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JOURNAL OF THE AMERICAN HEART ASSOCIATION

Nutrition and Stroke Prevention

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Stroke 2006;37;2430-2435; originally published online Jul 27, 2006;

DOI: 10.1161/01.STR.0000236633.40160.ee

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ISSN: 1524-4628

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Nutrition and Stroke Prevention

J. David Spence, MD, FRCPC

Abstract—Nutrition is much more important in prevention of stroke than is appreciated by most physicians. The powerful effects of statin drugs in lowering the levels of fasting cholesterol, combined with an unbalanced focus on fasting lipids (as opposed to postprandial fat and oxidative stress), have led many physicians and patients to believe that diet is relatively unimportant. Because the statins can lower fasting lipids by $\approx 50\%$ to 60% , and a low-fat diet only lowers fasting cholesterol by $\approx 5\%$ to 10% , this error is perhaps understandable. However, a Cretan Mediterranean diet, which is high in beneficial oils, whole grains, fruits, and vegetables and low in cholesterol and animal fat, has been shown to reduce stroke and myocardial infarction by 60% in 4 years compared with the American Heart Association diet. This effect is twice that of simvastatin in the Scandinavian Simvastatin Survival Study: a reduction of myocardial infarction by 40% in 6 years. Vitamins for lowering of homocysteine may yet be shown to be beneficial for reduction of stroke; a key issue is the high prevalence of unrecognized deficiency of vitamin B₁₂, requiring higher doses of vitamin B₁₂ than have been used in clinical trials to date. Efforts to duplicate with supplementation the evidence of benefit for vitamins E, C, and beta carotene have been largely fruitless. This may be related to the broad combination of antioxidants included in a healthy diet. A Cretan Mediterranean diet is probably more effective because it provides a wide range of antioxidants from fruits and vegetables of all colors. (*Stroke*. 2006;37:2430-2435.)

Key Words: diet ■ nutrition ■ prevention ■ stroke ■ vitamins

Nutrition is much more important in prevention of stroke than is appreciated by most physicians and, paradoxically, perhaps even by most nutritionists. Current issues that warrant discussion in this venue include the intake of animal fat and cholesterol, the Cretan Mediterranean diet, the failure of most studies to show benefit of supplements with antioxidant vitamins such as vitamins E and C, and the current controversy over failure of recent clinical trials to show reduction of stroke and other cardiovascular events by lowering plasma total homocysteine with folate, B₆, and B₁₂. A key issue is the recent recognition that vitamin B₁₂ deficiency is much more common in the elderly than is commonly appreciated, and therefore higher doses of B₁₂, and possibly additional therapies to lower homocysteine, may be required to achieve adequate reductions of total homocysteine.

Cholesterol and Animal Fat

The powerful effects of statin drugs in lowering of fasting cholesterol have seduced many patients and physicians into believing that diet is relatively unimportant: Why bother with a low-fat diet, which only lowers fasting cholesterol by $\approx 5\%$ to 10% ,¹ when a pill can reduce fasting cholesterol by 50% ?²

The reason that diet is still very important is that the blinkered focus on fasting lipids is inappropriate. Cholesterol is measured in the fasting state to minimize variability of the measurement; however, human beings are only in the fasting state for the last few hours of the night. What affects the endothelium for ≈ 18 hours of the day is the postprandial levels of lipids, cholesterol, oxidized cholesterol, and oxidative stress that follow meals containing trans fats, animal fat,³ or glucose.⁴ Diet is therefore much more important than would be predicted by effects on fasting lipids.⁵

A key problem with current dietary recommendations in North America is a failure to distinguish between kinds of fat and between red meat and poultry and fish. The mantra that “fat is bad” has led to a reduction of fat intake and a corresponding increase in carbohydrate intake, with harmful effects on cardiovascular disease and stroke risk.⁶ Willett and Stampfer⁷ indicate in an important review that standard dietary recommendations for low intake of fat arose from thin air, driven by a misplaced desire to simplify, and need to be corrected.

There is increasing evidence that postprandial fats and oxidative stress are as important or more important than fasting lipids.^{8,9} A high-fat meal impairs endothelial function for several

Received May 26, 2006; accepted June 5, 2006.

