Factors Related to Body Mass Index in Women with Rheumatoid Arthritis – TOMORROW study

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Abstract: *Objectives*: This study aimed to clarify the relationship between body mass index (BMI) and patient characteristics, lifestyle factors, and cardiovascular disease (CVD)-related clinical data in women with rheumatoid arthritis (RA).

Methods: A total of 171 female outpatients with RA and 170 age-matched females without RA (controls) from the TOMORROW study (UMIN: 000003876) were included in this cross-sectional study. We divided subjects into 3 groups based on BMI: underweight (BMI < 18.5 kg/m^2), normal weight (BMI ≥ 18.5 kg/m^2 and < 25 kg/m^2), and overweight (BMI ≥25 kg/m^2), and compared RA disease activity, activities of daily living (ADL) assessed by modified health assessment questionnaire (mHAQ) score, energy and nutrient intake, and CVD risk-related clinical data.

Results: In patients with RA, mHAQ scores were lower in the normal weight group compared with the underweight and overweight groups ($p < 0.05$). Disease activity showed a similar trend. Energy, protein, and carbohydrate intake showed a positive correlation with BMI ($p < 0.05$). Blood pressure, C-reactive protein, uric acid, triglyceride, fasting plasma glucose, immune reactive insulin, HbA1c, and leptin showed a positive correlation with BMI, and adiponectin showed a negative correlation with BMI ($p < 0.05$). Control subjects showed similar trends.

Conclusions: BMI is related to ADL, disease activity, energy, protein and carbohydrate intake, and CVD risk-related clinical data, and might be an indicator of total health status in female patients with RA.

Keywords: Rheumatoid arthritis, underweight, obesity, nutrition, cardiovascular disease, lifestyle.

BACKGROUND

A recent report showed that 36.9% of males and 38.0% of females worldwide are overweight or obese, defined as a body mass index (BMI) >25 kg/m^2 [1]. Although the definitions of overweight and obesity differ among professional associations and published guidelines, all publications agree that obesity is related to hypertension, glucose intolerance, dyslipidemia [2], and increases in cardiovascular disease (CVD) risk [3].

Worldwide, about 1% of the population has rheumatoid arthritis (RA), defined as an autoimmune disorder that results in disruption of joints and chronic inflammation [4]. CVD risk in patients with RA is higher than in subjects without RA [5], and obesity affects the RA patient's risk for CVD [6]. Reports indicate that obesity in patients with RA decreases quality of life (QOL), activities of daily living (ADL) [7], and the effect of anti-rheumatic medications [8]. Therefore, prevention and improvement of obesity are thought to be important in patients with RA. On the other hand, a relationship between increased inflammation and decreases in BMI in patients with RA have been reported [9], and underweight has been shown to be related to low QOL and ADL [10], and increases CVD risk [11] in patients with RA. These findings suggest the importance of maintaining a normal body weight, that is, neither underweight nor overweight.

Body weight is mainly affected by lifestyle factors such as energy and nutrient intake and exercise. However, few reports have investigated the relationship between body weight and lifestyle factors on patients

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with RA, or the relationship between BMI and disease activity, ADL, and CVD-related clinical data in patients with RA. We aimed to clarify the relationships between BMI and lifestyle factors, and also compared ADL, disease activity, and CVD-related clinical data in female patients with RA divided into underweight, normal, and overweight categories based on BMI.

