Diet and Systemic Lupus Erythematosus: A 4 Year Prospective Study of Japanese Patients

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ABSTRACT. ***Objective.*** To investigate the associations of dietary factors with the occurrences of active disease and vascular damage in female patients with systemic lupus erythematosus (SLE).

Methods. Clinical and questionnaire data were collected from 279 female patients with SLE in a 1995 baseline survey. Dietary nutrients were estimated by a semiquantitative food frequency questionnaire and disease activity was evaluated based on the Lupus Activity Criteria Count. Patients were followed over 4 years (1995–99) and changes in disease activity and occurrences of major organ damage were determined. Using data from 216 patients with inactive disease whose dietary data were complete at baseline, the association of each nutrient intake with occurrence of active disease was evaluated. The relation of diet with the development of 3 types of vascular injury (ischemic heart disease, cerebrovascular accident, thrombotic events) was examined in 196 patients who had been inactive with no history of these injuries. Patients who developed these vascular events were put in one category and nutrient intakes at baseline were compared between patients who did or did not develop vascular events.

Results. A total of 9966 person-months were accumulated from the 216 inactive patients, among whom 43 patients developed active disease. The proportional hazard model including indicator variables for tertiles of each nutrient, total energy, and confounding variables revealed an inverse association of intake of vitamin C (p for trend = 0.005) and crude fiber (p for trend = 0.06) with the risk of active disease. The inverse association with vitamin C intake was also significant after Bonferroni adjustment. Patients who developed vascular events (n = 7) consumed a greater amount of vegetable fat at baseline than patients who did not (p = 0.04).

Conclusion. Our findings suggest that dietary nutrients may modify clinical course of disease in female patients with SLE. Vitamin C intake is inversely associated with the risk of active disease, suggesting that vitamin C intake may prevent the occurrence of active SLE disease. (J Rheumatol 2003;30:747–54)

Key Indexing Terms:
DIET DISEASE ACTIVITY FAT PROSPECTIVE STUDY
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Studies on mouse models have shown that dietary factors may be associated with the development of autoimmune disease resembling human systemic lupus erythematosus (SLE)[1-3]. In particular, the beneficial effects of low fat diet and fish oil supplementation have been described; in mice receiving a low fat diet or fish oil supplement, onset of renal disease was delayed and survival improved. Concern with the role of diet in the development of SLE has been growing[4,5].

Based on findings from the mouse model studies, clinical trials have been conducted in humans[6-9]. Clark, *et al* showed that fish oil supplementation affected lipid metabolisms in patients with SLE[6], and Walton, *et al* revealed the beneficial effect of fish oil using unique outcome measures[8]. However, most clinical trials were small-scale. Little attention has been given to the effects of other nutrients. Consequently, it is uncertain whether a specific diet exists for the treatment of human SLE.

To confirm whether diet influences clinical course or prognosis, larger-scale studies are required. We considered that an observational epidemiological study method was most appropriate for this. Observational studies possibly provide more information on the effects of diet than small clinical trials. However, observational epidemiological studies investigating the associations of diet with the development of SLE are few[10,11].

To investigate the associations of diet with clinical course of disease in SLE, we started a prospective study of female patients with SLE in 1995. In this study, we followed them over 4 years and evaluated the associations between various dietary factors and clinical course. Changes in disease activity and the occurrence of major organ damage were chosen as outcome indicators.

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MATERIALS AND METHODS

The Miyagi Lupus Cohort. Study subjects were recruited from rheumatology or nephrology departments at 21 hospitals and 2 rheumatology clinics located in Miyagi Prefecture, northeastern Japan. All these institutions are designated SLE referral clinics. We organized the Miyagi Lupus Study Group with rheumatologists and nephrologists (physicians) in the institutions. Female patients with SLE seen by physicians during the period from June 1 to September 30, 1995, were recruited. All patients fulfilled the 1982 revised criteria for the classification of SLE[12]. Patients with serious symptoms, e.g., terminal symptoms and severe neuropsychiatric symptoms, were excluded in advance, because of the possible burden involved. At the initial visit during this period, physicians asked female patients without serious symptoms to participate in this study and gave them self-administered questionnaires. Of a total of 311 patients whom physicians asked, 279 consented and completed the questionnaires (89.7%).

