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Homocysteine, circulating vascular cell adhesion molecule and carotid atherosclerosis in postmenopausal vegetarian women and omnivores☆

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Abstract

Since the adoption of vegetarian diets as a healthy lifestyle has become popular, the cardiovascular effects of long-term vegetarianism need to be explored. The present study aimed to compare the presence and severity of carotid atherosclerosis (CA), and the blood levels of Vitamin B12, homocysteine (Hcy) and soluble vascular cell adhesion molecule-1 (sVCAM-1) between 57 healthy postmenopausal vegetarians and 61 age-matched omnivores. Carotid atherosclerosis, as measured by ultrasound, was found to be of no significant difference between the two groups. Yet, fasting blood glucose, low-density lipoprotein cholesterol, and Vitamin B12 were significantly lower, while Hcy and sVCAM-1 were higher in the vegetarians as comparing with the omnivores. Multivariate regression analysis showed that the level of Vitamin B12 was negatively associated with the level of Hcy. Vegetarianism itself and Hcy level were significantly associated with sVCAM-1 level in univariate analysis; however, after adjustment for covariates, we identified age but not vegetarianism as the determinant of sVCAM-1 level. Multiple linear regression analysis identified age and systolic blood pressure, but not vegetarianism, as determinants of common carotid artery IMT. In conclusion, there was no significant difference in CA between apparently healthy postmenopausal vegetarians and omnivores. The findings of elevated Hcy in vegetarians indicate the importance of prevention of Vitamin B12 deficiency.

Keywords: Vegetarians; Postmenopausal women; Carotid atherosclerosis; Cell adhesion molecule; Homocysteine

1. Introduction

Some studies have shown the harmful effects of adherence to a vegetarian diet. Vegetarian diets contain mainly vegetables, soybean products, and nuts. However, meat- and fish-free diets may be associated with nutritional imbalance. Vitamin B12 deficiency has been associated with elevated total plasma homocysteine (Hcy) level in vegetarians, and is often identified as an issue of concern in this specific group of persons [1–3]. Functional Vitamin B12 deficiency in vegetarians may contribute to hyperhomocysteinemia and

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decreased total antioxidant status, which may partly counteract the beneficial lifestyle of vegetarians [2]. Vitamin B12 and iron status are compromised by a vegetarian diet, and both lower lymphocyte and platelet counts are accompanied by metabolic evidences that indicate Vitamin B12 deficiency [4]. Some studies also did not confirm the protective effects of a vegetarian lifestyle. Vegetarian, especially vegan, diets are relatively low in α-linolenic acid and provide little eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) which would provide potent cardioprotective effects [5]. As demonstrated in a study on Hong Kong Chinese, the vegetarians have a lower blood or tissue n-3: n-6 polyunsaturated fatty acid ratio in comparing with omnivores [6].

Circulating soluble vascular cell adhesion molecule-1 (sVCAM-1) and intercellular adhesion molecule-1 (sICAM-1) have been demonstrated to have a positive association with carotid atherosclerosis (CA) and cardiovascular disease (CVD) [7,8]. However, the above associations have not been tested in vegetarians.

Subclinical extracranial carotid atherosclerosis and carotid intima-media thickness (IMT) measured by carotid ultrasound are strongly associated with CVD [9,10] and its risk factors [11,12]. With high reliability and reproducibility [13,14], ultrasound measurements of carotid arteries have been widely used in epidemiological and clinical studies for the evaluation of early CA [9–12]. However, to the best of our knowledge, there is still no report correlating vegetarianism with CA.

Vegetarianism as a healthy lifestyle has become more popular in recent years. It is timely to explore the effects of a vegetarian diet on cardiovascular risks. We chose postmenopausal women for this study because postmenopausal women have higher odds of carotid atherosclerotic plaque compared with premenopausal women [15]. This study was undertaken to determine whether CA, indexed by carotid artery IMT and extracranial carotid artery plaque score, differs between healthy postmenopausal vegetarian women and matched omnivore women. In this study, lipid profiles, fasting glucose, sVCAM-1, sICAM-1, Hcy, and associated certain micronutrients (Vitamins B6, B12 and folate) were also compared in both groups.

