Effect of Vitamin and Trace-Element Supplementation on Cognitive Function in Elderly Subjects

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OBJECTIVE: To determine whether supplementation with vitamins and trace elements in modest amounts influences cognitive function in apparently healthy, elderly subjects.

METHODS: The study was designed as a randomized, double-blind, placebo-controlled trial. Ninety-six, apparently healthy, independent men and women older than 65 y of age were recruited and randomized to receive a supplement of trace elements and vitamins or a placebo daily for 12 mo. Blood-nutrient levels were estimated at baseline and at the end of the study. The major outcome measure assessed was cognitive function consisting of immediate and long-term memory, abstract thinking, problem-solving ability, and attention.

RESULTS: Eighty-six subjects completed the 1-y trial. The supplemented group showed a significant improvement in all cognitive tests ($P < 0.001$ to 0.05) except long-term memory recall ($P > 0.1$). Those whose blood-nutrient levels were below the reference standard showed lower responses on cognitive tests. There was no significant correlation between individual nutrient levels and performance on various cognitive function tests.

CONCLUSIONS: Cognitive functions improved after oral supplementation with modest amounts of vitamins and trace elements. This has considerable clinical and public health significance. We recommend that such a supplement be provided to all elderly subjects because it should significantly improve cognition and thus quality of life and the ability to perform activities of daily living. Such a nutritional approach may delay the onset of Alzheimer's disease. *Nutrition* 2001;17:709–712. ©Elsevier Science Inc. 2001

KEY WORDS: elderly, aging, vitamins, trace elements, cognitive function, memory, Alzheimer's disease

INTRODUCTION

Aging is associated with a gradual impairment in cognitive function[1] and even mild dementia has been linked to an increase in mortality in the aged.[2] Also, the elderly show a high prevalence of undernutrition.[3,4] At least 40% of independently living elderly individuals in affluent industrialized countries of North America and Europe have been estimated to have dietary intakes and blood-nutrient levels compatible with "deficiency."

Many nutrients play a key role in the metabolism of neuronal cells and their appendages. Their actions may be mediated by their catalytic role in numerous enzymes, antioxidant action, and various other processes. In vitro, micronutrients potentiate the ability of immune cells to withstand the toxic effect of inclusion bodies found in brains of patients with Alzheimer's disease (R. K. Chandra, in preparation). Further, micronutrients may reduce the amount of amyloid material in brain biopsies of patients with Alzheimer's disease.

A preliminary cross-sectional one-point study suggested an association between dietary intake and blood levels of vitamin C, B12, B2, or folic acid and cognitive function as judged by the Weschler Memory Test and the Halstead-Reitan Categories Test.[5] However, no intervention was attempted and other vitamins and none of the trace elements were studied.

Therefore, nutritional deficiencies may be a contributing factor, perhaps even a causal factor, in the decline of cognitive function in old age. The hypothesis tested in this study was that an optimum intake of all essential micronutrients in modest physiologic amounts improves cognitive function in the elderly. We conducted a randomized, double-blind, placebo-controlled trial to test this hypothesis.

SUBJECTS AND METHODS

The study population and their nutritional status at baseline and at the end of the 12-mo study period were described previously.[6]

Subjects

Ninety-six, apparently healthy, independently living men and women older than 65 y volunteered to enroll for the double-blind, placebo-controlled trial. They were from the middle socioeconomic class, with an average family income of C$48,000 per annum. None of the subjects had any chronic or serious acute illness. Specifically, none suffered from any form of psychiatric illness or dementia. None had taken any nutritional supplements in

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the 3 mo before recruitment. They were not taking any other medications that might have interfered with their nutrition status or cognitive function.

Blood-Nutrient Levels

Two samples of blood were obtained at 1-wk intervals and subjected to nutrient-level analyses. The average of the two values was used for subsequent consideration. Vitamins A, B_6, E, and β-carotene were estimated by high-performance liquid chromatography, folates and vitamin B_{12} by radioimmunoassay, vitamin C by spectrophotometry, vitamin D by radioreceptor binding, ferritin by enzyme-linked immunoassay, zinc and copper by atomic absorption spectrophotomtery, selenium by neutron activation, albumin by bromocresol green, and hemoglobin by Coulter counter.

