JDI Journal of Diabetes Investigation Open access
Official Journal of the Asian Association for the Study of Diabetes
ORIGINAL ARTICLE

Association of mean corpuscular volume with sarcopenia and visceral obesity in individuals without anemia

Muhei Tanaka[1*], Hiroshi Okada[2], Yoshitaka Hashimoto[1], Muneaki Kumagai[3], Hiromi Nishimura[3], Michiaki Fukui[1]

[1]Department of Endocrinology and Metabolism, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan, [2]Department of Internal Medicine, Matsushita Memorial Hospital, Osaka, Japan, and [3]Medical Corporation Soukenkai, Nishimura Clinic, Kyoto, Japan

Keywords
Cell shrinkage, Mean corpuscular volume, Sarcopenia and obesity

***Correspondence**
Muhei Tanaka
Tel.: +81-75-251-5505
Fax: +81-75-252-3721
E-mail address:
muhei-t@koto.kpu-m.ac.jp

J Diabetes Investig 2021; 12: 1287–1292

doi: 10.1111/jdi.13466

ABSTRACT

Aims/Introduction: Sarcopenia and visceral obesity are major global public health issues, and higher mean corpuscular volume (MCV) levels are related to adverse outcomes. Nevertheless, no study has determined the association between MCV and body composition. Therefore, we evaluated the association between MCV levels and trunk muscle quality, muscle quantity and visceral fat area.

Materials and Methods: In our cross-sectional study, we investigated 702 middle-aged Japanese individuals without anemia and with normal MCV levels who underwent physical checkups. The cross-sectional area of skeletal muscle or visceral fat was analyzed by computed tomography.

Results: In the adjusted model, the MCV was independently associated with the visceral fat area index (β = –0.107, P = 0.0007), total skeletal muscle index (β = 0.053, P = 0.0341) and total skeletal muscle density (β = 0.099, P = 0.0012). MCV as a continuous variable was related to the prevalence of sarcopenia (odds ratios [OR] 0.93, 95% confidence intervals (CI) 0.88–0.98, per 1.0 fL increment; P = 0.0097) and visceral obesity (OR 0.91, 95% CI 0.86–0.97, per 1.0 fL increment; P = 0.0046). The highest MCV quartile was independently associated with the prevalence of sarcopenia (OR 0.48, 95% CI 0.27–0.83; P = 0.0089) and visceral obesity (OR 0.49, 95% CI 0.27–0.88; P = 0.0170), compared with the lowest quartile.

Conclusions: In individuals without anemia and with normal MCV levels, a lower MCV was associated with unfavorable body composition, including lower muscle quality, lower muscle quantity, sarcopenia and visceral obesity.

INTRODUCTION

Unfavorable body composition changes with aging include sarcopenia, characterized by muscle loss and decline in muscular strength, and body fat accumulation leading to obesity[1]. These are related to metabolic deteriorations and physical impairment, and contribute to adverse outcomes[2]. Sarcopenia often accompanies obesity and leads to a specific condition known as sarcopenic obesity[3]. Individuals with sarcopenic obesity might have more metabolic impairments and an elevated risk of mortality than sarcopenia or obesity alone[4].

Mean corpuscular volume (MCV) is a capacity of the mean size of red blood cells (RBCs), and is associated with mortality and morbidity[5,6]. In particular, some studies have shown that macrocytosis is associated with adverse outcomes[5,7,8].

No survey on the association between MCV and body composition is currently available in the literature. Given previous findings, we hypothesized that a higher MCV would be associated with unfavorable body composition, such as sarcopenia and obesity. Therefore, we analyzed the relationship between MCV and body composition parameters, including trunk muscle quality and quantity, and visceral fat area (VFA) by computed tomography (CT). As CT can classify skeletal muscle into areas of intermuscular adipose tissue (IMAT), normal-attenuation muscle (NAM) and low-attenuation muscle (LAM), we also analyzed whether the MCV was associated with IMAT, NAM and LAM. The present study aimed to investigate whether MCV levels were associated with muscle quality,

Received 18 August 2020; revised 8 November 2020; accepted 15 November 2020

muscle quantity, unfavorable body composition, sarcopenia and visceral obesity in middle-aged Japanese individuals without anemia and with normal MCV levels.

