza virus had significantly lower lung viral titers compared with infected mice who consumed adequate levels of vitamin E (30 ppm).⁴³ Others have reported protection against viral infection as well.⁴⁴ The studies of Christ- tou et al.,⁴ Cohn et al.,⁴ and Chandra⁴ further support the notion that quantitative changes in immune response are associated with decreased morbidity in the elderly. While data reported in the

The literature and our own observations in an animal model of influenza support the hypothesis that vitamin E has a protective effect against infections in the elderly, clinical trials using a large number of subjects are needed to determine the effect of vitamin E on the incidence of infectious diseases in the elderly.

In conclusion, our double-blind, placebo-controlled study shows that levels of vitamin E higher than currently recommended enhance in vivo indexes of T-cell–mediated function in healthy elderly. The enhancement of cell-mediated immunity by vitamin E was not associated with any adverse effects. Since age-associated decline in immune response is associated with increased morbidity and mortality in the elderly and is widely observed,⁴⁵ recommendations to increase the intake of vitamin E for elderly should be considered.

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References

Table 5.—Effect of Vitamin E Supplementation on IgG Antibody Levels Against Pneumococcal Vaccine (PN)

<table>
<thead>
<tr>
<th>Group (No. of Subjects)</th>
<th>Before Vaccination</th>
<th>After Vaccination</th>
<th>Fold Increase</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (16)</td>
<td>0.82</td>
<td>1.7</td>
<td>2.1</td>
<td>.02</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>0.84</td>
<td>2.7</td>
<td>3.2</td>
<td>.001</td>
</tr>
<tr>
<td>60 mg (18)</td>
<td>0.84</td>
<td>2.7</td>
<td>3.2</td>
<td>.001</td>
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<tr>
<td>200 mg (18)</td>
<td>0.46</td>
<td>1.7</td>
<td>3.7</td>
<td>.003</td>
</tr>
<tr>
<td>800 mg (18)</td>
<td>0.83</td>
<td>1.4</td>
<td>1.7</td>
<td>.003</td>
</tr>
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</table>

*Compared with values before vaccination by Wilcoxon signed rank test of log-transformed data followed by Bonferroni correction for multiple comparisons. Serum samples with undetectable levels were assigned one half the lower limit of detection (<0.03, 0.052, and 0.12 µg/mL for types 6B, 14, and 19F, respectively) for the purpose of calculating geometric mean.

Table 6.—Effect of Vitamin E Supplementation on Serum Autoantibody Titer

<table>
<thead>
<tr>
<th>Group (No. of Subjects)</th>
<th>Anti-DNA, Mean (SD)*</th>
<th>Anti-thyroglobulin, Mean (SD)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (18)</td>
<td>591 (109)</td>
<td>768 (302)</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>689 (166)</td>
<td>647 (391)</td>
</tr>
<tr>
<td>0 mg (19)</td>
<td>577 (167)</td>
<td>647 (104)</td>
</tr>
<tr>
<td>200 mg (20)</td>
<td>618 (348)</td>
<td>799 (507)</td>
</tr>
</tbody>
</table>

*Serum titers, as defined as dilutions required for an enzyme-linked immunosorbent assay (ELISA) reading of 0.1³; time ELISA values for a 1:100 serum dilution.

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