To obtain nutrient reference standards, fasting blood samples of 141 healthy men and women aged 66 to 88 y living in Newfoundland were analyzed for various nutrients. Each subject had been followed for a minimum of 1 y and a maximum of 3 y after blood-nutrient estimation, and only the results of those who had remained healthy were included in the calculation of 95% confidence intervals. Those results were published.[6] The distribution of values was approximately normal.

Subjects in the randomized trial whose blood-nutrient values fell below the 95% confidence intervals of those reference standards for the healthy elderly were considered "deficient."

Supplement

The subjects were randomly assigned to receive placebo or a supplement based on four blocks of 24 random numbers. The daily oral supplement contained 400 retinol equivalents of vitamin A, 16 mg of β-carotene, 2.2 mg of thiamine, 1.5 mg of riboflavin, 16 mg of niacin, 3.0 mg of vitamin B_6, 400 μg of folate, 4.0 μg of vitamin B_{12}, 80 mg of vitamin C, 4.0 μg of vitamin D, 44 mg of vitamin E, 16 mg of iron, 14 mg of zinc, 1.4 mg of copper, 20 μg of selenium, 0.2 mg of iodine, 200 mg of calcium, and 100 mg of magnesium. The placebo contained 200 mg of calcium and 100 mg of magnesium.

Cognitive-Function Tests

Cognitive function was assessed on the basis of several tests that gauge immediate and long-term memory, abstract thinking, problem-solving ability, and attention. All subjects were administered the identical assessment battery at the same time of the day to control for potential effects of diurnal variability.

WECHSLER MEMORY TEST.[7] The interviewer reads a one-paragraph story with a defined number of salient points to the subject who is asked to repeat the story immediately and then after 30 min.

HALSTEAD–REITAN CATEGORIES TEST.[8] This is a nonverbal, automated test of abstract thinking and problem-solving ability and serves as a sensitive indicator of minor changes in mental status.

BUSCHKE CONSISTENT LONG-TERM RETRIEVAL.[9] Subjects are read a list of 12 words that they must repeat. They are then told the words they missed and asked to repeat the entire list. The process is repeated until subjects repeat all 12 words or until 10 trials have been completed. Working memory is involved in this task.

DIGIT SPAN FORWARD. The subject hears an increasingly longer series of single digits and is asked to repeat these digits in the same order.

SALTHOUSE LISTENING SPAN TEST.[10] The test involves processing of information, brief storage, and subsequent retrieval. Six sentences are read out. The subject should be able to remember the last word of each and write down those words in the sequence in which they were read out. The subject should be able to answer questions related to each sentence.

LONG-TERM MEMORY RECALL. This test assesses memory of events that happened a long time ago, e.g., high school graduation, first job, etc.

MINI-MENTAL STATE.[11] This is a comprehensive assessment tool for gauging the cognitive state of healthy individuals and psychiatric patients.

Statistical Analyses

The number of subjects considered "deficient" for each nutrient at baseline and at the end of the 12-mo study was compared by the chi-square or Fisher's exact probability test. The two groups were compared with respect to mean change in cognitive function tests per individual by unpaired *t* test and multiple analysis of variance. Correlation between levels of various nutrients and cognitive function test results was calculated by Pearson's coefficient. Statistical tests were conducted on appropriately transformed data when the observed values were not normally distributed. SPSS and Minitab statistical programs were used.

RESULTS AND DISCUSSION

Eighty-six subjects completed the 1-y trial. Five placebo subjects and three supplemented individuals withdrew from the study for personal reasons. Two subjects died.

The demographic and nutritional data were reported briefly[6] and are shown in Table I. At baseline, the prevalence of nutrient deficiency did not differ significantly between groups. There was no significant change in the nutrition status of the placebo group at the end of 1 y. However, there was a significant reduction in the prevalence of deficiencies of vitamin A, β-carotene, vitamin B_6, vitamin C, iron, and zinc in the supplemented group.