METHODS

Study design

The Nishimura Health Survey has been described previously[9]. We carried out a cross-sectional analysis to investigate MCV and body composition parameters. From 20,852 individuals who received physical checkups from 1 April 2013 to 31 March 2018, 830 individuals had an abdominal CT scan. The CT is not included in the basic examination items; however, it can be carried out on request. We excluded two individuals in whom at least one variable was not assessed. From the remaining 828 individuals, we excluded 20 individuals with a history of malignant disease or high C-reactive protein (CRP) levels >95.2 nmol/L (10.0 mg/L), because such elevated levels might be related to active infection or systemic inflammatory processes. We also excluded five individuals who had indicators of renal dysfunction (defined based on thresholds of serum creatinine of 106.1 μmol/L for men and 88.4 μmol/L for women), 75 individuals with anemia (defined based on thresholds of hemoglobin 130.0 g/L for men and 120.0 g/L for women) and 26 individuals without normal MCV levels (defined based on thresholds of MCV <80 and >100 fL), because kidney dysfunction, vitamin B_{12} and iron deficiency affect erythropoiesis. Finally, 702 individuals were competent for the present study. All procedures were approved by the local research ethics committee of Kyoto Prefectural University of Medicine (ERB-C-1017-1), and carried out in accordance with the Declaration of Helsinki. Informed consent was obtained from all study participants.

Data measurements

Demographic data and biomarkers were investigated, as described previously[9].

CT

Evaluation of skeletal muscle area, skeletal muscle density (SMD) and VFA were carried out, as previously described[9].

Definitions

The study participants were classified by sex, and divided into four subgroups according to MCV quartiles: the cut-off quartile levels for men were 88.62, 91.349 and 93.74 fL, whereas those for women were 87.58, 89.92 and 92.15 fL, respectively.

Diabetes mellitus was defined according to the criteria recommended by the American Diabetes Association, in addition to a medical history of diabetes. Prediabetes was defined as a fasting blood glucose level from 100 to 125 mg/dL (5.6–7.0 mmol/L). Hypertension was defined as a systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg, in addition to a medical history of hypertension. Dyslipidemia was defined as either or a combination of low-density lipoprotein cholesterol ≥4.14 mmol/L, high-density lipoprotein cholesterol <1.03 mmol/L or triglycerides ≥1.69 mmol/L, in addition to a medical history of dyslipidemia.

The cross-sectional areas by CT scan were standardized for body mass index (BMI; $cm^2/[kg/m^2]$)[10], and described as the skeletal muscle index (SMI), NAM index, LAM index, VFA index and IMAT index. Sarcopenia was defined as SMI one standard deviation below the sex-specific mean level for young adults (18–40 years)[11]. In the present study, the cut-off levels were 6.06 $cm^2/(kg/m^2)$ for men and 4.35 $cm^2/(kg/m^2)$ for women. Visceral obesity was defined as a VFA ≥100 cm^2 according to the Japanese visceral obesity criteria[12]. Sarcopenic obesity was defined as a combination of obesity and sarcopenia, as defined by the International Obesity Task Force.

