Clinical, Cosmetic and Investigational Dermatology

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ORIGINAL RESEARCH

Dietary Habits in Japanese Patients with Alopecia Areata

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Purpose: Alopecia areata (AA) is characterized by non-scarring, patchy hair loss caused by autoimmune reactions to anagen hair follicles. The pathogenesis of AA may be affected by the diet. However, the dietary habits of patients with AA have not been precisely examined. Therefore, the aim of this study was to investigate the dietary habits of patients with AA in comparison to those of healthy controls.

Patients and Methods: We evaluated the dietary habits of 70 adult Japanese patients with AA using a brief-type self-administered diet history questionnaire and compared them to the habits of age- and sex-matched healthy controls.

Results: Japanese patients with AA had a higher body mass index (BMI) and higher intakes of vitamin C and fruit than the controls. Logistic regression analysis showed that AA was associated with BMI. Retinol intake was positively correlated with severity of alopecia tool (SALT) score, and linear regression analysis revealed that retinol intake was a predictor of SALT score. Retinol intake among patients with moderate to severe AA (ie, a SALT score >25) was higher than that in patients with mild AA (a SALT score ≤25). The mean age of AA patients with atopic dermatitis (AD) was lower than that of AA patients without AD; however, there were no differences in nutrient or food intake between these two groups. Logistic regression analysis showed that the comorbidity AD was negatively associated with age.

Conclusion: AA was associated with a high BMI, and high retinol intake was a predictor of SALT score. Further studies should be conducted to clarify whether dietary intervention to reduce BMI or limit retinol intake can alter the development or severity of AA.

Keywords: retinol, vitamin C, body mass index, atopic dermatitis

Introduction

Alopecia areata (AA) is an autoimmune disease characterized by patchy, non-scarring hair loss on the scalp, face, and sometimes other body areas.[1] Certain triggers, such as microtrauma, can induce resident skin T cells to produce interferon (IFN)-γ, which induces the expression of major histocompatibility complex (MHC) class I and II molecules and interleukin (IL)-15 in the follicular epithelium.[1] The hair follicles are then infiltrated by cytotoxic effector CD8+ T cells expressing natural killer group 2, member D (NKG2D), which depends on the survival cytokine IL-15. The hair follicles are also infiltrated by effector CD4+ NKG2D+ T cells expressing IFN-γ, which induces the follicular epithelium to produce IL-15 and the chemokines CXCL9/10, thus recruiting effector T cells bearing CXCR3. Then, autoreactive cytotoxic CD8+ NKG2D+ IFN-γ-producing T cells attack anagen hair follicles via granzymes. Although no specific target autoantigens for these

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Received: 21 August 2021
Accepted: 19 October 2021
Published: 28 October 2021

attacking cells have been identified, they may recognize putative hair follicle autoantigens presented by MHC class I molecules.[1] The ligands of NKG2D include MHC class I chain-related gene A (MICA) and cytomegalovirus UL16-binding protein 3, and expression of both of these ligands is upregulated in lesional hair follicles.[1] Type 17 helper T (Th17) cells that abundantly produce IL-17A infiltrate the area around the hair follicles in AA lesions and play a supporting role for cytotoxic effector cells.[2] The pathogenesis of AA also involves a decrease in the number or activity of regulatory T cells (Tregs), which suppress effector cells.[1,3]

Recently, the involvement of Th2 responses was suggested in the pathogenesis of AA, and the expression levels of the Th2 cytokines IL-4, IL-5, and IL-13 were shown to be increased in the lesional skin or serum of patients with AA.[4] Alopecia areata is frequently associated with atopic dermatitis (AD), a Th2-enhanced allergic disease.[4] Treatment of patients with AD using dupilumab, an anti-IL-4 receptor α antibody, was shown to improve concomitant AA,[5] indicating a supportive role for Th2 cytokines in the pathogenesis of AA.

Various genetic and environmental factors, including diet, are associated with the development and exacerbation of AA. Diet may modulate the pathogenesis of AA by altering hair follicles and immune responses.[6] It was suggested that a Western diet, with high levels of fat, sugar, and salt and low fiber, may promote the development and/or increase the severity of autoimmune diseases by inducing Th1/Th17 responses, suppressing Treg activity, or dysregulating the gut microbiota.[7] Severe protein deficiency, delayed or skipped breakfast, or high intake of mercury-rich fish may also trigger AA.[8] Deficiency of micronutrients, such as vitamins or minerals, may promote the development of AA,[6] as serum levels of vitamin D, zinc, and folate tended to be lower in patients with AA than in healthy controls. Some studies have suggested that too much or too little dietary vitamin A may favor the onset or exacerbation of AA.[6,9] Interestingly, switching patients with celiac disease to a gluten-free diet improved concomitant AA.[8] Dietary changes can also alter the composition of the gut microbiota, which modulates the immune system via the production of various microbial metabolites, such as short-chain fatty acids, that induce Tregs. Treatment of *Clostridium difficile* colitis in patients with AA with fecal microbiota transplantation resulted in hair growth after improvement of gut dysbiosis,[10] implying the involvement of the gut microbiota in AA. Although these previous studies suggest a role for diet in the pathogenesis of AA, the dietary habits of patients with AA have not been precisely examined.

Herein, we investigated the dietary habits of adult Japanese patients with AA and compared them to those of age- and sex-matched healthy controls using a brief-type self-administered diet history questionnaire (BDHQ).[11] We also examined the relationship between dietary habits and disease severity and the association with AD.

