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VIC-Japan

NEWSLETTER

English Version

No.103 July. 2001

Report on The Roche Vitamin Japan and Vitamin Information Center Joint Seminar "Vitamins and the Prevention of Circulatory System Disease"

The Roche Vitamin Japan and Vitamin Information Center's joint seminar in commemoration of the establishment of Vitamin Day was held on May 8 and 9, 2001 in Tokyo and Osaka on the theme of "Vitamins and the Prevention of Circulatory System Disease". In the seminar, Ms. Yuri Moriyama of the Public Health Institute of Kochi Prefecture gave a lecture on the relationship between blood homocysteine levels and the vitamin B group, a theme which has attracted attention in recent years, and Mr. Tetsuji Yokoyama of the Medical Research Institute, Tokyo Medical and Dental University, gave a lecture on the relationship between vitamin C and the risk of stroke based on 20-year study results in Japan. In addition, Dr. Dietrich Hornig from F. Hoffmann La Roche (Switzerland) gave a lecture on the relationship between vitamins and disease prevention centering on vitamin C. The following summarizes the lectures by these speakers.

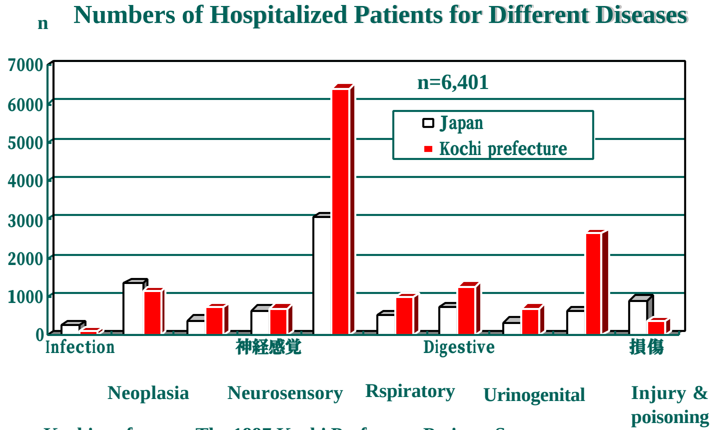
Relationship between blood homocysteine levels・Folic acid・Vitamin B12 and Arteriosclerosis

Dr. Yuri Moriayam, Public Health Institute of Kochi Prefecture

Today it is important for each person to make plans for his/her own health particularly for primary prevention based on his/her own judgment in order to realize a healthy aging society.

In Kochi Prefecture, the aging of the population is as much as fifteen years ahead of the rest of Japan. The number of sudden deaths of men of active working age and that of hospitalized patients with circulatory disease which may lead to a bed-ridden life or dementia (arteriosclerotic diseases including myocardial infarction and cerebral apoplexy) are twice as large as those for the rest of Japan. It is our urgent task to make plans for more effective prevention in order to improve the quality of life of local people and decrease medical and care insurance costs.

Numbers of Hospitalized Patients for Different Diseases



Kochi prefecture: The 1997 Kochi Prefecture Patients Survey
Japan :The 1996 National Patients Survey
Japan :Estimated number of patients obtained by multiplying the population of Kochi Prefecture by the average rate of hospitalized patients in Japan.
Kochi Prefecture: Results of survey in Kochi Prefecture as of September 1, 1997.

Are there more effective measures which can be taken against myocardial infarction, cerebral apoplexy, dementia, etc.?

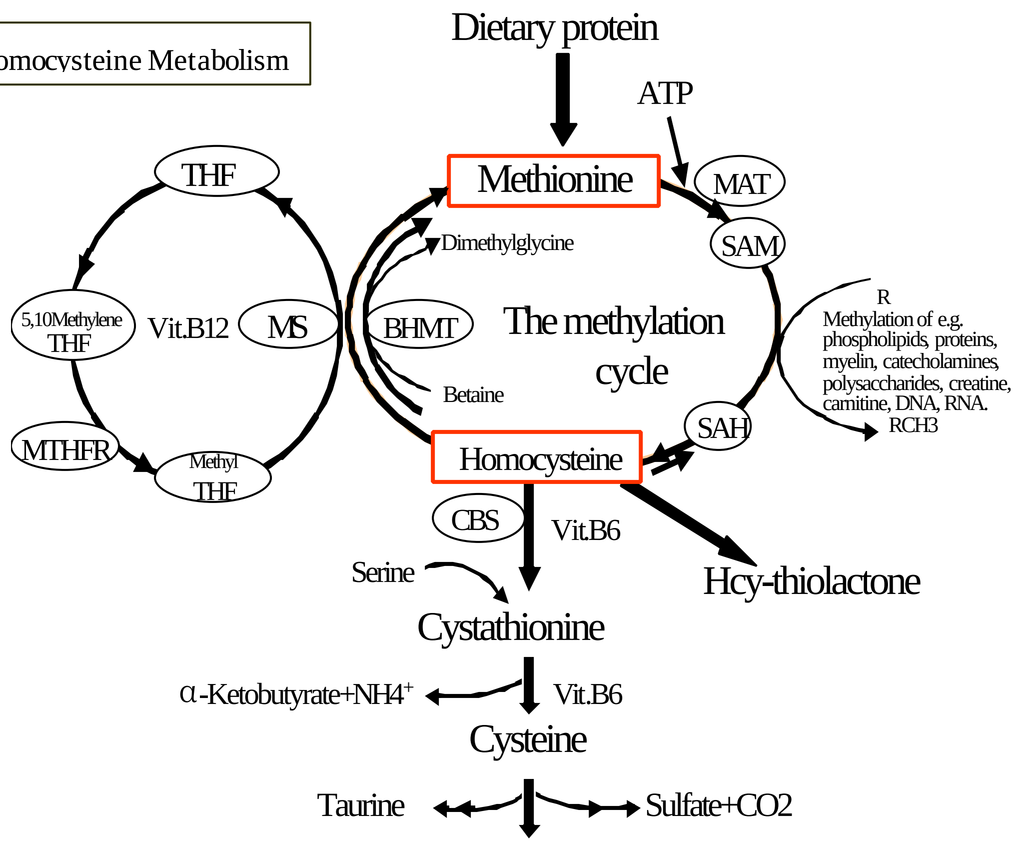
Lifestyle-related diseases (cancer, myocardial infarction, cerebral apoplexy, diabetes, hypertension, etc.) are closely related to our daily lifestyle. It is said that improvements in lifestyles (dietary habits, physical exercise, rests, etc.) may prevent or delay the progress of many diseases.