2. Methods

2.1. Study subjects

A total of 57 healthy postmenopausal vegetarians and 61 matched healthy omnivorous postmenopausal women were invited to participate in this study from about 1000 public service volunteers that visited the health center of the Buddhist Compassion Relief Tzu Chi Foundation in Taipei during the years 1999 and 2000. Menopause was defined as a cessation of menstruation cycles for at least 1 year and was verified with a structured questionnaire.

To fulfill the criteria of apparently healthy subjects, women with any of the following conditions were excluded: a history of diabetes mellitus or fasting blood glucose over 126 mg/dL; hyperlipidemia (cholesterol level ≥240 mg/dL or triglyceride level ≥200 mg/dL); regular alcohol drinking or smoking; any treatment that might affect lipid metabolism; history of CVD, hypertension (systolic blood pressure (SBP) ≥160 mmHg or diastolic blood pressure ≥95 mmHg), or use of anti-hypertensive medication; or serum creatinine level ≥125 μmol/L; thyroid disease; and malignancy of any kind. Vegetarians were defined as exclusive consumption of a vegetarian diet void of meat, fish, and poultry for at least 5 years. Written informed consent was obtained from each participant and this study was approved by the National Taiwan University Hospital.

2.2. Carotid atherosclerosis assessments

Maximal carotid IMT and extracranial carotid artery (ECCA) plaque score were used for the assessment of CA. Maximal IMT of the common carotid artery (CCA), bulb, and internal carotid artery (ICA) were measured on both sides using a high-resolution B-mode ultrasonographic system (Hewlett Packard SONO 4500 ultrasound system equipped with a 3–11 MHz real-time B-mode scanner and a 3.6 MHz pulsed-Doppler mode scanner, Andover, MA, USA). The protocol of measurements was described in our previous reports [12,13].

Maximal IMT of the posterior wall of the carotid artery was measured from the leading edge of the first echogenic line to that of the second echogenic line. The examiners (JSJ and TCS) were blinded to the study subjects' health status and risk factors. The inter-observer absolute difference of IMT measurements was 0.13 ± 0.10 and 0.11 ± 0.09 mm at CCA1 (0–1 cm from carotid bifurcation) and CCA2 (1–2 cm from bifurcation), respectively. The intra-observer absolute difference of IMT measurements was 0.14 ± 0.12 and 0.12 ± 0.13 mm at CCA1 and CCA2, respectively [13].

The scoring method for the extracranial carotid atherosclerotic plaques was described in our previous reports [10,12]. In this study, the sites of examination of the carotid system included the proximal and distal CCA (>20 and <20 mm proximal to the bulb bifurcation, respectively), bulb, ICA, and external carotid artery bilaterally. The plaque score was computed by summing the plaque grades of all the segments of the carotid arteries studied. Reproducibility of the plaque grade scoring was good with a kappa value of 0.70 [10,12]. All measurements were recorded on super-VHS videotape for subsequent off-line analysis.

2.3. Blood sample assays

After fasting for 10–14 h overnight, blood samples were drawn from the antecubital vein. Serum lipids, including total cholesterol, high-density lipoprotein cholesterol (HDL-C),

and triglyceride, were assayed by enzymatic methods with automatic multi-channel chemical analyzer (Hitachi 7450, Hitachi Corp., Tokyo, Japan) in the central laboratory of the National Taiwan University Hospital. Low-density lipoprotein cholesterol (LDL-C) was calculated by Friedewald's formula.