Patients and Methods

Study Population

This study was conducted in accordance with the Declaration of Helsinki (2004) and was approved by the ethics committee of Nippon Medical School Chiba Hokusoh Hospital. All study participants provided written informed consent. Seventy adult (≥18 years) Japanese patients with AA (19 men and 51 women) were recruited to participate in this study. These patients were seen in the dermatological departments of outpatient clinics. The diagnosis of AA was made clinically according to the guidelines of the National Alopecia Areata Foundation.[12] Disease severity was evaluated based on the severity of alopecia tool (SALT) score.[13] Fifty-six patients were treated with topical corticosteroids, nine patients were treated with oral corticosteroids, 12 patients were treated with intravenous methylprednisolone (500 mg/day for 3 consecutive days; steroid minipulse therapy), 10 patients were treated with excimer light, one patient was treated with narrow-band UVB, five patients were treated with topical injection of triamcinolone acetonide, and five patients were treated with regional immunotherapy using diphenylcyclopropenone. Of the 70 patients with AA, six had Hashimoto's thyroiditis, four had Basedow's disease, and two had ulcerative colitis. Seventy age- and sex-matched healthy subjects (19 men and 51 women) were included as controls. The patients and controls were living in Tokyo or Chiba. Body mass index (BMI) was calculated as the current body weight (kg) divided by the square of the body height (m).

Dietary Assessment

The dietary habits of the patients and controls were assessed using the BDHQ, a questionnaire regarding diet during the past month (120420_BDHQ_2012.pdf (ebnjapan.org)).[11] Estimates of the intake of food items, energy, and nutrients were calculated using an ad hoc

computer algorithm for the BDHQ, based on Standard Tables of Food Composition in Japan.

Statistical Analysis

All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan).[14] The Shapiro–Wilk test was used to assess the normality of the data distribution. Results are expressed as the mean ± standard deviation for variables with normal distribution or as median and as the interquartile range for variables with non-parametric distribution. Differences between patients with AA and the controls were analyzed by paired *t*-test for variables with normal distribution or by Wilcoxon signed-rank test for variables with non-parametric distribution. Patients with AA were divided into two groups, the moderate to severe AA group (n =16) with SALT scores >25 and the mild AA group (n = 54) with SALT scores ≤25. A SALT score of 25 is the point at which steroid minipulse therapy is considered as a treatment option in the AA guidelines published by the Japanese Dermatological Association.[15] Patients with AA were also grouped according to whether AA was associated with AD (n =16) or without (n = 54). Atopic dermatitis was diagnosed according to the guidelines of the Japanese Dermatological Association.[16] The differences between the mild and moderate to severe AA groups and between the groups with and without AD were analyzed by Student's *t*-test for variables with normal distributions or by the Mann–Whitney *U*-test for variables with non-parametric distributions. Fisher's exact test was used to assess the significance of differences in the frequency distributions.

In patients with AA, the correlation between SALT score and each variable was evaluated using Spearman's rho correlation coefficients. Statistical significance was set at $P < 0.05$. The predictive factors for SALT score were analyzed using linear multivariate regression analysis. The analysis included only variables with a p value < 0.05 in the univariate analyses and was adjusted for age, sex, and BMI.

The association of each variable with AA or AD comorbidity was analyzed using bivariate and multivariate logistic regression analyses. These analyses included only the variables with a p value < 0.05 in univariate analyses, adjusted for age, sex, and BMI. To avoid multicollinearity, variables with a variance inflation factor >10 were excluded.

Results

Comparison of the Dietary Habits Between Patients with AA and Healthy Controls

Patients with AA had higher BMIs than the controls (Table 1). The patients also had higher intake of both vitamin C and fruit than the controls. The alcohol intake in patients with AA appeared to be lower than that in the controls; however, the difference was not significant. According to the bivariate and multivariable logistic regression analyses (Table 2), AA was associated with a high BMI (odds ratio, 1.15; 95% confidence interval, 1.02–1.29; p = 0.0207). However, there was no significant association between AA and either vitamin C or fruit intake.

Correlation Studies

For the 70 patients with AA, the median (interquartile range) SALT score was 6.0 (2.25–18.75), and there was no difference in SALT scores between male (6.0 [2.5–32.0], n = 19) and female patients (6.0 [2.5–17.5], n = 51; p = 0.953, by Mann–Whitney *U*-test). Retinol intake was significantly correlated with SALT score (Table 3). In the linear multivariate regression analysis (Table 4), SALT score was predicted by high intake of retinol (β = 40.82, t = 2.214, p = 0.0303).

Comparison of the Groups with Mild and Moderate to Severe AA

There were no differences in sex ratio, age, or BMI between the mild and moderate to severe AA groups (Table 5). Retinol intake in the moderate to severe AA group was higher than that in the mild AA group.

Comparison of the AA Groups with and without AD

The mean age in the AA group with AD was lower than that in the AA group without AD (Table 6). However, there were no differences in sex ratio, BMI, SALT score, or the intake of nutrients/foods between the two groups. Meat intake in the AA group with AD appeared to be higher than that in the AA group without AD, however, the difference was not significant. Logistic regression analysis revealed that the comorbidity of AD in patients with AA was negatively associated with age (odds ratio, 0.941; 95% confidence interval, 0.901–0.984; p = 0.00743; Table 7).