MATERIALS AND METHODS

Study Design

In this study, we used year 2011 data from 171 female RA outpatients and 170 age-matched controls without RA who participated in the TOMORROW study (UMIN: 000003876). TOMORROW is a 10-year prospective cohort study conducted in Osaka City University Medical School starting in 2010 that includes 208 Japanese patients with RA and 205 age- and sex-matched Japanese subjects without RA [12]. All of the study's subjects are older than 20 years and control subjects were recruited by mass media. We performed a sub-analysis of 2011 data in this cross-sectional study. This study was conducted with approval from the Ethics Committee at Osaka City University Medical School, and all participants provided written, informed consent based on the Declaration of Helsinki. A diagnosis of RA was made according to the American College of Rheumatology criteria [13]. Using the year 2010 baseline registration data gained through a questionnaire, we assessed subjects' basic status regarding smoking, alcohol intake, current exercise habits, current exercise restrictions from doctors, walking time per day, and history and treatment for diabetes mellitus, dyslipidemia, and hypertension. BMI was calculated as weight divided by square of height (kg/m^2), and we divided patients into three BMI categories: underweight (BMI < 18.5 kg/m^2; RA, n = 21; controls, n = 23), normal weight (BMI ≥ 18.5 and < 25 kg/m^2; RA, n=112; controls, n = 119), and overweight (BMI ≥ 25 kg/m^2; RA, n = 38; controls, n = 28) [14]. Because the number of subjects with a BMI > 30 kg/m^2 was limited in both the RA group (n = 7) and control group (n = 3), we included these subjects in the overweight category. We set the ideal body weight (IBW) as the square of height (m) × 22 [15].

Disease Activity and ADL Assessment

Disease Activity Score for 28 joints based on erythrocyte sedimentation rate (DAS28-ESR) was used to assess disease activity [16], and the modified Health Assessment Questionnaire (mHAQ) was used to evaluate ADL [17]. Higher mHAQ scores indicate a lower ADL level.

Energy and Nutrient Intake Assessment

A brief-type dietary history questionnaire was used to assess energy and nutrient intake [18], and we excluded one subject in both the RA and control groups who had low energy intake (less than 600 kcal per day) [12].

Blood Chemistry and Physiological Assessment

We assessed systolic blood pressure (SBP), diastolic blood pressure (DBP), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), uric acid (UA), total cholesterol (T-chol), triglycerides (TG), high-density lipoprotein cholesterol, (HDL-chol), low-density lipoprotein cholesterol (LDL-chol), fasting plasma glucose (FPG), immunoreactive insulin (IRI), HbA1c, leptin, and adiponectin. Blood samples were collected after an overnight fast, and serum samples were stored at −80°C before analysis in 2010.

Statistical Analysis

Dr. SPSS II for Windows, version 11.0.1J (SPSS Japan Inc., Tokyo, Japan) was used for statistical analysis. Data are shown as number of subjects (%) or median (interquartile range [IQR]) because data were not normal distribution. The Kruskal-Wallis test and chi-square test were used to analyze differences between the three groups, and the Jonckheere-Terpstra test was used to estimate the trend of the *p* value. Correlation coefficient (R) was calculated as an age adjusted value for adjusting variable collinearity; values > 0.20 represented a correlation. A *p* value < 0.05 was considered statistically significant.

RESULTS

Subjects' Characteristics Based on BMI Group

Subjects' characteristics by BMI group are shown in Table **1**. In the RA group, there were significant differences in age ($p = 0.010$), waist circumference ($p < 0.001$), mHAQ score ($p = 0.035$), and the number of patients with a history of smoking ($p = 0.008$) among the three groups. DAS28-ESR, the number of patients with a history of diabetes mellitus, and the number of patients with a history of hypertension had a tendency to differ among the three groups. Age had a tendency to increase with BMI. There were no significant differences in exercise or medication status among the