Patients who gave consent were clinically evaluated. After a physical examination, physicians completed a form including clinical findings and laboratory data to assess disease activity, organ damage, and medications. Data obtained from the questionnaire survey and the clinical data were combined into baseline data for the prospective study.

This study was approved by the review board of Miyagi Cancer Center.

Questionnaire. The questionnaire covered personal and family histories, menstrual and reproductive histories, psychological and behavioral status, and smoking and drinking habits, along with a semiquantitative food frequency questionnaire (FFQ). The FFQ is generally regarded as the most appropriate method for dietary assessment in epidemiologic studies[13]. The FFQ used in this study has been validated in a Japanese population[14]. Briefly, subjects were asked to indicate the average frequency of intake of 169 food items and the usual serving size of each item during the year prior to the baseline survey. Based on the reported frequency of intake and size of each serving, their respective nutrient intake was computed using values from the *Standard Table of Food Composition in Japan*[15]. Nutrient intake was then adjusted for total energy intake, using regression analysis[13]. Energy-adjusted values reflect the composition of the diet independent of the total amount of food consumed.

Clinical data. Duration of disease was defined as the period from the date of diagnosis to the date of baseline data collection. Disease activity was evaluated according to the Lupus Activity Criteria Count (LACC). Patients with any 2 or more LACC items were defined as having active disease[16]. Although in clinical trials, several continuous scales are recommended as outcome measures for disease activity[17], we consider that a dichotomous outcome in the LACC is most appropriate for evaluating associations between dietary factors and disease activity in observational studies. Organ damage at baseline was measured using the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SLICC/ACR DI)[18], which evaluates cumulative damage due to the disease, to complications of therapy, or to intercurrent illness such as cancer. Ocular damage was not taken into account in this study, because of our incomplete assessment of ocular lesions. Information on laboratory data and the dose of prednisolone prescriptions was also obtained.

Followup survey. At the baseline survey in 1995, the mean age of 279 female patients was 40.6 ± 13.7 (SD) years. Thirty-four patients were diagnosed with active disease. In 4 patients, disease activity was not identified. The mean SLICC/ACR DI score was 1.10 ± 1.07 (SD).

Following the baseline survey, primary physicians regularly assessed patients and recorded occurrences of active disease and organ damage. Early in 2000, we started a followup survey to determine outcome (survival, mortality, relocation) and occurrences of active disease and major organ damage (angina or myocardial infarction, cerebrovascular accident, arterial or venous thrombotic event, endstage renal disease, aseptic necrosis of femoral head, and cancer) during the period 1995–99. The occurrence of active disease was examined in patients who had been inactive at the time of the baseline survey. We collected information on the outcome of each patient and the dates of change to active disease and diagnosed organ damage from each primary physician.

Table 1 presents the outcomes of 279 patients who participated in the 1995 baseline survey. At the end of the followup survey, 257 patients had survived, 7 were deceased, and 8 had relocated. Seven patients were lost to followup. Outcomes among patients with inactive disease are also given in Table 1.

Among the 241 patients who had been inactive, 4 were lost to followup. Disease activity was evaluated for the remaining 237 patients. To investigate associations between dietary factors and occurrence of active disease, we extracted data on the 216 patients who completed the FFQ and were diagnosed as having active or inactive disease in the followup survey.

We also investigated relations between dietary factors and the development of major organ damage. The study focused on vascular damage. We categorized patients who developed angina or myocardial infarction (confirmed by electrocardiography and elevation of related enzymes), cerebrovascular accident (confirmed by computed tomography or magnetic resonance imaging), or arterial or venous thrombotic event (confirmed by clinical signs and angiography) into one group (patients with vascular events), and investigated factors affecting this group. In the cross-sectional analysis of baseline data, we found some differences in nutrient intake between patients who had been active and inactive; patients with active disease consumed a smaller amount of total fat and a larger amount of carbohydrates than those in the inactive phase (data not shown). It was thought that disease activity at baseline might confound the association between dietary factors and the risk of vascular events. Thus, the 215 patients with no history of vascular events who were inactive at baseline were selected. Among them, the 196 patients whose dietary data were complete were identified for analysis.