Table 1 Demographic Characteristics and Intake of Nutrients and Foods in Controls and Patients with Alopecia Areata (AA)

	Control (n = 70)	AA (n = 70)	*p* values
Sex	**Male 19**	**Male 19**	**1[c]**
	Female 51	**Female 51**	
Age (years)[a]	49.0 (35.25–61.75)	47.5 (35.5–58.75)	0.144
Body mass index (kg/m^2)[a]	20.22 (19.21–22.38)	21.86 (20.0–24.17)	0.00506**
Energy intake (kcal/day)[a]	1778 (1461–2010)	1602 (1305–2005)	0.287
Nutrients			
Animal protein (% energy)[a]	8.746 (6.625–10.009)	8.823 (7.165–10.284)	0.730
Vegetable protein (% energy)[b]	6.50 ± 1.03	6.44 ± 1.19	0.687
Animal fat (% energy)[a]	12.69 (10.76–15.90)	13.25 (9.16–15.54)	0.314
Vegetable fat (% energy)[a]	15.10 ± 3 0.37	15.47 ± 3.89	0.503
Carbohydrate (% energy)[b]	50.45 ± 7.40	51.45 ± 8.44	0.467
Na (mg/kcal)[a]	2.13 (1.97–2.56)	2.27 (2.05–2.65)	0.377
K (mg/kcal)[a]	1.35 (1.10–1.69)	1.29 (1.13–1.62)	0.861
Ca (μg/kcal)[a]	283.0 (231.1–346.0)	272.0 (213.5–347.5)	0.748
Mg (μg/kcal)[a]	133.5 (114.5–160.8)	127.2 (110.1–158.2)	0.472
Pi (μg/kcal)[a]	549.5 (488.6–642.1)	552.2 (462.8–652.5)	0.627
Fe (μg/kcal)[a]	4.27 (3.43–5.07)	4.08 (3.41–5.04)	0.704
Zn (μg/kcal)[a]	4.41 (3.94–4.85)	4.35 (3.86–4.93)	0.386
Cu (μg/kcal)[a]	0.603 (0.521–0.670)	0.582 (0.513–0.676)	0.874
Mn (μg/kcal)[a]	1.65 (1.41–1.97)	1.64 (1.34–2.38)	0.311
Retinol (μg/kcal)[a]	0.256 (0.139–0.370)	0.174 (0.137–0.293)	0.114
β-carotene (μg/kcal)[a]	1.76 (1.03–2.95)	1.92 (1.14–3.06)	0.464
Vitamin D (ng/kcal)[a]	5.18 (3.47–7.77)	5.49 (3.55–8.52)	0.953
α-tocopherol (μg/kcal)[b]	4.145 ± 1.009	4.350 ± 1.093	0.178
Vitamin K (μg/kcal)[a]	0.165 (0.116–0.220)	0.137 (0.105–0.216)	0.364
Vitamin B1(μg/kcal)[a]	0.419 (0.369–0.499)	0.420 (0.349–0.514)	0.520
Vitamin B2(μg/kcal)[a]	0.730 (0.634–0.863)	0.716 (0.591–0.865)	0.911
Niacin (μg/kcal)[a]	9.53 (8.01–10.88)	9.48 (8.03–11.14)	0.497
Vitamin B6(μg/kcal)[a]	0.676 (0.587–0.805)	0.690 (0.531–0.827)	0.547
Vitamin B12 (ng/kcal)[a]	3.94 (2.98–5.77)	3.96 (3.17–5.84)	0.986
Foric acid (μg/kcal)[a]	0.176 (0.142–0.237)	0.172 (0.147–0.232)	0.865
Panthotenic acid (μg/kcal)[a]	3.62 (3.05–4.11)	3.52 (3.00–4.03)	0.717
Vitamin C (μg/kcal)[a]	55.3 (40.8–77.9)	61.1 (49.2–88.3)	0.0211*

(*Continued*)

Table 1 (Continued).

	Control (n = 70)	AA (n = 70)	*p* values
Sex	**Male 19**	**Male 19**	**1[c]**
	Female 51	**Female 51**	
SFA (% energy)[b]	8.016 ± 2.134	7.596 ± 2.083	0.216
MUFA (% energy)[b]	10.298 ± 2.082	10.126 ± 2.370	0.594
n-3PUFA(% energy)[a]	1.21 (1.06–1.45)	1.26 (1.03–1.55)	0.673
n-6PUFA(% energy)[b]	5.302 ± 1.046	5.509 ± 1.287	0.274
Cholesterol(μg/kcal)[a]	207.7 (164.6–250.9)	211.3 (168.8–247.4)	0.704
Dietary fiber (mg/kcal)[a]	6.281 (5.19–8.12)	6.161 (4.80–7.85)	0.874
Alcohol (% energy)[a]	1.886 (0.105–7.595)	0.0182 (0–3.009)	0.058
Foods			
Cereals (mg/kcal)[b]	183.90 ± 67.15	186.44 ± 64.89	0.803
Potatoes (mg/kcal)[a]	13.25 (7.72–31.59)	16.34 (9.78–34.53)	0.824
Pulses (mg/kcal)[a]	1.80 (1.07–3.17)	2.02 (1.30–4.60)	0.093
Green and yellow vegetables (mg/kcal)[a]	59.31 (34.76–83.83)	56.33 (30.60–90.18)	0.949
Other vegetables (mg/kcal)[a]	75.54 (54.64–105.52)	87.86 (57.44–22.99)	0.512
Fruit (mg/kcal)[a]	50.65 (28.56–86.91)	67.59 (23.39–115.67)	0.0313*
Fish and shellfish (mg/kcal)[a]	29.85 (20.49–47.44)	30.06 (22.23–44.76)	0.842
Meat (mg/kcal)[a]	46.29 (36.10–57.04)	43.32 (29.80–57.64)	0.109
Eggs (mg/kcal)[a]	15.88 (10.91–28.01)	20.83 (12.42–29.54)	0.505
Dairy products (mg/kcal)[a]	79.58 (28.40–107.61)	73.32 (24.59–12.70)	0.939
Oils and fats (mg/kcal)[b]	6.11 ± 2.67	6.63 ± 2.93	0.204
Confection (mg/kcal)[a]	26.18 (13.02–49.69)	25.39 (15.76–41.72)	0.819
Beverages (mg/kcal)[a]	427.85 (246.2–542.6)	382.17 (276.3–595.2)	0.574
Seasonings and spices (mg/kcal)[a]	101.85 (76.49–142.74)	124.67 (86.55–73.25)	0.139
Sugar/sweeteners (mg/kcal)[a]	1.80 (1.07–3.17)	2.01 (1.30–4.60)	0.093