Table 1: Subject Characteristics by BMI Group

	RA (n = 171)					Control (n = 170)				
	UW (n = 21)	NW (n = 112)	OW (n = 38)	*p* value	*p* for trend	UW (n = 23)	NW (n = 119)	OW (n = 28)	*p* value	*p* for trend
Age (years)	55 (21.5)	60 (18.5)	66 (12.5)	0.034	0.010	57 (10.0)	61 (17.0)	61 (16.0)	0.262	0.354
Height (cm)	155.2 (8.9)	153.9 (10.8)	150.8 (10.7)	0.025	0.008	158.1 (8.1)	155.0 (8.3)	155.5 (8.3)	0.371	0.477
Weight (kg)	43.3 (5.5)	50.8 (8.9)	63.6 (9.0)	<0.001	<0.001	43.9 (6.6)	52.9 (6.4)	63.6 (11.6)	<0.001	<0.001
BMI (kg/m^2)	18.1 (0.8)	21.2 (3.2)	27.3 (2.9)	<0.001	<0.001	17.5 (0.9)	22.0 (2.8)	26.4 (2.8)	<0.001	<0.001
Waist circumference (cm)	68.1 (7.4)	79.0 (11.1)	93.5 (10.3)	<0.001	<0.001	67.7 (7.8)	79.9 (9.4)	91.2 (9.9)	<0.001	<0.001
RA duration (years)	15.1 (18.0)	10.2 (14.0)	10.1 (15.4)	0.637	0.628	-	-	-	-	-
mHAQ score	0.4 (0.9)	0.1 (0.8)	0.3 (1.0)	0.035	0.681	-	-	-	-	-
DAS28-ESR	3.8 (1.5)	3.3 (1.9)	3.7 (1.9)	0.087	0.866	-	-	-	-	-
Smoking (%)	4 (19)	30 (27)	2 (5)	0.008	-	1 (4)	9 (8)	1 (4)	0.672	-
Alcohol drinking (%)	12 (57)	47 (42)	17 (45)	0.440	-	11 (48)	58 (49)	11 (39)	0.664	-
Exercise habits (%)	3 (14)	19 (17)	9 (24)	0.588	-	11 (48)	67 (56)	14 (50)	0.675	-
Exercise restriction (%)	5 (24)	34 (30)	9 (24)	0.657	-	0 (0)	2 (2)	3 (11)	0.026	-
Walking time (min/day)	60 (90)	30 (40)	40 (70)	0.130	0.520	60 (60)	60 (60)	60 (60)	0.424	0.227
Diabetes (%)	0 (0)	5 (4)	5 (13)	0.068	-	0 (0)	5 (4)	1 (4)	0.607	-
DM therapy: insulin injection (%)	0 (0)	1 (20)	0 (0)	1.000	-	0 (0)	4 (100)	1 (100)	-	-
DM therapy: oral medication (%)	0 (0)	2 (40)	4 (100)	0.167	-	0 (0)	2 (50)	0 (0)	1.000	-
Dyslipidemia (%)	6 (29)	34 (30)	12 (32)	0.971	-	10 (44)	71 (60)	15 (54)	0.338	-
Medication for DL (%)	2 (33)	14 (41)	7 (58)	0.500	-	1 (10)	20 (28)	5 (33)	0.403	-
Hypertension (%)	6 (29)	27 (24)	17 (45)	0.054	-	1 (4)	22 (19)	12 (43)	0.002	-
Medication for HT (%)	5 (83)	25 (93)	15 (88)	0.757	-	0 (0)	17 (77)	6 (50)	0.103	-
DMARD user (%)	20 (95)	103 (92)	35 (92)	0.871	-	-	-	-	-	-
Glucocorticoid user (%)	5 (24)	26 (23)	13 (34)	0.398	-	-	-	-	-	-
Biological DMARD user (%)	15 (71)	66 (58.9)	18 (47)	0.187	-	-	-	-	-	-

Data are shown as median (interquartile range) or number (%). Kruskal-Wallis test and chi-square test were used for statistical analysis. Jonckheere-Terpstra test was used for assessment of trend. BMI, body mass index; RA, rheumatoid arthritis; UW, underweight (BMI <18.5 kg/m^2); NW, normal weight (≥ 18.5 kg/m^2 and < 25 kg/m^2); OW, overweight (BMI ≥25 kg/m^2); mHAQ, modified Health Assessment Questionnaire; DAS28-ESR, Disease Activity Score 28 based on erythrocyte sedimentation ratio; DM, diabetes mellitus; DL, dyslipidemia; HT, hypertension; DMARD, disease-modifying anti-rheumatic drug.