Statistical analysis

Risk of active disease. For each patient who was inactive in 1995, person-months (30 days as one month) were calculated from the date of the baseline survey to the date of active disease diagnosis, date of death, date of relocation, or date of closing the followup survey. Patients lost to followup were deleted from analyses. Patients were categorized according to tertiles of energy-adjusted nutrient values. To assess associations between the dietary variables and risk of active disease, proportional hazard models were used[19]. In these models, age and other confounders were controlled simultaneously, and relative risks and 95% confidence intervals were computed, taking the lowest tertile as a reference category. Tests of trend across categories of the dietary variables were conducted in the models by treating the median values of the categories as continuous variables. To control for multiple comparisons, Bonferroni's adjustment was also conducted: the critical value of $0.05/k$, where k is the number of coefficients in the hazard model, was used as the alpha level for statistical significance[20,21].

Characteristics of patients with vascular events. As our sample was too small to compute relative risks of vascular events according to tertiles of energy-adjusted nutrient values, we compared the distributions of known risk factors for atherosclerotic vascular diseases and nutrient intakes at baseline between patients who did and those who did not develop vascular events, using t tests, chi-square tests, or analysis of variance[22]. Since nutrient intakes were not normally distributed, they were logarithmically transformed. The adjusted geometric mean of the nutrient intake was calculated taking account of age, total energy intake, and body mass index.

All statistical analyses were performed using the SAS program[23].

RESULTS

Risk of active disease. Table 2 shows the incidence of active disease during the period 1995–99 among 241 patients with inactive disease. The incidence among 216 patients whose FFQ data were complete is also shown. During the 4 year study period, a total of 9966 person-months of data were accumulated from the 216 patients, among whom 43 patients developed active disease. Table 3 shows baseline characteristics of the 216 patients. Their mean age was 40.6 ± 13.3 (SD) years, and 205 of them were taking prednisolone.

Table 4 shows the LACC data among the 216 patients.

Table 1. Outcomes in 1999 among 279 female patients with SLE. Number of patients with inactive disease in 1995 is shown in parentheses.

Age in 1995, yrs	Survived	Deceased	Relocated	Lost to Follw/up	Total
–19	9 (6)	0 (0)	1 (1)	0 (0)	10 (7)
20–29	64 (56)	0 (0)	5 (4)	0 (0)	69 (60)
30–39	43 (39)	2 (2)	1 (0)	0 (0)	46 (41)
40–49	69 (59)	3 (2)	1 (0)	3 (1)	76 (62)
50+	72 (66)	2 (2)	0 (0)	4 (3)	78 (71)
All ages	257 (226)	7 (6)	8 (5)	7 (4)	279 (241)

Table 2. Disease flare during 1995–99 among 241 patients with inactive SLE in 1995. Flare was evaluated not only in survivors but also in deceased or relocated subjects. Number of patients for whom we evaluated association of nutrient intake with the risk of active disease is shown in parentheses.

Age in 1995, yrs	Active	Inactive	Not Identified	Lost to Followup	Total
–19	1 (0)	6 (6)	0	0	7
20–29	17 (15)	43 (38)	0	0	60
30–39	8 (8)	33 (29)	0	0	41
40–49	11 (11)	50 (48)	0	1	62
50+	10 (9)	57 (52)	1	3	71
All ages	47 (43)	189 (173)	1	4	241

There was no large difference in frequency of variables and the total score in the LACC at baseline between the patients who did and those who did not develop active disease. In the followup survey, various findings in the LACC were recorded for the 43 patients who developed active disease. An abnormal laboratory test finding was most frequently observed at baseline and during the active phase.

Table 5 shows the association between nondietary factors and active disease. Although the relative risks for these factors were not statistically significant, we considered that nondietary factors might confound the associations between dietary factors and active disease. Accordingly, the nondietary factors presented in Table 5 were included in hazard models for evaluating the effect of nutrient intake. Among these nondietary factors, serum creatinine ≥ 1.0 mg/dl is used as an indicator of renal dysfunction, and the SLICC/ACR DI score also includes a history of renal damage. Therefore, it seems unreasonable to enter both these factors into hazard models. In addition, a weak association was observed between serum creatinine and dose of prednisolone. We consider that the SLICC/ACR DI score is a more important confounder than the serum creatinine level, since this score covers histories of renal and other major organ damages. Consequently, the SLICC/ACR DI score was entered into the hazard models for evaluating the effect of nutrient intake.

