B Vitamins and Antioxidants Intake is Negatively Correlated with Risk of Stroke in Iran

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Original Article

ABSTRACT

Background: Stroke is a leading cause of death in developed countries. However, current therapeutic strategies for stroke have been largely unsuccessful. Several studies have reported important benefits on reducing the risk of stroke and improving the post-stroke-associated functional declines in patients who ate foods rich in micronutrients, including B vitamins. Folic acid, vitamin B6, and vitamin B12 are all cofactors in homocysteine metabolism. Growing interest has been paid to hyperhomocyste inemia as a risk factor for stroke. Experimental studies suggest that oxidative stress plays an important role in the pathogenesis of ischemic cerebral injury, and higher intake of antioxidants has been associated with a lower risk of stroke in large population studies. The aim of this study was to examine whether the dietary intake of B vitamins and antioxidants in patients with stroke were comparatively worse than those in patients without stroke.

Methods: In this case control study, 69 stroke patients (46 male, age = 56 ± 18 years and 23 female, age = 52 ± 7 years) admitted to Azzahra hospital between April 2009 and May 2010 were matched for age and sex with 60 patients (30 male and 30 female) from the same hospital who were not affected with acute cerebrovascular diseases and did not have a history of stroke. Dietary intake was assessed with a validated self-administered food frequency questionnaire (FFQ). FFQ was collected conducting face-to-face interview with one of the patients' close relatives. Food intakes, translated into nutrient data, were compared between the two groups and with the recommended values.

Results: Intake of folic acid in men with stroke and vitamin B12 in women with stroke was significantly lower than that in the patients without stroke ($P < 0.05$), but there was no significant difference between the two groups in the level of antioxidant consumption in women and men ($P > 0.05$).

Conclusions: Our findings suggest that increased folic acid, vitamin B12, and vitamin E, C intake may be associated with decreased risk of stroke.

Keywords: Dietary quality, folic acid, stroke, vitamin B6, vitamin B12

INTRODUCTION

According to the World Health Organization, stroke and other cerebrovascular diseases are the second highest causes of mortality worldwide at 9.7% of the total mortality rate.[1] Over 85% of these deaths occur in low- and middle-income-rated countries.[2] Stroke is a major public health problem in developing countries.[3] According to a recent well-designed population-based study in Mashhad, Iran, incidence of stroke in Iran is considerably higher than in most Western countries.[4]

Risk factors associated with stroke have been divided into two main categories nonmodifiable and modifiable. Advanced age, sex, race, and genetic susceptibility are the most prominent nonmodifiable risk factors, whereas lifestyle risk factors such as diet, exercise, and use of tobacco and alcohol are considered modifiable risk factors.[5] An increase has been observed in the number of cerebrovascular events in developing countries that matches with the food and lifestyle changes arising from industrialization and urbanization.[6]

The deficiency of B vitamins and antioxidant vitamins E and/or C appears to be associated with stroke.[7,8] For example, folic acid in the 5-methyltetrahydrofolate form is a cosubstrate required by methionine synthetase to convert homocysteine (Hcy) to methionine; consequently, Hcy accumulates when folic acid is low.[9,10] High Hcy is strongly associated with atherosclerotic vascular disease and stroke.[11,12] Vitamin B12 is also required for methionine synthesis from Hcy.[12] Vitamin B6 may also contribute to increase the levels of Hcy.[12] Giles *et al.*, found that in a representative sample of US adults, Hcy concentration was independently associated with an increased likelihood of nonfatal stroke, and this association was present in both black and white adults.[13]

Experimental studies suggest that oxidative stress plays an important role in the pathogenesis of ischemic cerebral injury and evidence is mounting that systemic inflammation is involved in stroke etiology and pathology.[14] Several compounds in fruits and vegetables have been found to reduce inflammation and oxidative stress.[15] In addition, higher intake of antioxidants has been associated with a lower risk of stroke in a large population study.[16] Among the 87,245 US female registered nurses, aged 34-59 years, higher antioxidant vitamin consumption was associated with a reduced risk of ischemic stroke.[17] In addition, high consumption of cruciferous vegetables and citrus fruit juices reduced the risk of stroke.[18] A study of the intake of antioxidants and the risk of stroke provides evidence that vitamin E might be of value in reducing the risk of stroke.[19] An inverse association was seen between death from stroke and vitamin E intake from food, thus supporting a protective role of vitamin E.[19]

Accurately assessing and understanding the role of nutrition in the causes and consequences of stroke will be crucial in developing and implementing strategies to minimize the global burden of stroke, so the objective of this study was to determine whether there was a significant difference in vitamins intake between stroke patients and controls or not.

METHODS

In this case-control study, 69 stroke patients (46 male, age = 56 ± 18 years and 23 female, age = 52 ± 7 years) admitted to Azzahra hospital between April 2009 and May 2010 were matched for age and sex with 60 patients (30 male and 30 female) from the same hospital who were not affected with acute cerebrovascular diseases and did not have a history of stroke. Informed consent was obtained from all the stroke patients or their proxies and from all healthy controls.