three groups of patients with RA. In the control group, there was a significant difference between BMI groups in terms of exercise restriction, but there were no significant differences in exercise habits and walking time per day; other characteristics showed a similar trend to patients with RA. In the RA group, DAS28-ESR and mHAQ scores in the normal weight group were lower than scores in the underweight and overweight groups. We applied a quadratic curve to the scattergrams between BMI and both DAS28-ESR and mHAQ scores; these two parameters showed the lowest scores near a BMI of 22 kg/m^2 (Figure **1**). We also assessed the relationship between BMI and both DAS28-ESR and mHAQ scores after adjusting for age. BMI didn't show the significant correlation between DAS28-ESR (r = 0.024) or mHAQ scores (r = 0.039) in whole RA group. In patients who had BMI < 22 kg/m^2 (n = 88), BMI showed no correlation with DAS28-ESR score (r = -0.06). However, there was a negative correlation between BMI and mHAQ score (r = -0.20) in these patients, and the mHAQ score showed a positive correlation with DAS28-ESR score (r = 0.40). In patients who had BMI >22 kg/m^2 (n = 83), BMI showed no correlation between DAS28-ESR (r = 0.15) or mHAQ scores (r = -0.12). However, in the overweight group, BMI showed a positive correlation with DAS28-ESR score (r = 0.27), but not with mHAQ score (r = 0.01). There was a positive correlation between DAS28-ESR and mHAQ scores in the overweight group (r = 0.24) (data not shown).

Energy and Nutrient Intake Based on BMI Category

Energy and nutrient intake status as crude values and intake per ideal body weight (IBW) are shown in Table **2**. In the RA group, energy (*p* = 0.041), protein (*p* = 0.003), and carbohydrate intake (*p* = 0.015) showed

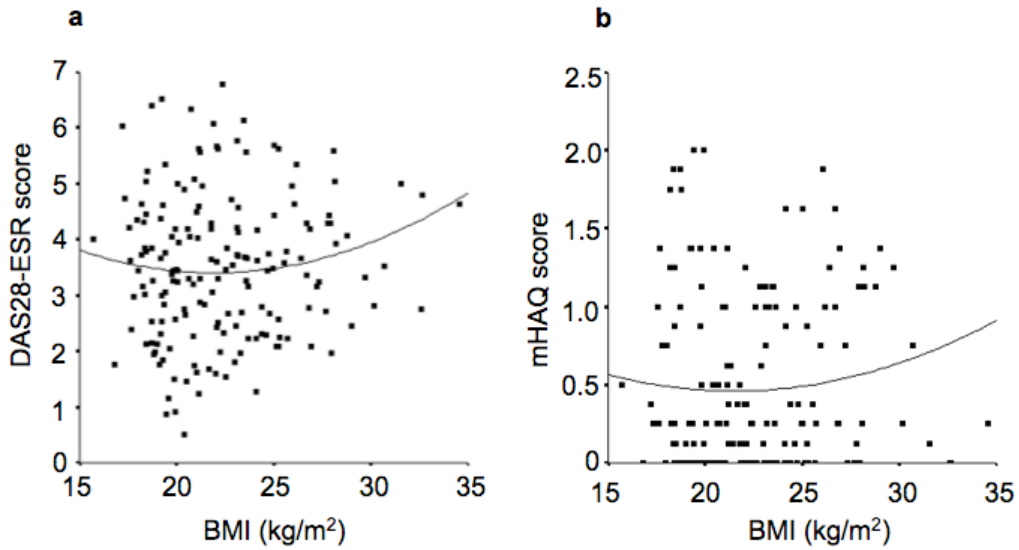

Figure 1: Scattergrams of BMI and RA variables. (**a**) BMI and DAS28-ESR; (**b**) BMI and mHAQ score. BMI, body mass index; DAS28-ESR, Disease Activity Score for 28 joints based on erythrocyte sedimentation rate; mHAQ, modified Health Assessment Questionnaire.