Table 3. Baseline characteristics of 216 female patients with SLE studied to assess effect of diet on disease activity.

Variables	Mean (SD)	Number (%)
Age, yrs	40.6 (13.3)	
Duration of disease, yrs	10.1 (6.9)	
SLICC/ACR DI score	1.1 (1.1)	
Renal dysfunction (serum creatinine ≥ 1.0 mg/dl)		16 (7.4)
Prednisolone use, mg*		
0		11 (5.1)
≤ 10		159 (73.6)
10–20		41 (19.0)
≥ 20		5 (2.3)
Body mass index, kg/m^2	22.0 (3.0)	
Education (beyond high school)		21 (9.7)

* Dose of steroid prescribed was converted to dose of prednisolone.

Associations between nutrient intake and active disease are presented in Table 6, together with the tertile values of each nutrient adjusted for total energy intake. A significant inverse association was observed between vitamin C intake and the risk of active disease (p = 0.005). The highest tertile of vitamin C was significantly associated with the risk of active disease (relative risk = 0.26, 95% confidence interval 0.10–0.67). The inverse association with vitamin C intake was also significant at the Bonferroni-adjusted alpha level. An inverse association was observed for intake of vitamins A and E, although it was nonsignificant.

A total of 27 patients reported taking vitamin supplements at least once a week at baseline. As we did not obtain detailed information on the type of supplement, vitamin C intake from vitamin supplements was ignored in the computation of nutrient intake. However, there was no difference in vitamin supplement use between patients who did and those who did not develop active disease, and the relative risk for the use of vitamin supplements was not statistically significant (relative risk 0.97, 95% CI 0.34–2.78).

Table 4. Frequency of variables (%) in the LACC and mean LACC among 216 patients with SLE studied to assess the effect of diet on disease activity.

	Frequency, %							
	Arthritis	Abnormal Laboratory Test	Rash	Pleurisy	Seizure	Vasculitis	Hematuria	Mean LACC
Patients who developed active disease (n = 43)								
Active phase	32.6	97.7	55.8	14.0	9.3	7.0	44.2	2.60
Baseline	7.0	20.9	11.6	0.0	0.0	2.3	4.7	0.47
Patients who did not develop active disease (n = 173)								
Baseline	6.9	18.5	9.8	0.0	0.0	2.3	4.6	0.42

LACC: Lupus Activity Criteria Count [16].

Table 5. Relative risk of active disease for nondietary factors.

Factor	Relative Risk[a]	95% CI
Age[b]	0.98	0.96–1.01
Duration of disease	0.99	0.94–1.04
SLICC/ACR DI score	1.11	0.86–1.43
Renal dysfunction (serum creatinine ≥ 1.0 mg/dl[c]	1.65	0.58–4.68
Dose of prednisolone[d]	1.44	0.88–2.34
Body mass index	0.93	0.83–1.05
Education[e] (beyond high school)	1.53	0.65–3.63

[a] Adjusted for age. [b] Relative risk estimated for age only. [c] Serum creatinine < 1.0 mg/dl taken as referent category. [d] Prednisolone dose treated as a continuous variable. [e] Below high school education taken as referent category.

Intake of crude fiber was inversely associated with the risk of active disease, and a trend test showed borderline significance at alpha 0.05 (p for trend = 0.06). Although not shown in Table 6, an inverse trend was also observed between intake of dietary fiber and the risk of active disease (p = 0.02). The highest tertile of dietary fiber was significantly associated with the risk of active disease (relative risk 0.34, 95% CI 0.14–0.83) at alpha of 0.05. However, the data on dietary fiber from the *Standard Table of Food Composition in Japan* used in this study are incomplete, so the risk estimate for dietary fiber intake may not be entirely accurate. The 5th edition of the *Standard Table of Food Composition in Japan*, published at the end of 2000, includes complete data on dietary fiber. In future studies, intake of dietary fiber in the FFQ must be validated using the new standard table.

Fat intake was not associated with the risk of active disease. In the analysis of type of fat consumed, i.e., animal, fish, and vegetable fat, we found no evidence of any association between fat intake and active disease. Total energy intake and protein intake were also not associated with the risk of active disease.