Homocysteine is attracting attention as a new risk factor for arteriosclerosis.

In recent years, homocysteine is attracting attention as a new risk factor for myocardial infarction and cerebral infarction. Homocysteine is a type of amino acid which is an intermediary metabolite produced when methionine contained in dietary protein is metabolized into cysteine. It is said that increased blood homocysteine levels result in autoxidation of homocysteine, and the oxidation processes cause oxidation stress by hydrogen peroxide and superoxide radicals, resulting in damage to endothelial cells, which often induces arteriosclerosis. Folic acid and vitamins B12 and B6 are involved in the metabolism of homocysteine.

The Public Health Institute of Kochi Prefecture is attempting to contribute to the prevention of arteriosclerotic diseases by studying the relationship between blood homocysteine and vitamin levels and arteriosclerosis in local people and by making plans for the prevention of increases in blood homocysteine levels.

Homocysteine Metabolism

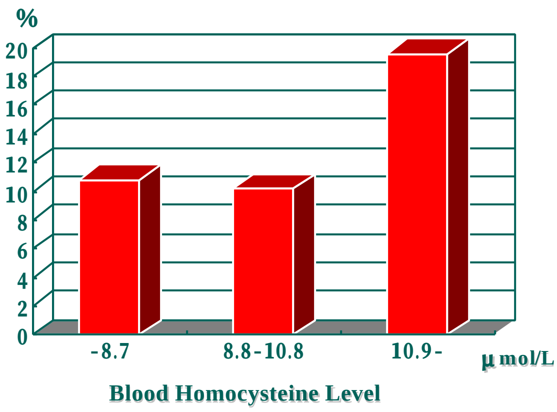


Christina Bolander-Gouaille, Focus on Homocysteine, 1999

Carotid sclerosis is found in many people in the high homocysteine group.

The study on the relationship between homocysteine levels and carotid sclerosis in elderly men living in areas of Kochi Prefecture found that carotid sclerosis was found in many people in the high homocysteine group.

Fig.1 Ratio of Carotid sclerosis by Blood Homocysteine



Comparison of associated factors in terms of existence and non-existence of arterioscleroticchanges

Table.1 Comparison of associated factors in terms of existence and non-existence of arteriosclerotic changes

associated factor	arteriosclerotic no- change (N=409)	arteriosclerotic change (N=82)	P
Age	67	68	<.01
hypertension (%)	32.8	62.2	<.001
hypercholesterolemia (%)	11.5	14.6	NS
Low HDL-cholesterolemia (%)	17.6	29.3	<.05
Diabetes (%)	7.6	18.3	<.01
Smoking(%)	31.3	35.4	NS
BMI,Kg/m^2	23	23	NS
Homocysteine μ mol/L	9.0	10.0	<.05
Folic acid, nmol/L	11.9	11.7	NS
Vitamin B12, pmol/L	510	515	NS

hypertension; SBP ≧160mmHg and/or DBP ≧95mmHg and/or taking hypotensive drugs
hypercholesterolemia; total cholesterol ≧ 240mg/dl and/or taking drugs
low HDL-cholesterolemia; HDL-cholesterol <40mg/dl
Diabetes; blood sugar 200mg/dl and/or taking drugs
Smoking; current smoker

Analyses of associated factor of carotid sclerosis

Table 2 Associated factor of carotid sclerosis (logistic analysis)

factor	Odds ratio (95% CI)
Age (+10 years)	2.0 (1.0-3.8)*
Hypercholesterolemia	1.2 (0.6-2.7)
Low **HDL-coholesterole,mia**	2.1 (1.2-3.8)*
Diabetes	2.8 (1.3-5.8)*
Hypertension	3.2 (1.9-5.4)*
Smoking	1.1 (0.6-1.9)
High Homocysteine level (high25% vs low25%)	2.3 (1.1-4.9)*
Folic acid (high25% vs low25%)	1.4 (0.7-2.9)
Vitamin B12 (high25% vs low25%)	1.0 (0.5-2.1)

* different significantly

Table.3 Relationship between plasma homocysteine(logarithm) and Vitamin (logarithm)

Vitamins	partial regression cofficient	P values
Folic acid (logarithm, nmol/L)	- 0.194	0.0001
Vitamin B12 (logarithm, pmol/L)	- 0.083	0.0006

*multiple linear regression analysis

Malinow et al. reported that people whose serum homocysteine levels are above the fifth percentile are 3.15 times more likely to have thickened carotid artery walls than those in the lowest fifth percentile. In addition, Selhub et al. pointed out that those whose serum homocysteine levels are 14.4 μmol/L or higher are twice as likely to have carotid stenosis (>25%) than those whose levels are 9.1 μmol/L or lower.