Table 2: Subject Energy and Nutrient Intake by BMI Group

	RA (n = 170)					Control (n = 169)				
	UW (n = 21)	NW (n = 111)	OW (n = 38)	*p* value	*p* for trend	UW (n = 23)	NW (n = 119)	OW (n = 27)	*p* value	*p* for trend
Energy (kcal)	1460 (483)	1422 (615)	1622 (648)	0.041	0.036	1539 (778)	1541 (554)	1765 (581)	0.417	0.492
Energy intake per IBW (kcal / kg)	27 (7)	27 (11)	33 (13)	0.003	0.003	29 (17)	29 (12)	32 (12)	0.448	0.463
Protein (g)	53.7 (19.5)	51.9 (24.2)	64.2 (34.0)	0.003	0.005	56.4 (24.0)	64.6 (28.9)	63.1 (40.3)	0.713	0.448
Protein intake per IBW (g / kg)	1.0 (0.3)	1.0 (0.6)	1.3 (0.6)	0.000	0.001	1.1 (0.6)	1.2 (0.6)	1.2 (0.8)	0.743	0.501
Fat (g)	44.6 (17.4)	38.0 (22.0)	46.2 (23.3)	0.067	0.297	42.1 (27.1)	47.2 (17.8)	51.8 (26.6)	0.230	0.085
Fat intake per IBW (g / kg)	1.2 (0.4)	1.4 (0.8)	1.1 (0.6)	0.022	0.078	1.3 (0.9)	1.1 (0.5)	1.0 (0.6)	0.223	0.081
Carbohydrate (g)	189.0 (76.8)	200.0 (78.6)	229.0 (91.0)	0.015	0.006	233.8 (113.5)	208.0 (80.9)	222.2 (76.0)	0.067	0.888
Carbohydrate intake per IBW (g / kg)	3.6 (1.3)	3.8 (1.7)	4.6 (1.8)	0.001	<0.001	4.1 (1.9)	3.9 (1.8)	4.4 (1.6)	0.054	0.939

Data are shown as median (interquartile range). Kruskal-Wallis test was used for statistical analysis. Jonckheere-Terpstra test was used for assessment of trend. Energy and nutrient intake are shown as crude value and per ideal body weight (IBW). IBW was calculated as height (m^2) × 22. BMI, body mass index; RA, rheumatoid arthritis; UW, underweight (BMI < 18.5 kg/m^2); NW, normal weight (≥ 18.5 kg/m^2 and < 25 kg/m^2); OW, overweight (BMI ≥ 25 kg/m^2).

significant differences among the three BMI groups. Energy and nutrient intake per IBW also showed a significant difference among the three BMI groups and showed a positive trend with BMI. The overweight group showed a higher value for energy and nutrient intake compared with the normal and underweight groups. In the control group, carbohydrate intake per IBW in the overweight group was higher than in the normal weight and underweight groups.

Blood Chemistry and Physiological Data Based on BMI Category

Table **3** shows blood chemistry and physiological data by BMI category. In the RA group, SBP (p = 0.001), DBP (p = 0.011), CRP (p = 0.014), UA (p = 0.004), TG (p = 0.005), FPG (p < 0.001), IRI (p < 0.001), HbA1c (p = 0.036), leptin (p < 0.001), and adiponectin (p = 0.007) showed significant differences among groups, and these parameters, excluding adiponectin, had a tendency to increase with BMI (p < 0.05 for trend). The control group showed similar trends.