Characteristics of patients with vascular events. During the study period, 7 patients developed the following vascular injuries: angina (n = 1), myocardial infarction (n = 1), cerebrovascular accident (n = 3), and arterial or venous thrombotic event (n = 2). One of the patients with a thrombotic event was diagnosed with active disease at the same time. In the analysis, these 7 patients were put into one group (vascular events).

Table 7 compares patients who did or did not develop vascular events in terms of their physical status and nutrient intake at baseline. The mean age of patients who developed vascular events was higher than in patients who did not (p = 0.004). The frequency of diabetes mellitus in patients who developed vascular events was higher than in patients who did not (p = 0.007). All patients who developed vascular events were taking prednisolone. No patient with more than a high school education had any vascular event. Patients who developed vascular events consumed a larger amount of total fat (p = 0.09) or vegetable fat (p = 0.04) at baseline. We attempted to estimate relative risks for vegetable fat intake, treating nutrient value as a continuous variable. The relative risk adjusted for age, duration of disease, prednisolone dose, history of diabetes mellitus, body mass index, smoking status, and total energy intake was significant for intake of vegetable fat, at alpha = 0.05 (relative risk 1.15, 95% CI 1.01–1.32). However, after Bonferroni adjustment, this relative risk turned out to be nonsignificant at alpha = 0.0062.

There were no differences in intake of some selected vitamins between patients who did and those who did not develop vascular events.

DISCUSSION

This relatively large-scale observational epidemiological study revealed that vitamin C or crude fiber intake is inversely associated with the risk of active disease of SLE, and that patients who developed vascular events consumed a greater amount of vegetable fat at baseline. There was no evidence of any association between total fat or fish fat intake with the occurrence of active disease.

Most animal or human studies to date, although mainly experimental, were small compared with our study. Further, in these previous studies, laboratory data or informal criteria were used as outcome indicators, and the effects of various nutrient intakes have never been distinguished from the effect of energy intake[24]. Our study provides a unique opportunity to clarify independent associations between nutrient intake and different outcome indicators, i.e., disease activity and vascular damage, in a relatively large patient sample.

Table 6. Relative risks[a] of active disease according to the tertiles of energy-adjusted daily nutrient intake.