Notes: [a]Data provided as the median (interquartile range), analyzed by Wilcoxon signed rank test. [b]Data provided as the mean ± standard deviation, analyzed by paired *t*-test. [c]Fisher's exact test was used to test the significance of difference in frequency distribution. *Significant differences at $p < 0.05$. **Significant difference at $p < 0.01$.
Abbreviations: SFA, saturated fatty acid; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid.

Discussion

The BMI of patients with AA was higher than that of the controls, and AA was associated with BMI in the logistic regression analysis. The results indicate that a high BMI may be related to the development of AA. Several studies have reported that the prevalence of obesity is higher in patients with AA and other autoimmune diseases, such as systemic lupus erythematosus and rheumatoid arthritis, than in the reference group.[17,18] Obesity is characterized by low levels of chronic inflammation, and the adipose tissues in obese subjects contain enlarged adipocytes that abundantly produce inflammatory adipokines, such as leptin, as well as excess infiltration of inflammatory M1 macrophages, IFN-γ-producing CD4+ and CD8+ T cells,

Table 2 The Association of Alopecia Areata with Each Variable Analyzed by Multiple Logistic Regression Analysis

	Odds Ratio	95% Confidential Interval	*P* values
(Intercept)	0.0438	0.00188–1.02	0.0517
Age (years)	0.986	0.963–1.01	0.232
Sex (M=1, F=2)	1.17	0.512–2.66	0.715
Body mass index (kg/m^2)	1.15	1.02–1.29	0.0207*
Vitamin C (μg/kcal)	1.01	0.99–1.02	0.522
Fruit (mg/kcal)	1.00	0.995–1.01	0.420

Note: *Statistically significant at $p < 0.05$.

Table 3 Correlations of Severity of Alopecia Tool with Intakes of Nutrients/Foods in Patients with Alopecia Areata Using Spearman Correlation Coefficients

	Rho	*p*		Rho	*p*
Age (years)	0.0435	0.72	**Nutrients II**		
Body mass index (kg/m^2)	0.218	0.07	SFA (% energy)	−0.0927	0.445
Energy intake (kcal/day)	−0.134	0.27	MUFA (% energy)	−0.0211	0.862
Nutrients I			n-3PUFA (% energy)	−0.161	0.182
Animal protein (% energy)	−0.0408	0.737	n-6PUFA (% energy)	−0.00796	0.948
Vegetable protein (% energy)	−0.199	0.0986	Cholesterol(μg/kcal)	−0.0727	0.55
Animal fat (% energy)	−0.0451	0.711	Dietary fiber(mg/kcal)	−0.0628	0.605
Vegetable fat (% energy)	−0.0441	0.717	Alcohol (% energy)	0.0711	0.558
Carbohydrate (% energy)	−0.168	0.163	**Foods**		
Na (mg/kcal)	0.0624	0.608	Cereals (mg/kcal)	−0.166	0.17
K (mg/kcal)	−0.0416	0.732	Potatoes (mg/kcal)	−0.0711	0.559
Ca (μg/kcal)	−0.0481	0.692	Pulses (mg/kcal)	0.133	0.273
Mg (μg/kcal)	−0.0199	0.87	Green and yellow vegetables (mg/kcal)	0.0104	0.932
Pi (μg/kcal)	−0.0812	0.504	Other vegetables (mg/kcal)	−0.0384	0.752
Fe (μg/kcal)	−0.0842	0.488	Fruit (mg/kcal)	−0.124	0.306
Zn (μg/kcal)	−0.172	0.156	Fish and shellfish (mg/kcal)	0.112	0.355
Cu (μg/kcal)	−0.117	0.334	Meat (mg/kcal)	−0.0605	0.619
Mn (μg/kcal)	−0.104	0.393	Eggs (mg/kcal)	−0.128	0.292
Retinol (μg/kcal)	0.272	0.0228*	Dairy products (mg/kcal)	0.0344	0.778
β-carotene (μg/kcal)	0.031	0.799	Oils and fats (mg/kcal)	0.0895	0.461
Vitamin D (ng/kcal)	0.0364	0.765	Confection (mg/kcal)	0.014	0.909
α-tocopherol (μg/kcal)	−0.0315	0.796	Beverages (mg/kcal)	−0.0221	0.856
Vitamin K (μg/kcal)	−0.0552	0.65	Seasonings and spices (mg/kcal)	−0.0788	0.516
Vitamin B1(μg/kcal)	−0.204	0.0903	Sugar/sweeteners (mg/kcal)	0.133	0.273

(*Continued*)

Table 3 (Continued).