Blood samples were first centrifuged at 3000 rpm for 15 min within 30 min of collection, and then stored at −70 °C until assayed. Plasma levels of Vitamin B12 and folate were measured by microparticle enzyme immonoassay technology with AxSYM® B12 and Folate kits (Abbott Laboratories, Chicago, IL). Plasma Vitamin B6 concentration was determined by HPLC with fluorometric detection (Hitachi, Tokyo, Japan) [16] while plasma total homocysteine was determined by competitive immunoassay with IMMULITE® Homocysteine kit (Diagnostic Products Corporation, Los Angeles, CA). Serum levels of sVCAM-1 and sICAM-1 were measured by enzyme linked immunosorbent assay with commercial kits (R&D Systems Inc., Minneapolis, MN).

2.4. Statistical analysis

In the data analysis, demographic and clinical characteristics and the clinical measurements were compared between vegetarians and omnivores. Continuous variables were expressed as mean ± standard deviation. Both *t*-test and ANOVA test were used to make comparisons. For categorical data, χ^2- test was used. Since the distributions of Vitamin B12, B6, and sVCAM-1 were not normal, Wilcoxon–Mann–Whitney test was used for analysis.

The total ECCA plaque score and the averaged values of bilateral IMTs at the CCA, bulb, and ICA were compared between vegetarians and omnivores. Because CVD risk factors influence the carotid IMT significantly, the comparisons of average IMTs were performed with values of least-square mean ± standard error after adjustment for age, LDL-C, SBP, and BMI. Plaque scores were also stratified into three levels (0, 1–3, >3) to evaluate the differences between vegetarians and omnivores.

Multiple linear regression analysis with stepwise procedure was conducted to evaluate the predictive value of Vitamin B12 on the levels of Hcy and sVCAM-1, respectively. The predictive value of Hcy on the level of sVCAM-1 also was calculated. The significant determinants of IMT of CCA were also evaluated by using multiple linear regression models to estimate the effects of vegetarianism after controlling major CVD risk factors (age, SBP, LDL-C, fasting glucose, BMI and menopausal year). Hcy was also taken into account with the vegetarian status in the multivariate analysis models. All statistical analyses were performed with SAS statistical software (Version 8.2, SAS Institute, Cary NC, USA).

3. Results

Baseline characteristics of the vegetarian group and the controlled omnivore group are shown in Table 1. In comparison with the omnivore group, the levels of fasting serum glucose, HDL-C and LDL-C were significantly lower in the vegetarian group. The duration of vegetarian diet averaged 10.4 ± 4.2 years for the vegetarian group. Most vegetarians adopted a vegan type diet (taking no egg or milk). The ratio of lactovegetarians/vegans was 6/51 in this study. The age of menopause was 2.1 years younger and the year after menopause was 3.8 years longer for the vegetarian group. The BMI was not statistically different between two groups.

As shown in Table 2, the concentration of Vitamin B12 was lower and the level of Hcy was higher in the vegetarian group. sVCAM-1 was higher, but sICAM-1 was not higher in vegetarians than in omnivores. However, levels of folate, Vitamin B6, and serum creatinine were not different between the two groups. In Table 3, carotid IMT (measured at bulb, CCA and ICA, and the average) and the ECCA plaque scores were not significantly different between the two groups of study subjects. The adjusted average of IMT was also not significantly different between the two groups.

In Table 4, multivariate linear regression analysis showed that vegetarians were positively and levels of Vitamin B12

Table 1
Demographic and clinical characteristics of the vegetarian and omnivore groups