There was no change in cognitive function in the placebo group after 1 y. In contrast, there was a statistically significant improvement in most of the cognitive function tests in the supplemented group (Table II). The subjects who showed deficient blood levels of one or more nutrients showed lower responses on all cognitive-function tests (Table III). There was no significant correlation between levels of individual nutrients and cognitive function test scores. In multiple regression analysis, no single nutrient appeared to influence cognition. However, those whose blood-nutrient levels were deficient at baseline and rose significantly after supplementation for 1 y showed a greater improvement in cognitive function than did those whose nutrient levels were normal at baseline or did not change significantly after supplementation.

The amounts of vitamins and trace elements in the supplement used in this trial were modest; most were within the physiologic range recommended by many countries and health organizations. β-carotene and vitamin E were in amounts slightly higher than those recommended for healthy adults. None of the nutrient amounts could be considered a "mega dose." No side effects or signs of overdose were expected in this study and none were observed.

TABLE I.

DEMOGRAPHIC DATA

Varible	Placebo group		Supplement group		Difference between S_0 and S_{12} (P)
	0 mo	12 mo	0 mo	12 mo	
n Subjects	48	41	48	45	—
Mean age (y)	74	—	75	—	—
Range	68–84	—	(66/86)	—	—
Male/female	21/27	17/24	20/28	18/27	—
*Nutrient deficiency (%)**					
Vitamin A	8.3	7.3	12.5	2.2	0.05
β-carotene	12.5	9.7	16.7	0	0.017
Vitamin B_6	10.4	9.7	16.7	4.4	0.046
Folic acid	4.2	7.3	6.2	2.2	NS
Vitamin B_{12}	6.2	9.7	6.2	4.4	NS
Vitamin C	18.7	16.6	22.9	4.4	0.008
Vitamin D	4.2	7.3	6.2	0	NS
Vitamin E	8.3	12.2	8.3	2.2	NS
Iron	12.5	9.8	14.5	2.2	0.032
Zinc	14.6	14.6	16.7	4.4	0.046
Selenium	2.1	2.4	0	2.2	NS
Copper	4.2	2.4	2.1	2.2	NS
Albumin	8.3	12.2	10.4	8.9	NS
Hemoglobin	6.2	4.9	6.2	2.2	NS

* Deficiency is defined as a blood concentration below the 95% confidence interval.
NS, not significant, $P > 0.05$; S_0, supplement group at 0 mo; S_{12}, supplement group at 12 mo.

None of the subjects had clinical evidence of Alzheimer's disease or any other type of dementia. A long-term follow-up on a large number of subjects would be required to assess any possible impact of nutrition supplements on the occurrence of Alzheimer's disease. Further, the amounts of nutrients that might influence the course of Alzheimer's disease might be quite different from those used in this trial.

I considered the possibility that poor cognitive function is a risk factor for poor nutrition. However, none of the subjects were mentally impaired, and there was no clinical evidence of dementia at the beginning and end of the trial. Moreover, the randomized, placebo-controlled nature of the trial and its results cannot be explained on this basis.

The possible underlying mechanism(s) of the beneficial influence of nutrients on cognitive function in the elderly are many. An enhanced immune response in those receiving the nutrition supplement may be instrumental in preserving the anatomy and function of neurons and their appendages. An intimate anatomic and functional relationship between the immune cells and neuronal cells is well recognized. An enhanced immune response in the

TABLE II.

COGNITIVE FUNCTION TESTS

Test	Placebo*		Supplement*		Difference (P)	
	0 mo	12 mo	0 mo	12 mo	S_0 and S_{12}	$P_0 \Rightarrow P_{12}$ and $S_0 \Rightarrow S_{12}$
Wechsler Memory Test (score)	5.3 ± 0.4	4.9 ± 0.5	5.1 ± 0.4	6.8 ± 0.5	<0.01	<0.001
Halstead–Reitan Categories (*n* errors, %)	76 ± 7	82 ± 6	80 ± 8	64 ± 7	<0.05	<0.01
Buschke Consistent Long-term Retrieval (*n* errors, %)	28 ± 4	34 ± 6	30 ± 7	11 ± 4	<0.001	<0.001
Digit Span Forward (score)	56 ± 4	61 ± 6	59 ± 7	80 ± 6	<0.01	<0.01
Salthouse Listening Span Task (impairment,%)	34 ± 5	31 ± 6	28 ± 5	16 ± 3	<0.01	<0.01
Long-term Memory Recall (score)	78 ± 9	83 ± 6	81 ± 7	88 ± 5	NS	NS
Mini-mental State (score)	21 ± 2	20 ± 3	18 ± 3	28 ± 4	<0.01	<0.01

* Results are presented as mean ± standard error of the mean,
NS, not significant; P_0 and P_{12}, placebo group at 0 and 12 mo; S_0 and S_{12}, supplement group at 0 and 12 mo.