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Stroke is available at <http://www.strokeaha.org>

DOI: 10.1161/01.STR.0000236633.40160.ee

hours,¹⁰ and this effect can be mitigated by pretreatment with vitamins C and E,¹¹ indicating that oxidative stress from free radicals is an important contributor to the endothelial dysfunction from high-fat meals.

Carluccio et al¹² found a direct antiatherosclerotic effect of oleic acid in endothelial cells. Tsimikas et al¹³ showed that subjects consuming an American diet had monocyte adhesion and chemotaxis induced by LDL, in contrast to subjects on a normal Greek diet. This effect could be reversed by oleic acid supplementation in subjects on the American diet.

Dietary intake of cholesterol probably is important. The National Cholesterol Education Program (NCEP) dietary guidelines specified a daily cholesterol intake <300 mg/d for low-risk and <200 mg/d for high-risk vascular disease candidates.¹⁴ A single egg yolk contains 275 mg of cholesterol, as much as an 8-ounce steak, and therefore it is difficult to understand how dietitians in our vascular wards can continue to advise patients that an intake of 3 eggs per week is acceptable. There is evidence that egg yolks should not be consumed by patients at risk of vascular disease.

Ginsberg et al¹⁵ showed a dose-response relationship between intake of eggs and increases in plasma cholesterol. Hu et al found that in diabetics, a group with a level of vascular risk equivalent to that of coronary survivors,¹⁶ consumption of 1 egg per day was associated with a doubling of coronary risk compared with <1 egg per week.¹⁷ It may be that this relates to dietary intake of oxidized cholesterol. Levy et al¹⁸ showed that an egg per day only raises levels of LDL cholesterol by 10% but increased LDL oxidation by 34%.

In the Indo-Mediterranean Diet Study, discussed below, the intake of cholesterol in the intervention arm was only 125 mg/d. A single egg yolk thus contains more than twice the daily intake of cholesterol achieved in that diet; so does an 8-ounce steak. A diet suitable for patients with vascular disease should therefore include no egg yolks and much less animal flesh, of any color, than North Americans are used to consuming. (The cholesterol content of all kinds of animal flesh is very similar; the emphasis on avoidance of red meat is based on the effects on fasting lipids of saturated fat, which is higher in red meat.)

Benefits of a Mediterranean Diet

The Ornish regression diet, together with other lifestyle changes, has been shown to regress coronary disease.¹⁹ However, it is very difficult for patients to persist with it. Among >16 000 patients with vascular disease that I have followed, only 2 were able to persist with the Ornish diet. A more palatable and acceptable diet is a Mediterranean diet, which is high in beneficial oils (from olive, canola, and fish), high in vitamins and antioxidants, and low in cholesterol, trans fats, and harmful animal fat. A recent Japanese prospective study with 477 325 person-years of follow-up showed a 37% reduction of coronary disease when the highest versus lowest quartiles of fish intake were compared.²⁰

A Mediterranean diet has been shown to improve endothelial function in hyperlipidemic men,²¹ perhaps in part because it reduces plasma lipid peroxidation.²² Vogel et al²³ found that the components of a Mediterranean diet that were responsible for this benefit appeared to be antioxidant-rich foods, including

vegetables, fruits, balsamic vinegar, and omega-3-rich fish and canola oil.

There is epidemiological evidence that people who follow a Mediterranean diet are at much lower risk of cardiovascular events.^{24,25} A Mediterranean diet has also been shown to improve endothelial function and reduce insulin resistance.²⁶

More importantly, there is strong evidence from randomized clinical trials that a Cretan Mediterranean diet is much more effective at reducing vascular events than the diet recommended by the NCEP and the American Heart Association.

Clinical Trials With the Cretan Mediterranean Diet

Two important studies have shown that a Mediterranean diet significantly reduced vascular events compared with a usual Western diet.