DISCUSSION

In this study, we assessed and compared subject characteristics, disease activity, ADL, energy and nutrient intake, and some CVD risk-related clinical data

Table 3: Subject Clinical Data by BMI Group

	RA (n = 171)					Control (n = 170)				
	UW (n = 21)	NW (n = 112)	OW (n = 38)	*p* value	*p* for trend	UW (n = 23)	NW (n = 119)	OW (n = 28)	*p* value	*p* for trend
SBP (mmHg)	117 (36)	130 (27)	145 (29)	0.001	<0.001	109 (16)	119 (27)	141 (26)	<0.001	<0.001
DBP (mmHg)	74 (16)	77 (14)	82 (19)	0.011	0.002	68 (9)	73 (16)	84 (12)	<0.001	<0.001
ESR (mm / hr)	20 (25)	20 (23)	30 (36)	0.052	0.075	8 (8)	10 (9)	8 (12)	0.267	0.45
CRP (mg / dl)	0.10 (0.22)	0.10 (0.34)	0.32 (0.91)	0.014	0.007	0.01 (0.01)	0.02 (0.04)	0.04 (0.11)	0.001	<0.001
UA (mg / dl)	4.1 (1.1)	4.3 (1.6)	5.1 (1.3)	0.004	0.001	4.3 (1.0)	4.6 (1.0)	4.7 (2.0)	0.034	0.01
T-chol (mg / dl)	196 (44)	212 (44)	206 (60)	0.533	0.407	214 (56)	219 (45)	209 (32)	0.546	0.37
TG (mg / dl)	61 (30)	79 (49)	88 (57)	0.005	0.006	52 (35)	72 (48)	88 (43)	<0.001	<0.001
HDL-chol (mg / dl)	72 (12)	69 (25)	64 (18)	0.056	0.018	85 (42)	70 (23)	62 (15)	<0.001	<0.001
LDL-chol (mg / dl)	112 (31)	120 (38)	119 (55)	0.169	0.104	109 (46)	124 (40)	113 (35)	0.403	0.461
FPG (mg / dl)	79 (8)	82 (10)	87 (13)	0.000	<0.001	83 (12)	89 (10)	93 (12)	0.002	<0.001
IRI (μIU / ml)	3.5 (2.2)	4.0 (2.9)	6.2 (3.6)	0.000	<0.001	2.0 (0.9)	3.1 (1.6)	4.9 (2.6)	<0.001	<0.001
HbA1c (NGSP value) (%)	5.3 (0.4)	5.5 (0.5)	5.6 (0.7)	0.036	0.011	5.6 (0.2)	5.7 (0.4)	5.6 (0.5)	0.182	0.563
Leptin (ng / ml)	2.2 (4.4)	6.5 (6.3)	17.1 (11.0)	0.000	<0.001	1.9 (1.8)	5.6 (4.9)	12.7 (10.8)	<0.001	<0.001
Adiponectin (μg / ml)	19.7 (11.0)	16.1 (12.9)	12.5 (10.0)	0.007	0.003	12.9 (17.1)	12.0 (8.6)	10.1 (5.7)	<0.001	0.008

Data are shown as median (interquartile range). Kruskal-Wallis test was used for statistical analysis. Jonckheere-Terpstra test was used for assessment of trend. BMI, body mass index; RA, rheumatoid arthritis; UW, underweight (BMI < 18.5 kg/m^2); NW, normal weight (≥ 18.5 kg/m^2 and < 25 kg/m^2); OW, overweight (BMI ≥ 25 kg/m^2); SBP, systolic blood pressure; DBP, diastolic blood pressure; ESR, erythrocyte sedimentation rate; CRP, C reactive protein; UA, uric acid; T-chol, total cholesterol; TG, triglyceride; HDL-chol, high-density lipoprotein cholesterol; LDL-chol, low-density lipoprotein cholesterol; FPG, fasting plasma glucose; IRI, immuno reactive insulin; NGSP, National Glycohemoglobin Standardization Program.