Nutrient	Tertile for Intake[b] Low		Middle			High			p for Trend
	No./person-months	RR	No./person-months	RR	95% CI	No./person-months	RR	95% CI	
Total energy, Kcal	< 1726.67		1726.67–2400.33			≥ 2400.33			
	17/3117	1.00	13/3426	0.63	0.30–1.32	13/3423	0.84	0.40–1.76	0.75
Total protein, g	< 81.57		81.57–91.37			≥ 91.37			
	16/3263	1.00	13/3290	0.89	0.42–1.90	14/3413	0.90	0.43–1.89	0.77
Animal protein, g	< 39.53		39.53–47.40			≥ 47.40			
	12/3356	1.00	18/3205	1.64	0.77–3.52	13/3405	1.03	0.46–2.32	0.93
Vegetable protein, g	< 39.22		39.22–44.70			≥ 44.70			
	19/3037	1.00	13/3445	0.58	0.28–1.22	11/3484	0.57	0.26–1.28	0.15
Carbohydrates, g	< 276.03		276.03–299.72			≥ 299.72			
	16/3260	1.00	14/3346	0.79	0.38–1.64	13/3360	0.84	0.38–1.83	0.64
Total fat, g	< 58.65		58.65–66.01			≥ 66.01			
	10/3495	1.00	18/3142	1.86	0.82–4.24	15/3329	1.49	0.62–3.58	0.41
Animal fat, g	< 23.67		23.67–29.79			≥ 29.79			
	12/3402	1.00	13/3309	1.08	0.48–2.43	18/3255	1.25	0.57–2.72	0.58
Fish fat, g	< 2.97		2.97–4.87			≥ 4.87			
	15/3244	1.00	15/3457	1.05	0.50–2.21	13/3265	1.01	0.47–2.20	0.98
Vegetable fat, g	< 28.73		28.73–33.34			≥ 33.34			
	15/3253	1.00	15/3253	0.93	0.44–1.97	13/3460	0.84	0.39–1.81	0.66
Cholesterol, mg	< 263.15		263.15–350.76			≥ 350.76			
	12/3331	1.00	16/3318	1.57	0.72–3.42	15/3317	1.29	0.59–2.84	0.57
Calcium, mg	<730.33		730.33–967.98			≥ 967.98			
	14/3368	1.00	14/3293	0.97	0.45–2.12	15/3305	1.07	0.51–2.27	0.84
Salt, g	< 12.09		12.09–14.37			≥ 14.37			
	15/3213	1.00	17/3287	1.11	0.54–2.27	11/3466	0.81	0.37–1.79	0.60
Crude fiber, g	< 4.56		4.56–6.06			≥ 6.06			
	18/3200	1.00	17/3227	0.99	0.49–2.02	8/3539	0.43	0.18–1.05	0.06
Vitamin A, IU	< 2560.46		2560.46–3895.43			≥ 3895.43			
	19/3248	1.00	14/3242	0.65	0.32–1.34	10/3476	0.50	0.22–1.14	0.09
Retinol, µg	< 206.09		206.09–282.03			≥ 282.03			
	13/3358	1.00	17/3204	1.61	0.74–3.53	13/3404	0.97	0.43–2.19	0.67
Carotene, µg	< 3448.09		3448.09–5891.15			≥ 5891.15			
	19/3286	1.00	12/3291	0.59	0.27–1.26	12/3389	0.68	0.32–1.46	0.35
Vitamin B1, mg	< 0.95		0.95–1.09			≥ 1.09			
	16/3038	1.00	16/3238	1.00	0.48–2.07	11/3690	0.59	0.25–1.36	0.18
Vitamin B2, mg	< 1.32		1.32–1.67			≥ 1.67			
	14/3284	1.00	17/3130	1.10	0.53–2.28	12/3552	0.75	0.34–1.67	0.49
Niacin, mg	< 14.78		14.78–16.92			≥ 16.92			
	16/3356	1.00	16/3270	1.11	0.53–2.29	11/3340	0.83	0.37–1.86	0.66
Vitamin C, mg	< 109.99		109.99–154.09			≥ 154.09			
	22/3132	1.00	13/3320	0.52	0.25–1.08	8/3514	0.26	0.10–0.67*,**	0.005*,***
Vitamin D, IU	< 184.06		184.06–291.06			≥ 291.06			
	15/3352	1.00	16/3263	1.29	0.60–2.76	12/3351	0.95	0.43–2.09	0.82
Vitamin E, mg	< 7.49		7.49–8.89			≥ 8.89			
	20/3103	1.00	12/3286	0.62	0.30–1.32	11/3577	0.56	0.25–1.25	0.16

[a] Model included indicator variables for tertiles middle and high, age, duration of disease, SLICC/ACR DI score, dose of prednisolone prescribed, education, and body mass index. [b] Nutrient value adjusted for total energy intake. * Significant at $p < 0.05$. ** Significant at $p < 0.0055$ after Bonferroni adjustment. *** Significant at $p < 0.0062$ after Bonferroni adjustment.

Role of diet in occurrence of active disease. In determining the outcome variable for disease activity, which criteria are suitable for measuring disease activity is an important issue. We divided patients into active and inactive disease groups based on the LACC and evaluated the effect of diet using proportional hazard models. In the baseline sample of our study, the LACC has 91.2% sensitivity and 77.8% specificity. These test characteristics are comparable to those reported by Urowitz, *et al*[16]. Although the imperfect specificity in the LACC suggests a possibility of nondifferential misclassification of outcome, which produces bias toward the null value in risk estimation, it is unlikely that this misclassification significantly changes the directions of the effects we observed[21]. On the other hand, in recent clinical trials of SLE, disease activity has

Table 7. Physical status and nutrient intake per day at baseline survey in terms of the onset of vascular events among 196 patients with inactive SLE with no history of vascular events.