In the Lyon Diet Heart Study, 423 survivors of myocardial infarction (MI) were randomized to a "prudent Western diet" amounting to a Step 1 NCEP diet¹⁴ or to a Mediterranean diet from Crete. This diet was low in cholesterol, low in animal fat, and high in olive oil, canola oil, fruits, and vegetables; canola margarine was substituted for butter. The proportion of calories from fat was the same ($\approx 30\%$) in the 2 diets, but the Mediterranean diet provided a significant reduction in dietary cholesterol and a significant increase of beneficial oils such as α -linolenic acid as opposed to the animal fats of the prudent Western diet. The patients assigned to the Mediterranean diet²⁷ had a 60% reduction in cardiac death and MI over 4 years ($P=0.0001$) compared with the prudent Western diet. Importantly, there was no difference in alcohol consumption between the 2 diets.

This reduction in MI and death was twice that achieved by simvastatin in the Scandinavian Simvastatin Survival Study (a reduction of coronary risk by 40% over 6 years).²⁸ Importantly, this benefit was achieved without any difference in fasting lipids between the 2 groups. It seems very likely that the benefit was attributable to reduction of postprandial fat, as well as the increased intake of antioxidants and other beneficial constituents of the Mediterranean diet. Whole grains, in addition to antioxidants and fiber, contain phytoestrogens, which may have beneficial effects on arteries.²⁹ Flax lignans, for example, are potent phytoestrogens.³⁰

These results have been replicated in a study of 1000 patients with coronary artery disease in India. Even though 60% of patients were already vegetarian, a Mediterranean version of the Indian diet reduced coronary and stroke events by half in 2 years, compared with an Indian version of a NCEP Step II diet.³¹ This was achieved by substituting beneficial oils such as mustard oil or soya oil for harmful fats, with an increase of fruits, vegetables, walnuts, almonds, and whole grains, and a reduction of cholesterol intake to 125 mg/d. Although there has been some concern about the validity of the Indo-Mediterranean diet study,³² an investigation by Berry indicated that despite some problems with record keeping, the results did not appear to be fabricated.³³

Beneficial Effects of Antioxidant Vitamins?

A single high-fat meal has been shown to impair endothelial function for several hours,¹⁰ and this effect can be reduced by

pretreatment with vitamins C and E.¹¹ A Mediterranean diet has been shown to improve endothelial function in hyperlipidemic men.²¹ A Mediterranean diet has a higher content of antioxidants and significantly lower indices of plasma lipid peroxidation.²² Vogel et al²³ studied the effect of components of the Mediterranean diet on endothelial function and found that the beneficial components appeared to be antioxidant-rich foods, including vegetables, fruits, balsamic vinegar, and omega-3-rich fish and canola oil.

Antioxidant vitamins may reduce vascular disease by reducing harmful effects of free radicals.^{34,35} Oxidation of LDL is thought to be important in atherosclerosis because oxidized LDL is chemotactic to monocytes, stimulates binding of monocytes to the endothelium, traps monocytes in the subendothelial space, and is cytotoxic to vascular cells; it is actively taken up by scavenger receptors on macrophages in the subintima to form foam cells.³⁶ Antioxidants such as probucol and various dietary antioxidants are antiatherosclerotic in animal models and human angiographic studies,³⁷ and epidemiological evidence indicates that high intake and high blood levels of antioxidants, particularly vitamin E, may be protective.^{36,38}

A clinical trial in coronary patients showed reduced vascular death and nonfatal coronary events, although cardiovascular mortality was not reduced.³⁹ In the Womens' Health Initiative study, vitamin E had no beneficial effects.⁴⁰ Meta-analysis showed no benefit, and possible harm, from high-dose supplements of vitamin E.⁴¹ In the Heart Outcomes Prevention Evaluation (HOPE) trial, vitamin E had no bene-