based on BMI category in female patients with and without RA. In patients with RA, patient age showed a positive correlation with BMI. One report in Japan showed that obesity in older females was higher than that in younger females [19], and our results in RA patients are consistent with this report. ADL and disease activity scores in the normal weight group were better than scores in the underweight and overweight groups, and these parameters were best at a BMI of 22 kg/m^2. The reason the underweight group showed higher disease activity might be related to a report that suggested that high disease activity is caused by acute inflammation related to decreased skeletal muscle mass [9]. The reason for lower ADL in the underweight group may also be related to high disease activity that has been shown in underweight patients with RA [10]. Our results are consistent with these reports. Disease activity scores were higher and ADL was lower in the overweight group than in the normal weight group. In patients with RA, obesity is related to attenuation of medication effects, although the reason for this is unclear [8]. Obesity is also related to high disease activity in patients with RA [7], and high disease activity is related to low ADL in patients with RA [20]. Based on these reports and our results, it is possible that patients with RA who are underweight or overweight may have higher disease activity or lower ADL than normal weight patients, and maintaining a normal weight might be a healthy status indicator in patients with RA. However, the benefit of weight control on disease activity and ADL in underweight or overweight patients with RA should be assessed.

In terms of energy and nutrient intake in patients with RA, energy, protein, and carbohydrate intake in the overweight group were higher than values in the normal weight and underweight groups. However, the status of energy and protein intake per IBW was similar in the underweight and normal weight groups. Carbohydrate intake per IBW showed a strong positive correlation with BMI in patients with RA, and the overweight control group also showed a higher carbohydrate intake per IBW than the underweight and normal weight control groups. In terms of weight loss in obese subjects, it is reported that the kind of energy source nutrient affects weight loss, and restriction from carbohydrate-derived energy is most effective for weight loss [21]. The current study also suggests that the kind of energy-derived nutrient affects weight in daily life, as our results showed a positive correlation between BMI and carbohydrate intake in patients with RA. Carbohydrate intake restriction in overweight patients with RA may contribute to weight loss, and an increase in carbohydrate intake in underweight patients

with RA may help with weight gain to help patients maintain a normal weight.

In patients with RA, higher BMI was related to higher blood pressure, CRP, TG, FPG, IRI, leptin, and lower adiponectin. This trend was similar in our control population, and has been reported in a general population [2]. Our results suggest that weight control in overweight patients with RA may improve CVD-related clinical data. It is reported that underweight in patients with RA is related to CVD risk [11], although our data showed that underweight patients with RA had the most healthy CVD-related clinical data among the three BMI categories. CVD risk in patients with RA is not fully explained with only traditional CVD risk factors, such as hypertension, glucose intolerance, and dyslipidemia; inflammation and disease activity also affect CVD risk [6]. These facts and our results may suggest that normal weight patients with RA whose inflammation status, disease activity, and CVD-related clinical data were relatively good compared with underweight and overweight groups may represent a lower CVD risk group among RA patients.

This study has some limitations. First, this subanalysis is cross-sectional. Longitudinal and intervention studies are needed to clarify the etiology between BMI and disease activity, ADL, and CVD-related clinical data. Second, we analyzed only women because the study population was limited. Data are also needed for male patients with RA. Third, in this study, although there was no significant difference in medication status for RA among three BMI category groups, some reports showed medications for RA treatment affected lipid metabolism profiles [22-24]. Fourth, we assessed Japanese population's data. Because of Asian ethnic characteristics, Japanese population with lower BMI might be susceptible to the change of obesity-related metabolism compared to other ethnics. The differences in baseline characteristic of BMI might affect the results in different studies [25, 26]. In this aspect, careful interpretation of the results regarding the effects of BMI in different ethnic population should be required.

CONCLUSIONS

In patients with RA, maintaining a normal weight may help keep disease activity, ADL, and CVD-related clinical data at relatively good levels. Energy intake, especially carbohydrates, may contribute to increased BMI in patients with RA.

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STATEMENT OF AUTHORSHIP

YM analyzed the data and drafted the manuscript. YS, MT, TO, KM, and KI participated in the study design and collected data. DH contributed to data analysis, statistical analysis, and interpretation of results. TK carried out the study design and data collection, and supervised drafting the manuscript.

FOUNDATION

There was no specific foundation for this study.

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