In 1997, Sutton-Tyrrell et al. reported that high serum homocysteine levels are associated with systolic hypertension in elderly people and that serum homocysteine levels were a risk factor for arteriosclerosis only in the normotensive group. Similarly, in 1999, Okamura et al. reported based on our study that serum homocysteine levels were a risk factor for arteriosclerosis only in the normotensive group. Further studies have found that in the overall population, those whose homocysteine levels are among the highest 25% of all levels are significantly more likely to have carotid sclerosis than those whose levels are among the lowest 25%, showing that high homocysteine levels are a risk factor for arteriosclerosis in addition to traditional risk factors of aging, low HDL cholesterol levels, diabetes, and hypertension. In addition, it was shown that low levels of folic acid and vitamin B12 in the blood may play a role in carotid sclerosis through an increase in homocysteine levels.

It has been shown that homocysteine levels are associated with dietary factors such as intake of folic acid and vitamins B6 and B12, and it is inferred that increased intake of these nutrients may lower homocysteine levels.

Vitamin C and the Risk of Stroke

Dr. Tetsuji Yokoyama
Department of Epidemiology, Medical Research Institute, Tokyo Medical and Dental University

Background and Purpose

There has been a growing interest in the potential role of antioxidative vitamins for the prevention of cardiovascular disease because epidemiological evidence suggests that an increased consumption of fruit and vegetables may decrease the risk of this disease. And several cohort studies reported the association of higher serum vitamin C levels with a decreased mortality from stroke. However, the detailed mechanisms of these associations have not been well revealed. One of the most common of these hypotheses may be the antioxidant hypothesis, that is, since oxidative modification of LDL is important, and possibly obligatory, in the pathogenesis of atherosclerotic lesions, antioxidative vitamins are protective against cardiovascular disease through their defensive effect on LDL oxidation. To clearly hypothesis of antioxidant, an analysis of the association between vitamin C and stroke according to subtype may advance the knowledge that is necessary to investigate the plausibility of these hypotheses. For example, if a decreased risk was observed for cerebral infarction but not for hemorrhagic stroke, a hypothesis linked with the prevention of atherosclerosis (eg, the antioxidant hypothesis) would be plausible. By contrast, if decreased risk were observed for any subtype, a combination of several mechanistic hypotheses may be required to explain these risk reductions. To gain the knowledge that would allow a more advanced discussion of these hypotheses, we analyzed the association of serum vitamin C concentration and fruit and vegetable intake with a subsequent 20-year incidence of stroke according to subtype using data based on a prospective cohort study conducted in a rural community in Japan.

Subject and Methods

Study District and Baseline Examination:

This study was performed in the A-I district of Shibata located in the northern part of Niigata Prefecture, Japan. All residents aged 40 years or older were considered the eligible population. A baseline examination was conducted in July 1977. The baseline examination included a serum vitamin C measurement and other blood studies; a dietary survey; a general health questionnaire; measurements of height, weight, and systolic and diastolic blood pressure; ECG; and a physical activity survey. From the eligible population, 998 men (response rate, 84%) and 1360 women (93%) underwent the baseline examination. Of these, a measurement of serum vitamin C concentration was completed for 919 men and 1266 women. When we excluded those with a previous history of stroke, 880 men and 1241 women were recruited for the current analyses.

The serum vitamin C concentration was determined in venous blood under nonfasting conditions by the 2,3-dinitrophenylhydrazine method with calorimetric analysis. Immediately after separation by centrifugation, serum was deproteinized, and the supernatant of the serum was stored at –20℃ on the basis of our stability study. Measurements were completed within 10 days. Intake of vitamin C-rich products was assessed with the use of a food frequency questionnaire. Trained dietitians interviewed the participants on the frequency of consumption of each food, as follows: (1) 0 to 2 d/wk, (2) 3 to 5 d/wk, (3) 6 to 7 d/wk.

Follow-up and Determination of Stroke

The cohort members were followed for 20 years (July 1977 through June 1997). To identify the occurrence of stroke, a surveillance and registration system was incorporated with the local administration and the regional medical association. According to the standard clinical criteria, cases of stroke were classified into the following subtypes: intracerebral hemorrhage (ICH), cerebral infarction, subarachnoid hemorrhage (SAH), and undetermined. If the clinical diagnosis conflicted with CT findings, the subtype was determined by the latter.

Statistical Analyses

The type of stroke is classified to cerebral infarction and hemorrhagic stroke (ICH and SAH) for analyses. Peason's correlation analysis or ANCOVA was used to examine the relationships between serum Vitamin C concentration and selected factors. Cox proportional hazards model was used to examine the association of risk factors with occurrence of all stroke, cerebral infarction, and hemorrhagic stroke (ICH plus SAH). Dummy variables were created to calculate the hazard ratios for the first (referent), second, third , and fourth quartiles of serum vitamin C concentration.