Variable	Vascular Events[a], n = 7		No Vascular Events, n = 189		p
	Mean	%	Mean	%	
Age, yrs	54.3		39.4		0.004*
Duration of disease, yrs	12.0		9.7		0.40
Body mass index, kg/m^2	23.4		22.0		0.23
Smoking		14.3		12.2	0.89
Prednisolone use		100.0		94.2	0.51
Beyond high school education		0.0		10.6	0.37
Physical status					
Diabetes mellitus		28.6		4.8	0.007*
Hyperlipidemia		14.3		12.7	0.90
Hypertension		28.6		18.0	0.48
Renal dysfuction (serum creatinine ≥ 1.0 mg/dl)		14.3		5.8	0.36
Nutrient intake[b]					
Total energy, kcal	1826.2		2142.1		0.30
Total protein, g	87.8		86.1		0.70
Carbohydrates, g	274.3		286.6		0.26
Total fat, g	67.7		61.5		0.09
Animal fat, g	27.3		26.0		0.67
Fish fat, g	3.2		3.5		0.72
Vegetable fat, g	35.9		30.4		0.04*
Cholesterol, mg	376.0		302.7		0.10
Salt, g	14.1		13.0		0.37
Crude fiber, g	5.4		5.2		0.69
Vitamin A, IU	3845.9		3104.6		0.19
Retinol, µg	262.7		254.3		0.87
Carotene, µg	5723.8		4277.7		0.13
Vitamin B1, mg	1.0		1.0		0.77
Vitamin B2, mg	1.5		1.5		0.68
Niacin, mg	14.7		15.6		0.38
Vitamin C, mg	129.5		127.5		0.93
Vitamin D, IU	217.2		223.6		0.89
Vitamin E, mg	8.8		8.1		0.27

[a] Vascular events include angina or myocardial infarction (n = 2), cerebrovascular accident (n = 3), and arterial or venous thrombotic event (n = 2). [b] Mean of each nutrient was adjusted for age, total energy intake, and body mass index. * Significant at $p < 0.05$.

tended to be measured by continuous scales such as the SLE Disease Activity Index (SLEDAI)[17]. When such scales are used as an outcome variable in statistical models, the relation of one unit-change in each nutrient to the change in scale score is estimated. However, most continuous scales are unequally weighted by several clinical findings. Therefore, it is not easy to explain the role played by one unit nutrient intake in changing the score. We consider that continuous scales conventionally used in clinical trials might not be suitable for our study. Although the LACC may not be a perfect diagnostic test, the dichotomous outcome in this measure seems appropriate for observational epidemiological studies of dietary factors like ours.

We observed the inverse association of vitamin C intake with the risk of active disease. This association was also significant after Bonferroni adjustment, indicating that this finding is reliable, i.e., not falsely significant. To our knowledge, this is the first evidence to indicate a significant association between intake of vitamin C and the risk of active disease in human SLE. Vitamin C is one of the antioxidant vitamins. The effect of vitamin C we found may be explained by antioxidant mechanisms. It is well known that intake of antioxidant vitamins increases the plasma concentration of these vitamins[25] and modulates immune functions and the release of inflammatory mediators[26,27]. Among patients with SLE, a state of oxidative stress exists during a period of disease exacerbation that may cause oxidative damage to DNA and autoimmunity. Some indicators of oxidative stress are elevated in patients with SLE compared with healthy subjects[28,29]. Vitamin C may mediate such a state of oxidative stress in SLE, and consequently exert beneficial effects on repairs of abnormal immune components and inflammation. A few studies provide evidence supporting this. Cooke, *et al*[30] and Evans, *et al*[31], for example, showed that vitamin C is associated with DNA repair among patients with SLE, although the association between vitamin C and disease activity was unclear. Studies on mouse models suggest such effects of antioxidant vitamins in SLE; supplementation of an antioxidant mixture including

vitamin C reduced IgG levels and anti-dsDNA titers in mice[32]. Our results may indicate that vitamin C intake relieves oxidative stress in SLE and suppresses the production of autoantibody, which leads to prevention of active disease. Insufficient intake of vitamin C may maintain oxidative stress and induce inflammation and abnormal laboratory data in the active phase, as shown in Table 4.

In this study, other antioxidant vitamins such as vitamin E and A were also inversely related to the occurrence of active disease, although the findings were nonsignificant. Intake of these antioxidant vitamins may have some effect on a state of oxidative stress in SLE[26,27,33].