	Rho	*p*		Rho	*p*
Vitamin B2(μg/kcal)	−0.0875	0.471			
Niacin (μg/kcal)	0.0365	0.764			
Vitamin B6(μg/kcal)	−0.0364	0.765			
Vitamin B12 (ng/kcal)	0.0984	0.418			
Foric acid (μg/kcal)	−0.00861	0.944			
Panthotenic acid (μg/kcal)	−0.0832	0.494			
Vitamin C (μg/kcal)	−0.087	0.474			

Note: *Statistically significant at < 0.05.
Abbreviations: SFA, saturated fatty acid; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid.

Table 4 The Predictive Factors for Severity of Alopecia Tool Analyzed by Linear Multivariate Regression Analysis

	β Coefficient	Standard Error	*t*	*p*
(Intercept)	25.33	25.78	0.983	0.329
Age	−0.0297	0.214	−0.139	0.890
Sex	−3.97	7.994	−0.497	0.621
Body mass index (kg/m^2)	−0.291	0.866	−0.336	0.738
Retinol (μg/kcal)	40.82	18.44	2.214	0.0303*

Note: *Statistically significant at $p < 0.05$.

and Th17 cells. In addition, the production of anti-inflammatory adipokines, such as adiponectin, M2 macrophages, and Tregs is decreased in the adipose tissues of obese subjects.[19] These inflammatory cytokines and adipokines may be released from the adipose tissues, circulate in the blood, and reach peripheral sites. In particular, IFN-γ might induce type 1 autoimmune diseases[18] and promote MHC class I/II expression in hair follicles, thus triggering AA. Leptin is an inflammatory adipokine that induces dendritic cells (DCs) to produce IL-12 and drives the polarization of naïve CD4+ T cells toward Th1 cells.[19] Furthermore, the decrease in the levels of the anti-inflammatory adipokine adiponectin may contribute to autoimmune inflammation. Compared to wild-type mice, adiponectin knockout mice developed worsened experimental autoimmune encephalomyelitis, with increased production of IFN-γ and IL-17A in CD4+ T cells.[20] A recent study reported that serum adiponectin levels in patients with AA were lower than those in the reference group.[21]

Intakes of vitamin C and fruit were higher in patients with AA than in the controls; however, none of these variables were independently associated with AA in the logistic regression analysis. Since vitamin C is abundant in fruit, increased intake of vitamin C in patients with AA may reflect the increased intake of fruit. The present results suggest that increased intake of vitamin C may be related to the development of AA, which may be associated with the Th1-inducible effects of vitamin C. In a previous study, vitamin C induced murine DCs to produce IL-12 via activation of the p38 mitogen-activated protein kinase and then promoted their activity to drive the differentiation of naïve T cells into Th1 cells.[22] Vitamin C induced the murine DCs to secrete more IL-12 and IL-15 and enhanced their ability to differentiate CD8+ T cells into IFN-γ+ cytotoxic memory T cells.[22]

Alternatively, patients with AA might intentionally consume larger amounts of vitamin C to manage their hair loss, as vitamin C is recommended for subjects with various types of hair loss, including AA, on websites, TV, and horizontal publications because vitamin C induces the synthesis of collagen fibers, a component of hair, and promotes the intestinal absorption of iron, which is required for hair growth.[23]

Table 5 Demographic Characteristics and Intake of Nutrients and Foods in Mild (Severity of Alopecia Tool [SALT] ≦25) and Moderate to Severe (SALT > 25) Alopecia Areata Groups

	Mild (n = 54)		Moderate to Severe (n = 16)		*p* values
Sex	**Male**	**14**	**Male**	**5**	**0.752[c]**
	Female	**40**	**Female**	**11**	
Age (years)[a]	48.50 ± 16.38		47.94 ± 18.20		0.907
Body mass index (kg/m^2)[b]	21.93 (19.54–24.40)		21.86 (21.06–23.75)		0.654
Energy intake (kcal/day)[b]	1606 (1361–2028)		1545 (1221–1853)		0.390
Nutrients					
Animal protein (% energy)[a]	8.578 ± 2.786		8.855 ± 4.296		0.760
Vegetable protein(% energy)[a]	6.507 ± 1.272		6.196 ± 0.831		0.362
Animal fat (% energy)[a]	12.77 ± 4.00		13.05 ± 5.88		0.830
Vegetable fat (% energy)[a]	15.51 ± 4.02		15.34 ± 3.56		0.885
Carbohydrate (% energy)[a]	52.17 ± 8.04		49.01 ± 9.56		0.190
Na (mg/kcal)[b]	2.230 (1.954–2.440)		2.456 (2.069–2.699)		0.506
K (mg/kcal)[b]	1.302 (1.133–1.635)		1.277 (1.109–1.506)		0.796
Ca (μg/kcal)[b]	273.5 (217.8–357.2)		257.9 (199.1–304.5)		0.413
Mg (μg/kcal)[b]	128.7 (110.4–161.5)		126.2 (110.2–156.8)		0.883
Pi (μg/kcal)[b]	555.1 (482.1–661.6)		522.1 (430.9–631.7)		0.506
Fe (μg/kcal)[b]	4.05 (3.48–5.03)		4.24 (3.38–5.07)		0.994
Zn (μg/kcal)[a]	4.384 ± 0.778		4.173 ± 1.145		0.398
Cu (μg/kcal)[a]	0.610 ± 0.135		0.587 ± 0.137		0.559
Mn (μg/kcal)[b]	1.60 (1.35–2.09)		1.95 (1.18–2.49)		0.711
Retinol (μg/kcal)	0.163 (0.134–0.214)		0.310 (0.181–0.412)		0.0165*
β-carotene (μg/kcal)[b]	1.88 (1.07–2.95)		2.28 (1.35–3.24)		0.525
Vitamin D (ng/kcal)[b]	5.68 (3.55–8.31)		4.69 (3.67–9.33)		0.994
α-tocopherol (μg/kcal)[a]	4.350 ± 1.050		4.351 ± 1.266		0.999
Vitamin K (μg/kcal)[b]	0.138 (0.107–0.216)		0.118 (0.098–0.231)		0.610
Vitamin B1(μg/kcal)[a]	0.438 ± 0.109		0.408 ± 0.133		0.363
Vitamin B2(μg/kcal)[b]	0.716 (0.613–0.867)		0.702 (0.545–0.801)		0.552
Niacin (μg/kcal)[a]	9.571 ± 2.514		10.297 ± 3.136		0.342
Vitamin B6(μg/kcal)[a]	0.700 ± 0.204		0.717 ± 0.253		0.782
Vitamin B12 (ng/kcal)[b]	4.10 (3.17–5.72)		3.92 (3.13–7.20)		0.872
Foric acid (μg/kcal)[b]	0.167 (0.147–0.232)		0.189 (0.148–0.236)		0.742
Panthotenic acid (μg/kcal)[b]	3.520 (3.063–3.996)		3.474 (2.608–4.078)		0.543
Vitamin C (μg/kcal)[b]	61.12 (51.09–88.30)		62.92 (45.11–87.33)		0.629