Results

Baseline Examination

The mean serum vitamin C concentration was higher in women than in men and lower in the elderly. Weak but significant inverse correlations were observed between serum vitamin C concentration and blood pressure variables even after adjustments for age and sex ($r= -0.1$, $p<0.001$). The correlation between serum vitamin C concentration and total cholesterol was very weak ($r=0.054$). Means of serum vitamin C concentration were higher in those who frequently ate vegetables or fruit, drank less alcohol, were physically active, and were not using antihypertensive mediation.

Risk Analyses

During observation period, 196 incident cases of all stroke (38 ICH and 16 SAH) were documented. Sex- and age-adjusted risks of all stroke and cerebral infarction were lower at higher serum vitamin C levels (Fig.1a). Additional multivariate adjustments for MBP, BMI, TC, presence of atrial fibrillation, personal history of IHD, use of antihypertensive medication, cigarette smoking, and alcohol drinking slightly attenuated these associations, but the associations remained significant (for all stroke) or marginally significant (Fig.1b). As for dietary intake, the sex- and age-adjusted risks of all stroke and cerebral infarction were less than half in those who consumed vegetables 6 to 7 times per week than in those consuming vegetables 0 to 2 times per week, indicating a significant inverse trend (Fig.2a). The risk reduction for hemorrhagic stroke was not significant. Similar to the results observed for serum vitamin C concentration, these relationships were slightly attenuated after multivariate adjustments but remained significant for all stroke (Fig.2b). The frequency of fruit intake was inversely associated with cerebral infarction in women, but the sex difference was not significant.

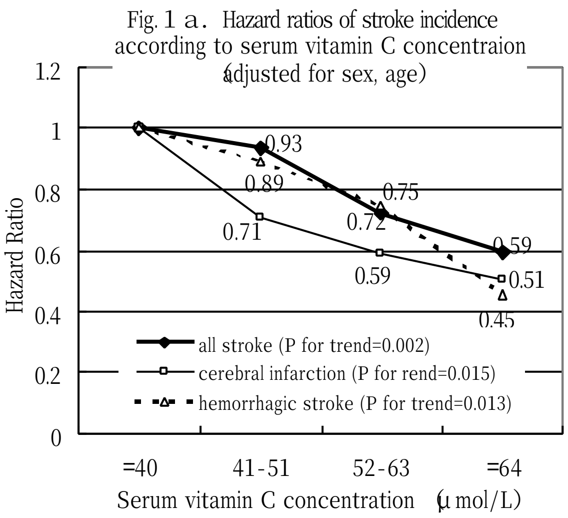


Fig. 1 a. Hazard ratios of stroke incidence according to serum vitamin C concentraion (adjusted for sex, age)

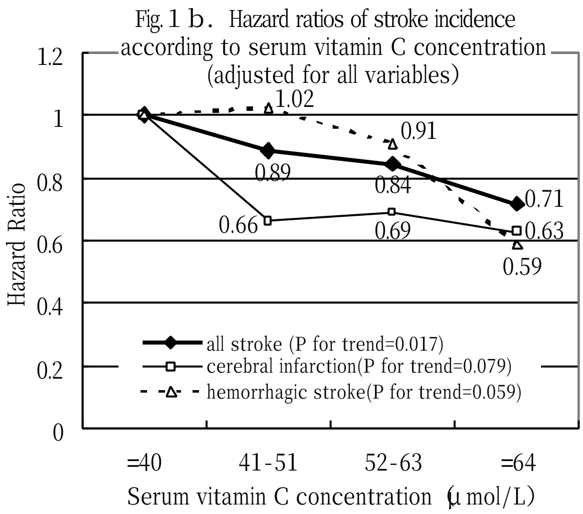


Fig. 1 b. Hazard ratios of stroke incidence according to serum vitamin C concentration (adjusted for all variables)

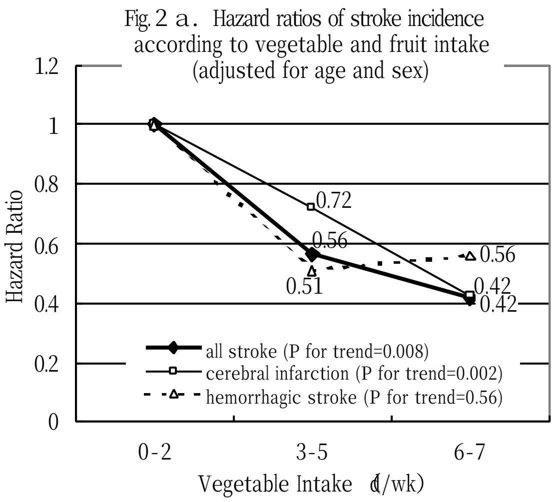


Fig. 2 a. Hazard ratios of stroke incidence according to vegetable and fruit intake (adjusted for age and sex)

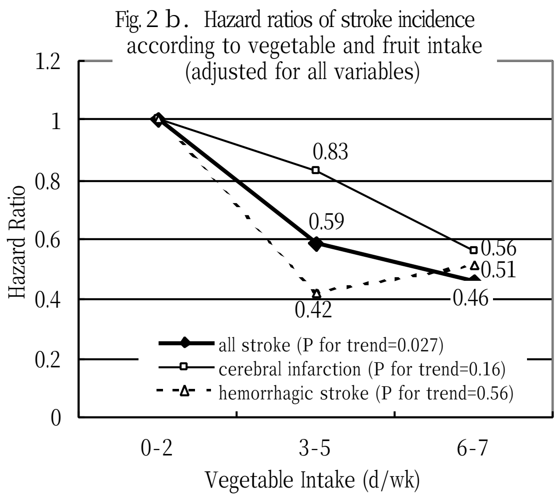


Fig. 2 b. Hazard ratios of stroke incidence according to vegetable and fruit intake (adjusted for all variables)