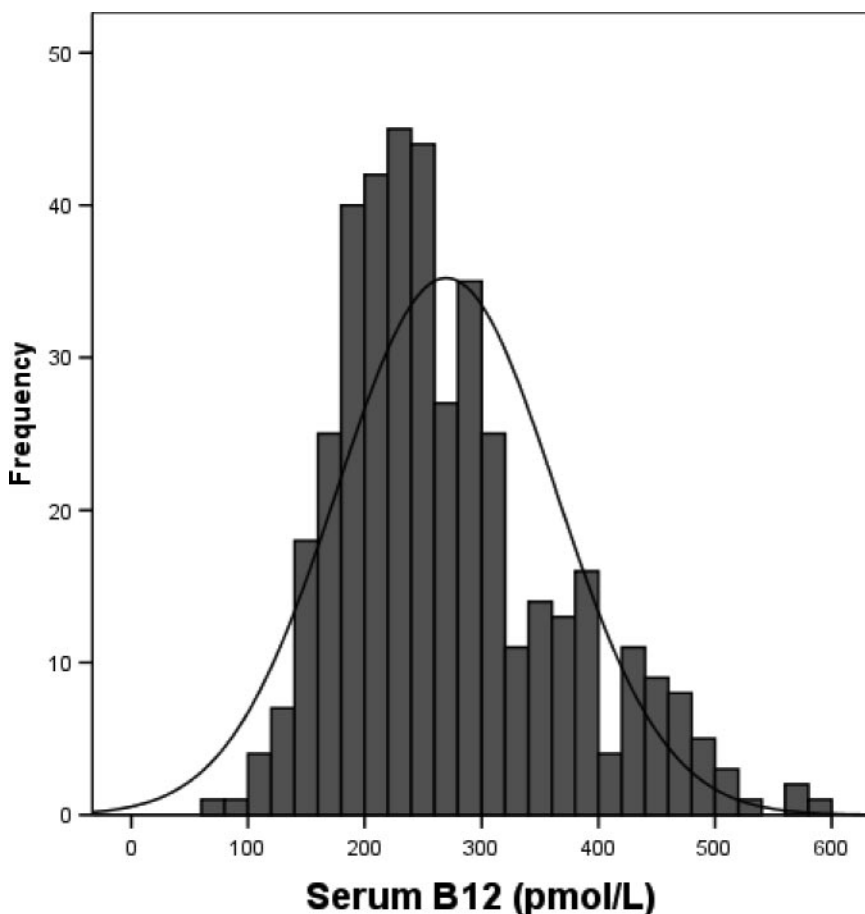
ficial effects and appeared to increase the risk of heart failure.⁴² A recent pooled analysis of vitamins and antioxidants showed a small cardiovascular benefit of vitamin C.⁴³ Confusion in this area may result from the need to combine vitamins: vitamin E forms the tocopheryl radical, which may require detoxification by other antioxidants such as vitamin C; Salonen et al⁴⁴ hypothesized that this effect accounted for their finding of reduced progression of intima-media thickness by combined vitamin E and slow-release vitamin C.

This point raises a general principle that a diet high in antioxidant vitamins may be more beneficial than taking supplementary vitamins and antioxidants because of the combined effects of antioxidants.⁴⁵ Fruits and vegetables often get their color and flavor from antioxidants: beta carotene in carrots; lycopene in tomatoes, strawberries, and watermelon; resveratrol in grape juice and red wine; and anthocyanins in blueberries. Naringin is the color and flavor of grapefruit; naringin is similar to hesperitin from orange juice and genistein from soy; all of these have beneficial anticancer effects and potential cardiovascular benefits.⁴⁶⁻⁴⁸ A useful slogan in this regard is that "we should eat fruits and vegetables of all colors."

An exception to this principle may be the use of B vitamins for lowering of homocysteine.

B Vitamins for Lowering of Homocysteine

Despite recent reports of studies showing no reduction of stroke or MI by vitamin therapy for lowering of plasma total homocysteine,⁴⁹⁻⁵¹ it may be too early to discard the hypoth-



Serum B₁₂ levels in a stroke prevention clinic.