(*Continued*)

Table 5 (Continued).

	Mild (n = 54)		Moderate to Severe (n = 16)		*p* values
Sex	**Male**	**14**	**Male**	**5**	**0.752**[c]
	Female	**40**	**Female**	**11**	
SFA (% energy)[a]	7.623 ± 1.898		7.504 ± 2.686		0.843
MUFA (% energy)[a]	10.109 ± 2.350		10.185 ± 2.512		0.911
n-3PUFA(% energy)[a]	1.276 ± 0.348		1.400 ± 0.461		0.250
n-6PUFA(% energy)[a]	5.470 ± 1.195		5.643 ± 1.596		0.639
Cholesterol(μg/kcal)[a]	214.01 ± 71.37		196.83 ± 80.60		0.414
Dietary fiber (mg/kcal)[b]	6.11 (4.80–7.92)		6.57 (5.11–7.31)		0.939
Alcohol (% energy)[b]	0.018 (0–1.065)		0.454 (0–7.249)		0.496
Foods					
Cereals (mg/kcal)[a]	188.30 ± 61.55		180.16 ± 76.99		0.663
Potatoes (mg/kcal)[b]	15.36 (9.92–38.02)		24.97 (9.25–30.68)		0.796
Pulses (mg/kcal)[b]	1.92 (1.35–4.60)		2.78 (1.28–4.57)		0.711
Green and yellow vegetables (mg/kcal)[b]	53.79 (29.82–90.18)		63.23 (41.17–83.14)		0.732
Other vegetables (mg/kcal)[a]	90.284 ± 46.788		85.674 ± 43.021		0.724
Fruit (mg/kcal)[b]	72.41 (26.40–121.93)		35.40 (14.39–84.32)		0.105
Fish and shellfish (mg/kcal)[b]	29.30 (22.31–43.03)		35.21 (20.68–64.87)		0.454
Meat (mg/kcal)[a]	43.27 ± 20.43		45.29 ± 22.99		0.737
Eggs (mg/kcal)[b]	21.13 (13.99–29.24)		15.16 (7.27–29.80)		0.317
Dairy products (mg/kcal)[b]	74.09 (29.87–113.76)		52.80 (21.38–83.39)		0.506
Oils and fats (mg/kcal)[a]	6.445 ± 2.814		7.250 ± 3.303		0.338
Confection (mg/kcal)[b]	26.31 (17.11–43.87)		20.42 (14.86–35.06)		0.543
Beverages (mg/kcal)[b]	382.2 (287.8–591.0)		400.1 (223.6–863.4)		0.928
Seasonings and spices (mg/kcal)[b]	122.6 (95.5–167.3)		151.9 (79.1–181.3)		0.774
Sugar/sweeteners (mg/kcal)[b]	1.918 (1.353–4.599)		2.781 (1.279–4.572)		0.711

Notes: [a]Data provided as the mean ± standard deviation, analyzed by Student's *t*-test. [b]Data provided as the median (interquartile range), analyzed by Mann–Whitney *U*-test. [c]Fisher's exact test was used to test the significance of difference in frequency distribution. *Significant difference at $p < 0.05$.
Abbreviations: SFA, saturated fatty acid; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid.