Discussion

To the best our knowledge, this is the first prospective cohort study to examine the relationship between serum vitamin C concentration and the incidence of stroke. Most interestingly, an inverse association of serum vitamin C concentration was observed not only with cerebral infarction but also with hemorrhagic stroke, which would not be explained by the antioxidant hypothesis alone. Therefore, additional mechanistic hypotheses should be considered to explain the simultaneously reduced risks of cerebral infarction and hemorrhagic stroke. It is plausible that the preventive effect of vitamin C against stroke is partly mediated by lowering blood pressure because (1) serum vitamin C concentration was inversely correlated to blood pressure in this cohort as well as in other population; (2) elevated blood pressure increased the risks of both cerebral infarction and homorrhagic stroke; and (3) adjustment for blood pressure slightly attenuated the hazard ratios of cerebral infarction and hemorrhagic stroke.

In several hypotheses, it is speculated that serum vitamin C dose not have a protective effect against stroke but is a marker of other preventive factors or healthy behaviors, by which the simultaneous reduction of risks for cerebral infarction and hemorrhagic stroke may be partly explained. For example, serum vitamin C concentration may be lower among those who are sedentary, heavy smokers, or heavy drinkers because the intake of fruits and vegetables, the major sources of vitamin C, is lower among such persons. The confounding effect of physical activity on hemorrhagic stroke, as mentioned above, would be one of such phenomena. However, such confounding by smoking or alcohol consumption was not detected in this study. Serum vitamin C concentration may be a marker of intake of other nutrients abundant in fruit and vegetables such as potassium, magnesium, calcium, fiber, and carotene, and these nutrients may be preventive against stroke. Whether causal or confounding, none of the individual effects of each mechanism seems to explain sufficiently the simultaneous large reduction of risks for cerebral infarction and hemorrhagic stroke. After all, vitamin C may reduce the risk of stroke through a combination of several mechanisms, including an antioxidative effect on LDL, lowering of blood pressure, being a marker of other preventive factors or healthy behaviors such as physically active lifestyles, and, possibly, as yet unknown mechanisms.

A potential weakness of our study may be that the serum vitamin C concentration and fruit and vegetables intake were measured only at the baseline examination, and intraindividual changes during the 20-year observation period could not be taken into account for the analysis. However, we had an opportunity to reexamine 862 of the cohort members 4 years after the baseline examination using a comparable protocol. The correlation coefficients between the 2 measurements were 0.54 for serum vitamin C concentration, 0.21 and 0.27 (rank correlation) for frequencies of fruit and vegetable intake, respectively, 0.53 for TC, 0.64 for SBP, and 0.59 for DBP, indicating that the reproducibility of serum vitamin C concentration was similar to that of TC. Although a high degree of reproducibility does not always ensure validity, correlations on the order of 0.5 to 0.7 among subjects who live freely in the community over a period of years indicate that only one measurement of a variable would provide a fairly good measure of its long-term level. The lower reproducibility of fruit and vegetable intake may be one of the reasons why their association with stroke was not as clear as that of serum vitamin C concentration.

Conclusion

A higher serum vitamin C concentration was strongly associated with a reduced risk of subsequent incidence of cerebral infarction and hemorrhagic stroke. A mass screening for such high-risk people may be effective to decrease the occurrence of stroke if appropriate control measures were developed. Until then, we must remember that the effect of controlling risk factors can be determined only by an intervention study, and these do not always show the expected benefits.

The Potential Role of Vitamin C in the Prevention of CVD

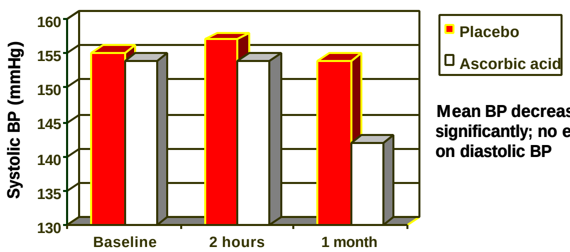
Dietrich Hornig Ph.D, F.Hoffmann-La Roche Ltd.

The aging of the population is an increasingly serious problem. The aging of society has been accompanied by an increase of non-infectious disease and lifestyle-related disease (chronic disease) as well as increased health management costs. It is well known that a major cause of lifestyle-related disease is oxidation by reactive oxygen species, which can be produced by nitrogen monoxide, ozone, alcoholic drinks, ultraviolet rays, and cigarettes. These may cause neural disease, aging, cancer, heart disease, cataracts, age-related macula degeneration, etc. As a defense system from attacks by these reactive oxygen species, humans have enzymes including superoxide dismutase, catalase, and glutathione peroxidase. On the other hand, antioxidants such as vitamin C, vitamin E and carotenoids also play a major role in defense systems. These antioxidants can be ingested through meals and supplements.

Today I would like to introduce study results obtained so far centering on vitamin C among the antioxidants.
First, as epidemiological evidence, Eichholzer et al. have shown that blood vitamin C levels below 0.5 mg/L increase the rates of deaths due to CVD. In addition, Nyyssonen et al. have shown in a study in Finnish people that low vitamin levels (<11.4μmol or <0.2mg/ml) are a risk factor for coronary heart disease.