esis that treatment with folate, vitamin B₆, and vitamin B₁₂ may reduce stroke and other cardiovascular events. Indeed, the HOPE-2 trial showed a significant reduction of stroke and acute coronary syndrome. There is a strong, independent, and graded risk of elevated total homocysteine,^{52,53} and many mechanisms provide a strong rationale for lowering of homocysteine: High levels of total homocysteine increase thrombosis,⁵⁴ impair endothelial function,^{55–57} and increase oxidative stress.^{58–60} Treatment to lower total homocysteine with folate, B₆, and B₁₂ reverses many of these effects and has other benefits, including reducing Lp(a) and fibrinogen,⁶¹ halting the progression of carotid plaque in patients whose plaque was progressing despite treatment of traditional risk factors,^{62,63} reducing progression of peripheral vascular disease,⁶⁴ and, in 1 study, reducing restenosis in coronary angioplasty.⁶⁵ A contrary study, which did not show benefit of vitamin therapy in coronary angioplasty, used a much smaller dose of B₁₂ (40 versus 400 µg/d).⁶⁶

This discrepancy raises the issue of unrecognized deficiency of vitamin B₁₂ in the elderly and its relationship to failure of B vitamin therapy in lowering of homocysteine. The Vitamin Intervention for Stroke Prevention (VISP) trial, which showed no reduction of stroke, coronary events, or vascular death in a comparison of high-dose vitamins with low-dose vitamins, faced a number of challenges. Folate fortification of grain products in North America coincided with the start of the trial, and in the face of folate fortification, the key determinant of plasma homocysteine is vitamin B₁₂.⁶⁷ Both treatment arms received a multiple vitamin tablet containing the usual doses of many vitamins, with either a low or high dose of folate, B₆, and B₁₂. Unfortunately, the low-dose arm received the recommended daily intake of B₁₂ (6 µg), and the high-dose arm received only 400 µg of B₁₂. We thought that we were using a generous dose of B₁₂ in the high-dose arm, but a subsequent dose-response study in people aged >65 years with serum B₁₂ <212 pmol/L showed that elderly subjects require much higher doses, of 1000 µg/d or more.⁶⁸ In both treatment arms, patients with low levels of B₁₂ received injections of B₁₂ to avoid subacute combined degeneration of the spinal cord.

In a recent efficacy analysis of the VISP trial, patients capable of responding to the study vitamin were found to have a significant reduction of stroke, death, and coronary disease, and B₁₂ status at the beginning of the trial was a significant determinant of response.⁶⁹

Vitamin B₁₂ deficiency is much more common in the elderly than is usually recognized because many factors are involved in absorption of B₁₂, all of which may go wrong. The conceptual problem for many physicians is the meaning of the word *normal*. Most biochemistry laboratories report a “normal” or “reference” range based on the mean ±2 SD. Thus, by definition, only the top 2.5% and the bottom 2.5% of the population are abnormal. This statistical definition of normality results in a “normal” range for serum B₁₂ of ≈160 to 600 pmol/L, and most physicians think that if the serum B₁₂ level is in the normal range, then it is adequate. However, when adequacy of B₁₂ is assessed in metabolic terms, ie, the level of B₁₂ sufficient to prevent an elevation of methylmalonic acid >271 nmol/L or homocysteine >14 µmol/L in folate-replete patients, then a much higher proportion of the

population is identified as deficient in B₁₂. In the Framingham Study, 40% of the elderly had B₁₂ levels <258 pmol/L, and 12% were B₁₂ deficient. Andres et al⁷⁰ found that 20% of the elderly are B₁₂ deficient. In my Stroke Prevention Clinic, the “normal” range is substantially lower than in a general population (Figure). A previously unpublished analysis of the database used for the study by Robertson et al⁶⁷ from our clinic revealed a prevalence of B₁₂ deficiency defined metabolically as above, by tertiles of age, of 12% below age 50 years, 13% between ages 50 and 71 years, and 30% at age 71 years or older.

To successfully reduce total homocysteine to sufficiently low targets may, in the future, require higher doses of B₁₂. As suggested by Loscalzo,⁷¹ it may also require other therapies. Promising candidates include betaine⁷² and thiols.^{73–75}

Conclusion

Diet is much more important for stroke prevention and B₁₂ deficiency is much more common in the elderly than is commonly realized. Patients at risk of stroke should consume a Cretan Mediterranean diet, avoid egg yolks, eat less animal flesh than do most North Americans, and require higher doses of B₁₂, and in the future they may benefit from improved therapies to lower levels of total homocysteine.

Disclosures

None.

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