Alcohol intake tended to be lower in patients with AA than in the controls, although the difference was not significant. The results are consistent with those of a previous study showing that alcohol consumption was associated with a decreased risk of AA.[24] This finding might reflect the fact that intake of a moderate amount of alcohol (30 g/day) decreased both the expression of nuclear factor-κB in leukocytes and plasma levels of pro-inflammatory IL-18 and increased plasma levels of anti-inflammatory adiponectin, indicating immunosuppressive effects of moderate amount of alcohol.[25]

Intake of retinol, also called vitamin A1, was correlated with SALT score. This result suggests that high retinol intake may exacerbate AA via retinoic acid (RA), which is an active

Table 6 Demographic Characteristics and Intake of Nutrients and Foods in Alopecia Areata (AA) Groups with and without Atopic Dermatitis (AD)

	AA without AD (n = 54)		AA with AD (n = 16)		*p* values
Sex	**Male**	**13**	**Male**	**6**	**0.343[c]**
	Female	**41**	**Female**	**10**	
Age (years)[a]	51.59 ± 16.60		37.50 ± 11.96		0.00239**
SALT[b]	6 (2–17.5)		8 (3–41.5)		0.556
Body mass index (kg/m^2)[b]	21.69 (19.43–23.93)		22.28 (20.35–24.53)		0.321
Energy intake (kcal/day)[b]	1595 (1326–1995)		1789 (1221–2047)		0.321
Nutrients					
Animal protein (% energy)[b]	8.59 (6.68–10.28)		9.30 (7.19–10.16)		0.506
Vegetable protein (% energy)[a]	6.49 ± 1.20		6.25± 1.14		0.485
Animal fat (% energy)[a]	12.44 ± 4.39		14.16 ± 4.53		0.177
Vegetable fat (% energy)[b]	15.22 (13.14–18.33)		15.22 (13.87–16.04)		0.905
Carbohydrate (% energy)[a]	51.39 ± 8.91		51.63 ± 6.85		0.921
Na (mg/kcal)[b]	2.27 (2.03–2.65)		2.26 (2.14–2.57)		0.785
K (mg/kcal)[b]	1.302 (1.128–1.635)		1.255 (1.135–1.544)		0.534
Ca (μg/kcal)[b]	273.5 (226.8–347.5)		268.2 (190.9–347.1)		0.498
Mg (μg/kcal)[b]	130.6 (116.3–161.6)		114.7 (108.1–141.1)		0.196
Pi (μg/kcal)[b]	552.2 (478.3–652.5)		553.3 (449.7–636.9)		0.764
Fe (μg/kcal)[b]	4.08 (3.49–5.13)		4.02 (3.27–4.55)		0.506
Zn (μg/kcal)[a]	4.295 ± 0.899		4.4769 ± 0.776		0.468
Cu (μg/kcal)[b]	0.582 (0.520–0.698)		0.587 (0.506–0.606)		0.48
Mn (μg/kcal)[b]	1.67 (1.35–2.38)		1.57 (1.16–2.21)		0.571
Retinol (μg/kcal)[b]	0.173 (0.134–0.285)		0.197 (0.145–0.306)		0.515
β-carotene (μg/kcal)[b]	1.923 (1.068–3.184)		2.052 (1.326–2.487)		0.828
Vitamin D (ng/kcal)[b]	5.512 (3.798–9.029)		4.957 (2.305–7.019)		0.291
α-tocopherol (μg/kcal)[a]	4.408 ± 1.162		4.154 ± 0.818		0.418
Vitamin K (μg/kcal)[b]	0.140 (0.107–0.251)		0.115 (0.096–0.158)		0.164
Vitamin B1 (μg/kcal)[a]	0.429 ± 0.120		0.438 ± 0.099		0.780
Vitamin B2 (μg/kcal)[b]	0.715 (0.591–0.862)		0.722 (0.624–0.864)		0.994
Niacin (μg/kcal)[a]	9.865 ± 2.857		9.304 ± 1.871		0.463
Vitamin B6 (μg/kcal)[b]	0.715 ± 0.222		0.666 ± 0.184		0.432
Vitamin B12 (ng/kcal)[b]	3.91 (3.18–5.89)		4.37 (2.72–5.72)		0.961
Foric acid (μg/kcal)[b]	0.180 (0.150–0.238)		0.166 (0.137–0.207)		0.413
Panthotenic acid (μ/kcal)[b]	3.493 (3.029–4.032)		3.574 (2.856–3.981)		0.883

(*Continued*)

Table 6 (Continued).

	AA without AD (n = 54)		AA with AD (n = 16)		*p* values
Sex	**Male**	**13**	**Male**	**6**	**0.343**[c]
	Female	**41**	**Female**	**10**	
Vitamin C (μg/kcal)[b]	62.20 (51.09–90.01)		52.74 (39.01–80.83)		0.186
SFA (% energy)[a]	7.384 ± 1.986		8.311 ± 2.309		0.119
MUFA (% energy)[a]	9.995 ± 2.531		10.570 ± 1.708		0.398
n-3PUFA (% energy)[a]	1.333 ± 0.396		1.207 ± 0.296		0.241
n-6PUFA (% energy)[a]	5.550 ± 1.404		5.371 ± 0.791		0.627
Cholesterol (μg/kcal)[a]	203.87 ± 74.50		231.06 ± 67.23		0.195
Dietary fiber (mg/kcal)[b]	6.476 (5.059–7.918)		5.908 (4.417–6.838)		0.304
Alcohol (% energy)[b]	0 (0–5.418)		0.537 (0–2.484)		0.703
Foods					
Cereals (mg/kcal)[a]	181.31 ± 68.59		203.74 ± 48.28		0.227
Potatoes (mg/kcal)[b]	15.36 (9.67–28.81)		30.40 (10.45–45.07)		0.184
Pulses (mg/kcal)[b]	2.015 (1.277–4.725)		2.127 (1.406–3.024)		0.916
Green and yellow vegetables (mg/kcal)[b]	56.33 (29.82–90.96)		58.32 (38.64–78.10)		0.817
Other vegetables (mg/kcal)[a]	90.01 ± 44.61		86.60 ± 49.59		0.794
Fruit (mg/kcal)[b]	72.13 (23.39–134.11)		46.38 (24.75–75.47)		0.193
Fish and shellfish (mg/kcal)[b]	31.64 (22.63–48.94)		26.53 (20.11–40.47)		0.338
Meat (mg/kcal)[b]	40.06 (25.38–55.42)		47.94 (41.88–58.79)		0.0974
Eggs (mg/kcal)[b]	19.33 (12.04–27.19)		25.80 (16.03–31.36)		0.254
Dairy products (mg/kcal)[b]	74.08 (27.17–114.80)		68.38 (21.38–92.55)		0.600
Oils and fats (mg/kcal)[a]	6.593 ± 3.168		6.750 ± 1.988		0.852
Confection (mg/kcal)[b]	25.62 (17.93–41.11)		23.22 (12.64–42.28)		0.905
Beverages (mg/kcal)[b]	382.1 (287.8–621.2)		397.5 (230.4–535.7)		0.382
Seasonings and spices (mg/kcal)[b]	121.6 (81.5–153.7)		144.1 (114.1–183.7)		0.160
Sugar/sweeteners (mg/kcal)[b]	2.015 (1.277–4.725)		2.127 (1.406–3.024)		0.916