The Western Electric Company Study reported the association between vitamin C intake and death rates. The study by Duffy et al. reported the effects of vitamin C on the treatment of hypertension (Figure 1).

Fig.1 Treatment of hypertension with vitamin C (Duffy et al Lancet 1999; 354, 2048-9)

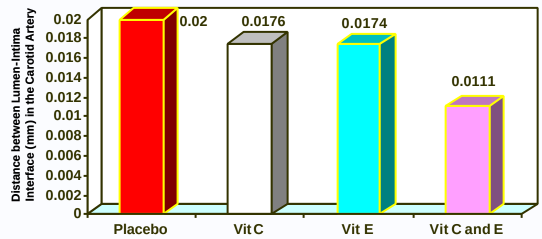


Mean BP decreased significantly; no effect on diastolic BP

45 patients with hypertension; 500 mg/day vitamin C over 30 days

Moreover, it has been shown that concurrent intake of vitamins C and E is more effective on the decrease in deaths due to coronary heart disease (Losonczy, 1996) and on slowing the progression of atherosclerosis (Figure 2).

Fig.2 Retardation of carotid atherosclerotic plaques progression by the combination of vitamins C and E in smokers (The ASAP Study)



Treatment: Vit C 500 mg/d; Vit E Acetate 200 mg/d; over 3 years; 500 hypercholesterolemic subjects
Salonen et al J Int Med 2000; 248: 377-386

As a result of these studies, it has been found that dietary habits have much to do with the prevention of lifestyle-related disease. In the future progress of societal aging, preventive measures by each person will be important. I would like you to recognize the roles of each nutrient and be careful to actively ingest antioxidative nutrients.

Reference: Nutrients and risk reduction of chronic disease

Health Condition	Nutrients (Strongest — Strength of Scientific Evidence — Weakest)
Bone Health (Osteoporosis)	Ca D K Isoflavones Mg C B_6
Circulatory (CHD)	E n-3 PUFA C, Folate B_6 B_{12}
Eye Health (Cataract/AMD)	E C Lutein/Zeaxanthin
Immune System	E B_{12} B_6 Zn
Cognition (Cognitive Impairment)	E Folate C Beta carotene B_{12} B_6
Metabolic Syndrome (Diabetes, Obesity, Aging)	C E n-3 PUFA Folate B_{12} B_6

Report on Committee of investigation for next revised RDA "Progress of Dietary Reference Intake"

Sponsor: Japanese Society of Nutrition and Food Science,
Committee of investigation for next revised RDA
(This committee was established by Japanese Society of Nutrition and Food Science in 2000)
Supporter: ILSI-Japan, Vitamin Information Center (Japan), Meiji Milk Products Co., Ltd.
Date: May.7 2001, Place: Kyoto International Hall, Japan
Speaker: Dr. Dietrich Hornig , F. Hoffman-La. Roche Ltd
Prof. Naotaka Hashizume, Toho University School of Medicine

Current Trends in the Recommendations for Vitamin Intake

Dietrich Hornig, Ph.D. F.Hoffmann-LaRoche Ltd

The first RDAs (Recommended Dietary Allowances) were published in 1943 by the National Research Council of the United States with the objective of "providing standards to serve as a goal for good nutrition in connection with national defense". Since then, the application of RDAs has broadened and now serves other purposes, for example in planning and procuring food supplies, in the interpretation of food consumption data, and as basis for nutritional labeling values.

Over the recent years, more scientific evidence regarding the role of vitamins has emerged and expert groups are reviewing these recommendations in many countries. The US Food and Nutrition Board has established a new approach in the assessment of requirement. It was mainly influenced by new scientific results from epidemiological, biochemical, and clinical studies as well as of studies with vitamins at the molecular level. This new concept represents a paradigm shift and indicates that nutrient requirement is no longer determined by avoidance of deficiency (indicated by clinical manifestation and status), but by its contribution to maximize health and to increase quality of life (determined by functional parameters including reduction of risk of chronic disease such as cardiovascular disease, cancer, eye disease, and osteoporosis). The DRIs (Dietary Reference Intake) values is to be understood as a collective term for the respective nutrient and is covering the range from avoidance of deficiency to its potential role in reducing risk of chronic disease. The new DRIs are the results of an extensive review of the overall knowledge base, with special emphasis on human data. DRIs are a set of up to four values: Estimated Average Requirement EAR, Recommended Dietary Allowance RDA, Estimated Average Intake AI, and Tolerable Upper Level of Intake UL. Their definitions are as follows:

Estimated Average Requirement EAR: a daily nutrient intake value that is estimated to meet the requirement of half the healthy *individuals* in a group.

Recommended Dietary Allowance RDA: the average daily dietary intake level that is sufficient to meet the nutrient requirement of nearly all (97 to 98 %) healthy *individuals* in a particular life stage (age, pregnancy, lactation) and gender group.

Adequate Intake AI: a recommended daily intake value based on observed or experimentally determined approximations of nutrient intake by a *group (or groups)* of healthy people that are assumed to be adequate. The AI is a goal for the nutrient intake of *individuals*. The AI can be considered as a surrogate to the RDA if the RDA cannot be determined due to lack of scientific data.

Tolerable Upper Intake Level UL: the highest level of daily nutrient intake that is likely to pose *no risk of adverse health effects* to almost all *individuals* in the general population. As intake increases above the UL, the risk of adverse effects increases.