Dietary intake was assessed with a validated self-administered FFQ that included 168 food items and mixed dishes commonly consumed in Iran. FFQ was collected conducting face-to-face interview with one of the patients' close relatives. It was used with a portion-size color picture booklet of 122 photographs of foods, each with three to five different portion sizes. Participants were asked to report their average consumption and portion size for each food/dish during the previous year. Frequencies were reported as the number of times per month, week, or day. A dietitian provided verbal and written instruction on how to record food consumption. Intake of nutrients was calculated using the food composition database.

FFQ categorized the food items into six food groups: (1) mixed dishes (cooked or canned); (2) grains (different types of bread, cakes, biscuits, and potatoes); (3) dairy products (dairies, butter,

and cream); (4) fruits and vegetables; (5) meat and protein (meat, fish, turkey, legume, and eggs); and (6) miscellaneous food items and beverages (sweets, fast foods, nuts, desserts, and beverages).

The statistics in this study were done by SPSS (version 16.0) software. Results are expressed as mean ± SD. Student's *t*-tests were performed to compare the means of the two groups. Statistical significance was defined as $P < 0.05$.

RESULTS

Male

Age, waist, body mass index, and waist-to hip ratio in stroke patients are shown in Table 1. The mean daily intake of vitamin B12, riboflavin, thiamin, and niacin and folic acid was 1.6 ± 1.2 µg, 2.2 ± 1.3 mg, 1.8 ± 1.1 mg, 19.5 ± 4.2 mg, 285 ± 155 µg, respectively [Table 2]. Mean daily intake of folic acid and vitamin B12 was lower than recommended dietary allowances (RDA; 67% ± 50, 71 ± 39, respectively) but mean daily intake of thiamin, riboflavin and niacin was higher than RDA (150% ± 92, 170% ± 100, 122% ± 26). On the other hand, there was no significant difference between the two groups in the levels of vitamin B12, riboflavin, thiamin and niacin consumption ($P > 0.05$). Intake of folic acid in men with stroke was significantly lower than that in men without stroke ($P < 0.05$).

The median daily intakes of vitamin C and vitamin E were 68 mg and 13.5 mg, respectively and were lower than RDA (vitamin E 90% and vitamin C 76%), but there was no significant difference between two groups in level of antioxidant consumption ($P < 0.05$).

Table 1: General characteristics of the subjects

Age (year)	WHR	Waist (cm)	BMI (kg/m^2)
52±7	0.9±0.1	92±8	25.5±3.5

WHR=Waist to hip ratio, BMI=Body mass index

Female

Mean daily intake of thiamin, riboflavin, niacin, folic acid and vitamin B12 was 1.3 ± 1.2 mg, 1.4 ± 1.3 mg, 12.7 ± 4.8 mg, 320 ± 44 µg, 1.1 ± 0.8 µg, respectively. Mean daily intake of folic acid, vitamin B12 and niacin was lower than RDA (80% ± 11, 46% ± 33, and 72 ± 34, respectively), but mean daily intake of thiamin and riboflavin was higher than RDA (118% ± 109 and 127% ± 109). On the other hand, there was no significant difference between two groups in levels of folic acid, riboflavin, thiamin and niacin consumption ($P > 0.05$). Intake of vitamin B12 in women with stroke was significantly lower than that in women without stroke ($P < 0.05$).

The median daily intakes of antioxidants were the following: Vitamin C 83 mg and vitamin E 11.7 mg and the mean daily intakes of antioxidant were lower than RDA (vitamin E 78% and vitamin C 83%). There was no significant difference between two groups in level of antioxidant consumption ($P < 0.05$) [Table 3].

DISCUSSION

This is the first study to investigate the diet quality of patients with cerebral injury in Iran. This study revealed that patients with cerebral injury had lower dietary quality than patients without cerebral injury.

The results from this study reveal mean daily intake of folic acid and vitamin B12 in men was lower than RDA (67% ± 50, 76% ± 40, respectively) and daily intake of folic acid, vitamin B12, and niacin in women was lower than RDA (80% ± 11, 46% ± 33, and 72 ± 34, respectively).

Vitamin B12 and folic acid are the key mediators of Hcy metabolism. Low plasma vitamin B12

Table 2: Mean daily selected vitamins intake compared with RDA in men

Vitamins	Men with stroke	RDA	RDA%	*P* value	Men without stroke	*P* value
Thiamin (mg/day)	1.8±1.1	1.2	150±92	0.07	1.5±1.3	0.9
Riboflavin (mg/day)	2.2±1.3	1.3	170±100	0.1	1.9±0.8	0.85
Niacin (mg/day)	19.5±4.2	16	122±26	0.13	15.5±3.4	0.05
Folic acid (µg/d)	285±155	400	71±39	0.03	340±195	0.03
Cobalamin (µg/d)	1.6±1.2	2.4	67±50	0.05	1.8±1.7	0.9
Ascorbic acid (mg/day)	68±36	90	79±40	0.06	84±55	0.8
Vitamin E (mg/day)	13.5±7.5	15	90±50	0.25	12.7±4.5	0.9