Notes: [a]Data provided as the mean ± standard deviation, analyzed by Student's *t*-test. [b]Data provided as the median (interquartile range), analyzed by Mann–Whitney *U*-test. [c]Fisher's exact test was used to test the significance of difference in frequency distribution. **Significant difference at $p < 0.01$.
Abbreviations: SALT, severity of alopecia tool; SFA, saturated fatty acid; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid.

metabolite of retinol. Retinoic acid may increase the susceptibility of hair follicles to attack by NKG2D+ effector cells by inducing hair follicle stem cells to enter anagen phase via signalling through the wingless-type mouse mammary tumor virus integration site family[26] and by increasing the expression of NKG2D ligands such as MICA[27] or MHC class I.[28]

Dietary retinol, which is abundant in fish, liver, eggs, and cheese, is absorbed in the intestine and delivered to the liver where it is stored as retinyl esters. Retinol released from liver stores may be delivered via the blood to the skin surrounding the hair follicles,[29] And taken up by hair follicle epithelial cells or immune cells, and

Table 7 The Association of Comorbid Atopic Dermatitis in Alopecia Areata Patients with Each Variable Analyzed by Multiple Logistic Regression Analysis

	Odds Ratio	95% Confidential Interval	p
(Intercept)	1.82	0.0247–134.0	0.785
Age (years)	0.941	0.901–0.984	0.00743**
Sex (M=1, F=2)	0.826	0.219–3.11	0.777
Body mass index (kg/m^2)	1.05	0.904–1.23	0.502

Note: **Statistically significant at $p < 0.01$.

oxidized to RA.[9,29] In the nucleus, RA binds to RA receptor α, β, or γ, which heterodimerizes with the retinoid X receptor, and these dimers bind to RA response elements in various genes to activate their transcription.[9] The expression levels of RA synthesis enzymes were higher in AA skin lesions than in healthy skin.[9] The higher levels of dietary retinol in patients with AA may robustly promote lesional RA synthesis and RA-induced gene expression, thus exacerbating autoimmune attack.

However, RA also has immunoregulatory effects;[30] it promotes the expression of *Foxp3* and induces the generation of peripheral Tregs. C3H/HeJ AA model mice fed a vitamin A-deficient diet had more severe disease,[9] which may be due to Treg defects. The balance of the stimulatory and regulatory effects of RA in AA may differ depending on the dose of RA. Further studies should elucidate the dose-dependence of the stimulatory and regulatory effects of RA on the progression of AA.

The incidence of AD in AA patients was negatively associated with age, which may reflect a general trend, irrespective of AA, since the onset of AD declines with age.[31] Meat intake was higher in AA patients with AD than in AA patients without AD, although the difference was not significant. The results might reflect the younger age of the former group, since meat consumption is associated with younger age.[32] Alternatively, higher intake of fried or microwaved meats might generate higher amounts of advanced glycation end products, which function as alarmins triggering allergic diseases.[33] However, the present study did not reveal any significant differences in the intake of the evaluated nutrients/foods between AA patients with AD and those without AD. Further studies with larger sample sizes are needed to evaluate the involvement of dietary habits in the association between AD and AA.

This study has some limitations. First, the sample size was small, and the study was performed in a limited area, Chiba and Tokyo in the Kanto region of Japan. Dietary habits may vary regionally in Japan, thus the present results might not be representative of Japan as a whole. We should further extend this study to include a larger number of subjects from different regions of Japan. Second, the BDHQ calculates the intake of nutrients only from the diet and thus might overlook the intake of supplementary micronutrients. Further studies should examine all nutrient intake, including supplements. Thirdly, this study examined the dietary habits of each patient only once, and thus the correlation of dietary habits with disease course or activity is unknown. Such correlations should be examined by assessing the dietary habits of all patients several times.

Conclusion

Adult Japanese patients with AA had a higher BMI and higher intake of vitamin C and fruit than a group of age- and sex-matched healthy controls. AA was associated with BMI. Retinol intake was a predictor of SALT score. This is the first study to examine the dietary habits of patients with AA. Further studies should clarify whether dietary interventions to reduce the BMI or the intake of retinol can alter the development or severity of AA.

Acknowledgments

This work was partly supported by scholarship grants from Taiho Pharmaceutical, Torii Pharmaceutical, and Maruho Co., Ltd.

Disclosure

The authors report no conflicts of interest in this work.

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