TABLE III.

COGNITIVE FUNCTION TESTS

	Nutrition status*		
	Deficient	Adequate	*P*
Wechsler Memory Test (score)	4.1 ± 0.7	6.1 ± 0.5	<0.01
Halstead-Reitan Categories (*n* errors, %)	86 ± 8	60 ± 7	<0.01
Buschke Consistent Long-term retrieval (*n* errors, %)	41 ± 5	15 ± 3	<0.001
Digit Span Forward (score)	46 ± 5	87 ± 7	<0.001
Salthouse Listening Span Task (impairment, %)	43 ± 4	12 ± 4	<0.001
Long-term Memory Recall (score)	84 ± 8	91 ± 3	NS
Mini-mental State (score)	17 ± 4	28 ± 3	<0.001

* Results are presented as mean ± standard error of the mean.
NS, not significant.

supplemented group may have prevented the accumulation of β-amyloid, neurofibrillary tangles, and other pathologic deposits that are associated with serious neuronal damage and neuropsychiatric disorders such as Alzheimer's disease.

We previously discussed the rationale of preventing disease in the elderly by using a mixture of nutrients rather than a single nutrient supplement.[12,13] It is expensive and impractical to estimate dietary intake or blood levels of several nutrients in individuals. There is no evidence to suggest that modest amounts of vitamins and trace elements given for prolonged periods have any toxic or adverse consequences. Given the high frequency of nutrient deficiencies in old age, it would be prudent to opt for a suitable micronutrient supplement for all elderly subjects to achieve the maximum physiologic and health benefits with the least risk of toxicity.

The results of this randomized, double-blind, placebo-controlled trial showed that cognitive function tests in elderly subjects improve after 1 y of administration of an oral supplement containing all essential vitamins and trace elements in modest amounts. Mega doses are not warranted and can have serious side effects. We recommend providing a micronutrient supplement to all elderly subjects to significantly improve cognitive function. Such an intervention might significantly delay or prevent the onset of overt Alzheimer's disease.

REFERENCES

1. Nandy K, Sherwin I, eds. *The aging brain and senile dementia*. New York; Plenum Press, 1997
2. Neilsen J, Homma A, Bjorn-Henriksen T. Follow-up 15 years after a geronto-psychiatric prevalence study. J Gerontol 1977;32:554
3. Munro H, Schlierf G, eds. *Nutrition of the elderly*. New York; Raven Press, 1992
4. Hoffer LJ. Nutritional supplements and health. Ann RCPSC 1996;29:11
5. Goodwin JS, Goodwin JM, Garry PJ. Association between nutritional status and cognitive functioning in a healthy elderly population. JAMA 1983;249:2917
6. Chandra RK. Effect of vitamin and trace-element supplementation on immune responses and infection in elderly subjects. Lancet 1992;340:1124
7. Russel EW. A multiple scoring method of assessment of complex memory function. J Consult Clin Psychol 1975;43:800
8. Reitan R, Davidson L, eds. *Clinical neuropsychology, current status and applications*. New York; John Wiley, 1974
9. Buschke H. Selective reminding for analysis of memory and learning. J Verbal Learning Verbal Behav 1973;12:543
10. Salthouse T. The aging of working memory. Neuropsychology 1994;8:535
11. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state." A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189
12. Chandra RK. Nutrition, immunity and infection; from basic knowledge of dietary manipulation of immune responses to practical application of ameliorating suffering and improving survival. Proc Natl Acad Sci USA 1996;93:14303
13. Chandra RK. Graying of the immune system. Can nutrient supplements improve immunity in the elderly? JAMA 1997;277:1398