Characteristics	Vegetarian group ($n = 57$)	Omnivore group ($n = 61$)	P
Average age (years)	59.2 ± 6.4	57.7 ± 5.1	0.178
Duration of vegetarian (years)	10.4 ± 4.2	–	–
Age of menopause (years)	48.0 ± 5.0	50.1 ± 4.2	0.017
Years after menopause (years)	11.4 ± 6.1	7.6 ± 6.2	0.002
Body mass index (kg/m^2)	23.0 ± 2.7	23.5 ± 2.7	0.300
Systolic blood pressure (mmHg)	127.8 ± 15.7	126.7 ± 14.8	0.699
Diastolic blood pressure (mmHg)	71.1 ± 7.2	73.0 ± 9.4	0.220
Pulse pressure (mmHg)	56.6 ± 12.4	53.6 ± 11.6	0.179
Cholesterol (mmol/L)	4.9 ± 0.8	5.5 ± 0.7	<0.001
Triglyceride (mmol/L)	1.4 ± 0.7	1.3 ± 0.6	0.267
HDL-C (mmol/L)	1.5 ± 0.3	1.7 ± 0.4	0.002
LDL-C (mmol/L)	2.8 ± 0.7	3.2 ± 0.7	0.002
Fasting blood glucose (mmol/L)	5.0 ± 0.5	5.2 ± 0.5	0.009

Table 2
Plasma concentrations of homocysteine, Vitamins B6 and B12, folate and cell adhesion molecules in vegetarians and omnivores

	Vegetarian group	Omnivore group	*P*
Folate (nmol/L)	22.0 ± 7.5	22.7 ± 6.1	0.595
Vitamin B12 (pmol/L)[a]	265.2 ± 179.3	380.3 ± 199.4	<0.001
Vitamin B6 (nmol/L)[a]	121.8 ± 63.1	108.8 ± 48.2	0.890
Homocysteine (μmol/L)	11.0 ± 3.3	9.0 ± 2.1	<0.001
sVCAM-1 (ng/mL)[a]	724.7 ± 418.3	547.5 ± 259.9	0.033
sICAM-1 (ng/mL)	277.6 ± 111.3	252.2 ± 70.2	0.145
Creatinine (μmol/L)	71.5 ± 8.0	72.5 ± 7.5	0.373

[a] Analysis with Wilcoxon–Mann–Whitney test.

were negatively associated with levels of Hcy, but not sVCAM-1. Hcy had a borderline significant association with sVCAM-1 levels; however, we identified age but not vegetarianism as the determinant of sVCAM-1 levels after adjustment for associated covariates.

In Table 5, after adjustment for the covariates, multiple linear regression analysis identified age, fasting glucose, and SBP as the determinants of CCA IMT. Vegetarianism, sVCAM-1 and Hcy were not significant determinants of CCA IMT. However, we found there was a trend of significance for vegetarians on CCA IMT in Model 3. In Table 6, the multivariate logistic regression models found that age, years after menopause, and SBP were the significant risk factors for CA (higher ECCA score ≥ upper tertile). However, only age was identified as significant risk for higher IMT (IMT ≥ upper tertile).

4. Discussion

In the present study we showed that CA was not significantly different between vegetarians and omnivores in apparently healthy postmenopausal Chinese women. However, we found that plasma Hcy and sVCAM-1 were elevated and plasma Vitamin B12 was lower in vegetarians as compared with omnivores, which seemed to be contradictory to

Table 3
Carotid artery intima-media thickness (IMT) and extracranial carotid artery (ECCA) plaque score of the vegetarian and the omnivore groups

	Vegetarian group	Omnivore group	*P*
IMT			
CCA (mm)	0.773 ± 0.187	0.739 ± 0.132	0.421
Bulb (mm)	0.941 ± 0.279	0.938 ± 0.308	0.902
ICA (mm)	0.651 ± 0.139	0.669 ± 0.121	0.171
IMT, average	0.789 ± 0.173	0.772 ± 0.159	0.910
IMT, average after adjusted [a]	0.790 ± 0.021	0.771 ± 0.020	0.526
ECCA total score[b]	0.772 ± 1.476	0.754 ± 1.337	0.583
ECCA score			
0	36 (63.2%)	38 (62.3%)	0.866
1–3	16 (28.1%)	19 (31.2%)	
>3	5 (8.8%)	4 (6.6%)	

[a] Values are least-square mean ± standard error after adjustment for age, BMI, LDL-C, and fasting blood glucose.
[b] Analysis with Wilcoxon–Mann–Whitney test.