Besides the USA, in several other countries new recommendations were recently published (Germany, Switzerland, Austria (D.A.CH.), France, Japan, China) and in others the evaluation is either still on-going or is in the process to be started (e.g. Australia, Netherlands, SEA countries, Nordic countries). Tolerable Upper Levels of Intake have so far only been assessed in the USA, Japan and China.

Reports on the most recent evaluations in Germany, Switzerland, Austria (D.A.CH.), France, Japan, China, Korea and the USA/Canada indicate:

- An increasing acceptance of the potential role of specific vitamins in the reduction of risk of chronic diseases, such as the role of vitamins C and E in cardiovascular disease, the reduction of risk of prostate cancer with vitamin E, and the role of B-vitamins (folate, vitamins B_6 and B_{12}) in the reduction of risk of cardiovascular disease mediated by homocysteine
- Increased recommendations for vitamin C: D.A.CH. (100 mg/day); France (110 mg/day); USA/Canada (75-90 mg/day); Japan (100 mg/day), Korea (70 mg/day), China (100 mg/day)
- Additional recommendations for vitamin C in smokers: D.A.CH. (plus 50 mg/day), France (plus 15 mg/day), USA/Canada (plus 35 mg/day
- An increase in the RDA for Vitamin E: USA/Canada (15 mg alpha-tocopherol/day); D.A.CH. (15 mg alpha-tocopherol equivalents/day); China (14 mg alpha-tocopherol equivalents/day)
- An increase in the RDA for folate: D.A.CH. and USA/Canada (to 400 μg folate/day); Korea (new 250 μg folate/day); China (new 400 μg folate/day)
- An increase in the recommendation for vitamin K (to 120/90 μg/day); China (new: 120 μg/day); Japan (new 65/55 μg/day)
- The recommendation for vitamin A was slightly reduced (USA/Canada: to 900/700 μg/day). Retinol activity equivalents were introduced with 12 μg of *dietary beta-carotene* from food sources to be equivalent to 1 μg retinol activity, or with 2 μg of beta-carotene in oil (*supplemental beta-carotene*) to be equivalent to 1 μg of retinol activity. Dietary provitamin A carotenoids other than beta-carotene (α-carotene; β-cryptoxanthin) require 24 μg to be equivalent to 1μg of retinol activity.
- Recommendation to cover part of the requirement as supplements (USA/Canada; D.A.CH.):
  - vitamin B_{12} in the elderly (USA/Canada: preferentially to be taken with fortified food or supplements; D.A.CH.: elderly with atrophic gastritis 100 μg/day as supplement)
  - additional folic acid as supplement (400 μg folic acid/day) to reduce the risk of neural tube defects in women of the childbearing age planning a pregnancy
- USA/Canada, Japan, and China have introduced tolerable upper levels of intake (UL) indicating total intake of a vitamin with food, fortified food, and food supplements which on long term intake

does not cause any adverse effects. D.A.CH. and Korea did not determine tolerable upper levels of intake, but commented on the safety of vitamins in the text.
- Japan and China have for the first time issued recommendations for all vitamins

The various RDA Committees have also elaborated on, which additional research would be required in order to be able to minimize the current gaps of knowledge and allowing a satisfactory assessment of the recommendations and the tolerable upper levels of intake of nutrients. Major research areas were identified:

- Studies to estimate average requirement in apparently healthy humans
- Studies on the nutrient needs of infants, children, adolescents, pregnant or lactating women
- Studies to accumulate more evidence on the role of nutrients in lowering the risk of certain chronic diseases including the validation of biomarkers
- Studies on the bioavailability of selected nutrients

Government authorities are now considering the incorporation of these new science-based recommendations into the legislatory framework by re-assessing the currently valid so-called labeling RDAs, that are the basis for the declaration of the vitamin content in fortified foods and food supplements. Within the European Commission's Scientific Committee on Food and the UK Ministry of Agriculture, Fisheries and Food, special expert working groups are currently evaluating the safety of vitamins and minerals. The final reports are expected to be published by end of this year containing respective Upper Tolerable Levels of Intake (UL) as basis for the legislation on food supplements and food fortification, and for labeling the nutrient content of these products.

Basic Idea and Problems in the Sixth Revision of the Japanese Recommended Dietary Allowance

Prof. Naotaka Hashizume, Toho University School of Medicine

Introduction

Recommended Dietary Allowance (RDA) is utilized in many situations including nutritional guidance and school lunch planning and is the basis for national health promotion and nutritional policies. It is an index for the promotion of people's health and the improvement of nutritional conditions, and many countries in the world have established their own RDA.

The Japanese RDA is reviewed and revised about every five years based on the following: changes in living conditions such as food supply and lifestyles; physical and medical conditions; and improvements in sciences such as medicine and nutritional science. Recently, the Ministry of Health and Welfare issued the Sixth Revision of the Japanese Recommended Dietary Allowance on June 23, 1999. (See 'The Sixth Revision of the Japanese Recommended Dietary Allowance – Dietary Reference Intakes', Daiichi-Shuppan, 1999.)

Basic Idea

The recent revision introduced a new concept, the "Dietary Reference Intakes", based on international trends. The Dietary Reference Intakes show standards for the intake of energy and nutrients for healthy people for the maintenance and promotion of health and the prevention of lifestyle-related disease.