RDA=Recommended dietary allowances

Table 3: Mean daily selected micronutrient intake compared with RDA in women

Vitamins	Women with stroke	RDA	RDA%	*P* value	Women without stroke	*P* value
Thiamin (mg/day)	1.3±1.2	1.1	118±109	0.2	1.2±1.1	0.7
Riboflavin (mg/day)	1.4±1.2	1.1	127±109	0.1	1.1±0.9	0.3
Niacin (mg/day)	12.7±4.8	14	72±34	0.09	10.5±3.2	0.08
Folic acid (µg/d)	320±44	400	80±11	0.04	355±70	0.09
Cobalamin (µg/d)	1.1±0.8	2.4	46±33	0.01	1.6±1.3	0.04
Ascorbic acid (mg/day)	62±29	75	83±39	0.05	64±25	0.9
Vitamin E (mg/day)	11.7±3.5	15	78±23	0.03	10.5±4.2	0.4

RDA=Recommended dietary allowances

and folic acid concentrations are associated with hyperhomocysteinemia.[20,21] In a meta-analysis of observational studies, a 25% reduction in Hcy concentrations (roughly 3 µmol/L [0.41 mg/L]) corresponded with an 11% lower risk of ischemic heart disease and a 19% lower risk of stroke.[22] One meta-analysis suggested a benefit of vitamin-B supplementation when it was given for a longer duration (>36 months), led to a greater than 20% reduction in Hcy levels.[23] Plasma Hcy is very responsive to intervention with B vitamins required for its metabolism: Folic acid, vitamin B12, and to a lesser extent, vitamin B6, and riboflavin.[24,25] Previous studies showed that intake of folic acid between 300 µg and 821 µg reduced the risk of stroke.[26-28] Park *et al.*, also observed a 90% stroke risk reduction in subjects with daily folic acid intake of more than 412 µg.[29] In addition, intakes of vitamin B6, riboflavin, and niacin were negatively associated with the risk of stroke in the present study. There is growing evidence that niacin inhibits vascular inflammation by decreasing endothelial reactive oxygen species production and subsequent LDL oxidation and inflammatory cytokine production, key events involved in atherogenesis.[30]

Larsson *et al.*, showed during a mean follow-up of 13.6 years (360,187 person-years) that dietary folic acid intake was statistically significantly inversely associated with the risk of stroke after adjustment for age and supplementation group and, in multivariate models, further adjusted for cigarettes/day, body mass index, systolic and diastolic blood pressure, serum total and HDL cholesterol, histories of diabetes and coronary heart disease, leisure-time physical activity, and alcohol and total energy intakes.[31]

Our results also show mean daily intake of vitamin C and vitamin E in men and women were lower than RDA (79% ± 40 and 90 ± 50% in men and 83 ± 39 and 78 ± 23, respectively), but there was no significant difference between the two groups in the level of antioxidant consumption.

Vitamins E and C have been investigated in a large number of epidemiological, clinical, and experimental studies.[32,33] Antioxidant nutrients have important roles in cell function and have been implicated in processes associated with ageing, including vascular, inflammatory, and neurological damage. The evidence regarding the link between vitamin E deficiency and neurological sequelae in man is now firmly established. That several neuropathological observations are associated with vitamin E deficiency indicates the importance of this nutrient in the central nervous system for normal neurological function.[34-36]

A study evaluated the intake of antioxidants and the risk of stroke, providing evidence that vitamin E might be of value in reducing the risk of stroke. This study looked at the diets of over 34,000 postmenopausal women as well as their risk of death from stroke.[19] A total of 215 of the women died of strokes during the study period. Interestingly, the study noted that the greater the amount of vitamin E in the diet, the lower the risk of death from stroke.

Vitamin C is capable of essentially influencing the course of many metabolic processes, and it is therefore used in the treatment and prophylaxis of many diseases, including processes associated with reactive oxygen species and oxidative stress. Therefore, because it appears that free radicals are relevant molecules associated with vascular pathologies, some studies have focused on the possibility of using vitamin C to lower or eliminate these molecules.[37]

Regarding the effect of single antioxidants, data from the subanalysis limited to ischemic stroke cases suggest that vitamin C is inversely related

to this type of stroke.[7,16] A study by Kurl *et al.*, examined whether plasma vitamin C modifies the association between overweight, hypertension and the risk of stroke in middle-aged men from eastern Finland. Interestingly, low plasma vitamin C was associated with an increased risk of stroke, especially among hypertensive and overweight men.[38] The recent study by Myint *et al.*, examined the relationship between baseline plasma vitamin C concentrations and the risk of incident stroke in a British population. The study was conducted in 20,649 men and women aged 40-79 years without prevalent stroke at baseline. This study concluded that plasma vitamin C concentrations may serve as a biological marker of lifestyle or other factors associated with reduced stroke risk and may be useful in identifying those at high risk of stroke.[39]

CONCLUSIONS

Our findings seem to suggest that antioxidants and B vitamins may play a role in reducing the risk of stroke, as already noted. Our patients with stroke indicate a more insufficient intake of beneficial food groups, which results in a low nutrition density diet and poor overall dietary quality, than subjects without stroke. A large-scale prospective study to identify the dietary patterns of patients with stroke in Iran should be conducted.

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