Table 4
Multiple linear regression analyses for individual risk factors on the level of homocysteine (μmol/L) and sVCAM-1 (10^{-2} ng/mL)

Variable	Homocysteine		sVCAM	
	β (S.E.)	*P*	β (S.E.)	*P*
Model 1				
Vegetarians	1.51 (0.55)	0.0068	1.06 (0.67)	0.1181
Age (years)	0.01 (0.05)	0.7686	0.12 (0.06)	0.0575
Model 2				
Vitamin B12 ($\times 10^{-2}$ pmol/L)	−0.49 (0.11)	<0.0001	−0.19 (0.13)	0.1661
Age (years)	0.05 (0.05)	0.3120	0.16 (0.06)	0.0108
Model 3				
Homocysteine (μmol/L)			0.21 (0.12)	0.0719
Age (years)			0.13 (0.06)	0.0408

Models were expressed after adjustment for age, body mass index, low-density lipoprotein cholesterol, fasting sugar, and systolic blood pressure, in addition to above variables. Model 1 includes vegetarians and age, model 2 includes Vitamin B12 and age, and model 3 includes homocysteine and age.

Table 5
Multiple linear regression analysis for the common carotid artery intima-media thickness (IMT)

Variable	IMT ($\times 10^{-2}$ mm)					
	Model 1		Model 2		Model 3	
	$\beta \pm$ S.E.	P	$\beta \pm$ S.E.	P	$\beta \pm$ S.E.	P
Vegetarians	4.48 ± 2.83	0.116	4.80 ± 3.01	0.114	4.97 ± 2.86	0.085
Homocysteine ((mol/L)	–	–	0.38 ± 0.52	0.465	–	–
VCAM-1 ($\times 10^{-2}$ ng/mL)	–	–	–	–	0.5 ± 0.4	0.252
Age (years)	0.83 ± 0.25	0.001	0.92 ± 0.26	0.001	0.88 ± 0.26	0.001
Systolic BP (mmHg)	0.22 ± 0.10	0.025	0.22 ± 0.10	0.029	0.22 ± 0.10	0.022
Fasting glucose (mmol/L)	7.39 ± 2.88	0.013	7.39 ± 3.06	0.018	7.03 ± 2.88	0.021
Adjusted R^2	0.239		0.247	0.241	0.241	

The regressions coefficient ($\beta \pm$ S.E.) and P value are indicated. Model 1 excludes homocysteine and VCAM-1 in the multivariate analysis. Model 2 excludes VCAM-1 and model 3 excludes homocysteine, respectively. All models are after adjustment for all above covariates, body mass index, years after menopause, and LDL-C levels. VCAM-1, vascular cell adhesion molecule-1.

the common belief that a vegetarian diet is beneficial to CVD. Thus, all the evidence and inference should be under careful scrutiny.

4.1. Vegetarians and carotid atherosclerosis

We could not demonstrate any significant beneficial effects of vegetarian diets on CA in this study. A consistent effect of increased SBP, fasting glucose, and age on IMT was found after multiple linear regression analysis, which corroborated the current hypothesis of atherosclerosis and validated this study. Our previous studies and other reports demonstrated that SBP, hypertension, fasting glucose, and age are important predictors for carotid IMT and CA [10–12,15,17]. The longer duration of years after menopause in vegetarians was associated with earlier atherosclerosis and might partially attenuate our major findings in this study.

4.2. Vegetarians and lipids

This study found advantageous cardiovascular effects of a vegetarian diet on plasma cholesterol and LDL-C, which are in line with previous reports [18–20]. Vegetarian diets contain less total fat, especially saturated fat, and less cholesterol (none in vegan diets), which may contribute to lower levels of cholesterol and LDL-C compared with controlled omnivores [18,19]. In vegetarians, in addition to elevation in Hcy and sVCAM-1, the findings of lower levels of HDL-C in this study also could counterbalance the beneficial effects of lower LDL-C from vegetarian diet. A study of Chinese people living in Hong Kong revealed similar results [6].