Problems

The Japanese Society of Nutrition and Food Science has established the Dietary Reference Intakes Committee, and its subcommittee chairmen have given their proposals on the problems in the Sixth Revision of the Japanese Nutritional Requirements. The following are the vitamin-related problems which remain to be examined in the future:

1) Isn't the Tolerable Upper Intake Level (UL) for vitamin A too low?
2) While the vitamin D allowance for a Japanese adult is 2.5 ? g, that for a U.S. adult is 5 ? g, taking into consideration the prevention of osteoporosis. Isn't the Japanese allowance too small?
3) The folic acid allowance for a Japanese adult is 200 ? g, while that for a U.S. adult is 400 ? g. The reason for the U.S. allowance is that keeping down the levels of homocysteine in the blood, which is a risk factor for arteriosclerosis, requires 400 ? g of folic acid. The low Japanese allowance has been criticized by the U.S. and Germany.
4) The U.S. RDA of vitamin C reported in May of 2000 says the allowance for a male adult is 90 mg and that for a female adult is 75 mg, and the UL is 2000 mg. The Japanese version says 100 mg regardless of sex and there is no UL. The Japanese RDA is calculated from Estimated Average Requirements, which is not used in the calculation of the U.S. version. International discussion is necessary.
5) Nutrients in breast milk are calculated based on 750 mg in the Sixth Revision, while that in the Fifth Revision was calculated based on 850 mg. Isn't it necessary for Japan to re-examine the vitamin contents in breast milk?

Reference) Supplement Advisor system

Our dietary habits have much influence on the recent prevalence of lifestyle-related disease. Therefore, many people are looking for foods effective in health maintenance and disease prevention. However, the information on so-called health foods conveyed every day by mass media including television, newspaper and magazines does not include sufficient basic information on the effects of the foods, such as their scientific foundation, generality, safety and relationship with medical drugs. Under current circumstances, consumers cannot help being confused by individual pieces of information. In addition, supplements are considered "medical foods" which are between foods and medicines. Therefore, they are effective but side effects cannot be overlooked. It thus became necessary to establish an organization to provide information on supplements and a system to provide qualified specialists.

Both food manufacturers and pharmaceutical companies are involved in supplements. Therefore, the Japanese Association of Clinical Nutrition, which is a non-profit organization, was put in charge of establishing the Japanese Supplement Advisor Accreditation System.

1. **Objective and Roles**

The purpose of the supplement advisor system is to educate consumers. Supplement advisors are merely one component for this plan but are indispensable for the future education of the general public. Consumers must be responsible for their own use of supplements, but with today's scattered information it is difficult to make a correct decision. The role of supplement advisors is thus to help consumers with making a fair, correct decision. Supplement advisors must therefore acquire knowledge and technique to make fair, correct decisions for themselves.

2. Educational Program for Supplement Advisors

Although there will be some difference between centers, the program will be categorized by required subjects including knowledge on clinical nutrition, food safety, information and laws and regulations on supplements, and optional subjects on basic knowledge.

3. Keys to Accreditation

An examination system is necessary in order to insure the quality of supplement advisors. The examination must be fair and hold good for the rest of the world as well. In addition, in order to keep up with the progress of science even after passing the exam, a renewal system is also necessary.

Dietary Lutein/Zeaxanthin and AMD

(The Eye Disease Case-Control Study: Seddon et.al, JAMA 1994; 272: 1413-1420)

Objective

To evaluate the relationship between dietary intake of carotenoids and risk of AMD(age-related macular degeneration)

Subjects:

AMD patients 356; average age 71 years old (range, 55 to 80 years old)
Control 520; average age 68 years old (range, 55 to 80 years old)

Method

The relative risk for AMD was estimated according to dietary indicators of antioxidant status, controlling for smoking and other risk factors, by using multiple logistic-regression, analyses.

Results

Higher levels of carotenoid intake ware associated with a reduced risk for exudative neovascular AMD. Controlling for other potential risk factors, we estimated the risk for AMD to be reduced by 43% among people whose consumption of dietary carotenoids placed them in the highest quintile of dietary catotenoid intake compared with those in the lowest quintile (OR, 0.57; 95% CI, 0.35 to 0.92; P for trend=0.02).

When carotenoid fractions were evaluated separately, beta carotene and lutein/zeaxanthin were associated with a statistically significant trend for reduction in risk for AMD with higher intake (Table.1).

The inverse trend associated with lutein/zeaxanthin intake (lower risk for AMD with higher intake) was seen for all categories of smoking (Fig.1). We found that persons in the high-risk group (low quintile of intake, current smoker) had almost a six fold elevated risk for AMD compared with persons in the low-risk group (high quintile of intake, nonsmoker)

Table1. Odds ratios for Exudative AMD by Quintile of Nutrient Intake

Nutrient		Quintiles				
		1	2	3	4	5
α-carotene	Median intake(IU)	152.5	303.3	499.8	1085	1830
	Odds Ratio	1.0	0.94	0.67	0.64	0.69
β-carotene	Median intake(IU)	1143	1997	3094	4728	8053
	Odds Ratio	1.0	0.79	0.78	0.65	0.51
β-cryptoxanthin	Median intake(IU)	17.44	51.12	76.37	118.58	224
	Odds Ratio	1.0	0.71	0.93	0.74	0.65
Lycopene	Median intake(IU)	217.7	509.4	1367	1837	3450
	Odds Ratio	1.0	0.94	0.61	0.64	1.06
Lutein/Zeaxanthin	Median intake(IU)	560.8	1211	1708	2487	5757
	Odds Ratio	1.0	1.14	0.82	0.74	0.40

*Adjusted for age and sex

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Fig.2 Odds ratios for age-related macular degeneration