An inverse association with risk of active disease was also observed for intake of crude fiber, although this association was of borderline significance at alpha 0.05. In 1976, Trowell reported that many autoimmune diseases such as rheumatoid arthritis and multiple sclerosis are rare and/or less severe in populations taking high carbohydrate, high fiber diets[34]. Our result is the first to suggest the association of crude fiber intake with the risk of active disease in SLE. However, there is a possibility this may be a false association, because of nonsignificance at the Bonferroni adjustment. The effect of fiber intake in SLE remains to be investigated.

A vegetarian diet has been reported to improve laboratory data in a young Japanese female patient with SLE[35]. Vegetables are rich in vitamin C and fiber. This case report may support our findings.

Role of diet in development of vascular events. Among 196 female patients with no history of vascular events, 7 developed such events. Compared with the incidence predicted in western countries, the number of events in this study may seem small. Based on these 7 events, we calculated the respective incidence rates of myocardial infarction and cerebrovascular accident in our study population. The incidence rate of cerebrovascular accident among the patients aged 40 and over was 5.77 per 1000 person-years, similar to that in the general Japanese female population (4.36 per 1000 person-yrs)[36]. The incidence rate of myocardial infarction was 1.92 per 1000 person-years, which was higher than in the general Japanese female population (0.59 per 1000 person-yrs)[37]. It is unlikely that outcome was misclassified and that the incidence of vascular events is underestimated in our study.

There were some significant differences at alpha = 0.05 in characteristics between patients who did and those who did not develop vascular events. However, due to the small number of events, there is a possibility of type I error among these findings[21]. Further, categorizing 3 different types of vascular disease into one group, i.e., vascular events, may pose a problem. To obtain valid results, patient followup must be continued. The risk estimate for vegetable fat intake, which was nonsignificant at a Bonferroni adjusted alpha level, should be reevaluated in future.

Despite these limitations, our findings are consistent with previous results and are biologically plausible. Patients who developed vascular events were older[37,38]. The association between diabetes mellitus and the risk of ischemic heart disease and cerebrovascular disease has been established[37-39]. No vascular events occurred among well educated patients, suggesting that socioeconomic status might be related to the development of vascular events.

The results for nutrient intake, especially the risk estimate for vegetable fat intake adjusted for confounders, may provide an important clue for future studies. Although the detailed composition of vegetable fats consumed could not be estimated from our FFQ, the main sources of vegetable fat in diet were cooking oils. Cooking oil is rich in n-6 polyunsaturated fatty acids, which may be influential. It is known that intake of n-6 polyunsaturated fatty acids is associated with a lower risk of coronary heart disease in a general population[40]. It has been thought that intake of these polyunsaturated fatty acids has beneficial effects among healthy subjects. However, in SLE, n-6 polyunsaturated fatty acids may affect inflammation through their role as a precursor of inflammatory mediators[4,7] that may be involved in the development of vascular events. The beneficial effects of n-6 polyunsaturated fatty acids observed in a general population may not be applicable to patients with SLE. It seems that mechanisms underlying the association between diet and the development of vascular injuries in SLE may be more complicated.

Regarding risk factors for thrombotic events in SLE, plasma homocysteine was shown to influence the risk, suggesting that vitamin supplementation could prevent thrombotic events in SLE[41]. However, since no data regarding folate or vitamin B6 and B12 are given in the *Standard Table of Food Composition in Japan* used in our study, the effects of these vitamins on clinical course could not be investigated.

This is the first prospective study indicating associations between nutrient intake and the clinical course of SLE. We have reported a case-control study showing that dietary factors may be associated with the onset of SLE[10]. However, nutrient intake was not evaluated, and information bias has been a serious problem. In this study, since the effects of nutrient intakes were assessed by a prospective study method without this bias, the results are regarded as highly reliable.

This observational study suggests that dietary nutrients may modify the clinical course of disease in female patients with SLE. Vitamin C intake was found to be inversely associated with the risk of active disease, suggesting that vitamin C intake may prevent the occurrence of active SLE disease. Intake of vegetable fat may be associated with the risk of vascular events. It will be necessary to confirm the direct effects of significant dietary nutrients such as vitamin C on symptoms and clinical findings in SLE using clinical trials. The clarification of biological mechanisms explaining the effects of dietary nutrients is also required.

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