4.3. Vitamin B12, homocysteine, and sVCAM-1 in vegetarians

In vegetarians, Hcy was reported to be elevated [1–4]. This finding was confirmed in our study and could be attributed to the relative lower levels of Vitamin B12, which was corroborated by the simultaneous measurements of Vitamin B6 and folate. In our study, multivariate regression analysis also demonstrated a strong inverse association between Hcy and Vitamin B12 levels. Plasma Hcy has emerged as a risk factor for CVD [21], and has been associated with ECCA IMT in the Atherosclerosis Risk in Community Study [22]. Though we could not find significant effects of plasma levels of Hcy on carotid IMT in this study, the elevation of Hcy in vegetarians may exert certain adverse effects on CA.

This study demonstrates a significant association between levels of Hcy and sVCAM-1, and between vegetarians and sVCAM-1; however, these relationships were attenuated after adjustment for associated covariates. Age, not being vegetarian, was found to be the major determinant of sVCAM-1, which echoed the findings of Richter et al. that sVCAM-1 is an age-dependent parameter independent of vegetarian

Table 6
Multivariate logistic regression analysis for carotid atherosclerosis

	IMT $\geq$ upper tertile, OR (95% CI)	ECCA score $\geq$ upper tertile, OR (95% CI)
Vegetarians	0.844 (0.408, 1.744)	0.964 (0.457, 2.034)
Age (years)	1.090 (1.019, 1.166)*	1.192 (1.101, 1.290)‡
Years after menopause	1.048 (0.988, 1.112)	1.101 (1.033, 1.172)‡
Body mass index (kg/m^2)	1.089 (0.948, 1.252)	1.058 (0.919, 1.217)
Systolic BP (mmHg)	1.019 (0.995, 1.045)	1.026 (1.000, 1.053)*

Models are after adjusting all above covariates, LDL-C, and fasting glucose. IMT, mean value of intima-media thickness; ECCA score, total extracranial carotid atherosclerosis score.

* $P < 0.05$.

‡ $P < 0.005$.

status and cardiovascular risk factors [23]. Hcy has been proved to activate the transcription factor NF-κB in vascular smooth muscle cells and thereby increase the expression of sVCAM-1 [24]. Hcy may contribute to the pathogenesis of atherosclerosis through increased monocyte and T-cell adhesion to human aortic endothelial cells [25]. Thus, the elevated Hcy and VCAM-1 in vegetarians in this study indicate that vegetarianism is not always healthy in nature; at least the issue of Vitamin B12 deficiency deserves further attention.

4.4. Study limitations

There are some limitations for this study. The cross-sectional design may limit the causal inference. The participants were recruited from healthy volunteers, but not a randomized population may under-estimate the true effects of a long-term vegetarian diet. Moreover, our subjects were in general only about 8 years after menopause, which might not be long enough to develop a significant atherosclerosis in a regular Chinese diet. In other words, we might not have sufficient induction time to observe such a difference. Thus, over-matching might partially explain the negative findings of no difference in CA and carotid IMT. The small sample size of this study may not have had sufficient statistical power to detect a difference between vegetarians and omnivores.

5. Conclusions

There was no significant difference in CA between apparently healthy postmenopausal vegetarians and omnivores. In apparently healthy postmenopausal vegetarians, elevation in Hcy and sVCAM-1 levels may attenuate the potential beneficial effects of a vegetarian diet on plasma lipids which may possibly lower the development of CA. In adopting a vegetarian diet as a mode of healthy lifestyle, one should pay special attention to the prevention of Vitamin B12 deficiency, as suggested by Haddad et al. [26].

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