Statistical analysis

We used one-way analysis of variance (ANOVA) and the χ^2-test. Multiple regression analyses were carried out to determine the associations between MCV and several muscle parameters or the VFA index. Multivariate logistic regression analyses were carried out to determine the association between erythrocyte indices as a continuous variable or quartiles, and the prevalence of sarcopenia, visceral obesity and sarcopenic obesity after controlling for confounding factors. The following parameters were determined as potential covariates: model 1, adjusted by age and sex; model 2, adjusted by model 1 covariates plus smoking status, drinking status and exercise status; model 3, adjusted by model 2 covariates plus the prevalence of hypertension, dyslipidemia, diabetes mellitus, albumin, estimated glomerular filtration rate and CRP levels; and model 4, adjusted by model 3 covariates plus hemoglobin level. We divided the participants into three groups: normal, prediabetes and diabetes; and subgroup analyses were carried out. We used JMP version 11.0 software (SAS Institute Inc., Cary, NC, USA) for statistical analyses.

RESULTS

The characteristics of the 702 participants (462 men and 240 women) are shown in Table 1. There was a significant difference across MCV quartiles in terms of age ($P < 0.0001$), BMI ($P < 0.0001$), regular exercise ($P = 0.0002$), alcohol consumption ($P < 0.0001$), current smoker ($P = 0.0021$), estimated glomerular filtration rate ($P = 0.0018$) and CRP levels ($P = 0.0016$). There was no significant difference across the MCV quartiles in terms of VFA index, IMAT index, total SMI, NAM index, LAM index and total SMD, as well as the prevalence of sarcopenia, visceral obesity and sarcopenic obesity.

The results of multiple regression analyses are shown in Table 2. In model 4, MCV was independently associated with the VFA index ($\beta = -0.107$, $P = 0.0007$), total SMI ($\beta = 0.053$, $P = 0.0341$), NAM index ($\beta = 0.061$, $P = 0.0166$) and total SMD ($\beta = 0.099$, $P = 0.0012$).

Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) of MCV levels for the prevalence of sarcopenia, visceral

Table 1 | Clinical characteristics of the study participants according to the mean corpuscular volume quartiles

	Q1	Q2	Q3	Q4	*P*-value
n	175	175	176	176	
Age (years)	46.6 ± 9.8	51.2 ± 10.4	52.4 ± 10.5	53.8 ± 10.3	<0.0001
Men	115 (65.7)	115 (65.7)	116 (65.9)	116 (65.9)	1.0000
Body mass index (kg/m^2)	24.1 ± 4.4	23.4 ± 3.9	22.6 ± 3.1	22.4 ± 3.1	<0.0001
Regular exercise	27 (15.4)	46 (26.3)	61 (34.7)	56 (31.8)	0.0002
Alcohol drinking habit	10 (5.7)	31 (17.7)	44 (25.0)	61 (34.7)	<0.0001
Current smoker	23 (13.1)	20 (11.4)	36 (20.5)	44 (25.0)	0.0021
Ex-smoker	40 (22.9)	50 (28.6)	40 (22.7)	48 (27.3)	0.4721
Hypertension	46 (26.3)	41 (23.4)	54 (30.7)	54 (30.7)	0.3443
Dyslipidemia	48 (27.4)	47 (26.9)	43 (24.4)	42 (23.9)	0.8361
Diabetes mellitus	14 (8.0)	15 (8.6)	16 (9.1)	7 (4.0)	0.2425
Albumin (g/L)	45.0 ± 2.8	45.1 ± 2.7	45.3 ± 2.2	44.8 ± 2.6	0.3161
Estimated glomerular filtration rate (mL/min/1.73 m^2)	80.1 ± 14.3	76.9 ± 12.0	76.0 ± 12.1	75.2 ± 11.9	0.0018
C-reactive protein level† (nmol/L)	9.4 ± 14.0	9.4 ± 13.2	6.1 ± 8.0	6.6 ± 11.3	0.0016
White blood cell count (×10^9/L)	5.79 ± 1.40	5.70 ± 1.72	5.58 ± 1.42	5.46 ± 1.65	0.2153
Red blood cell count (×10^{12}/L)	5.0 ± 0.4	4.8 ± 0.3	4.7 ± 0.3	4.6 ± 0.3	<0.0001
Hemoglobin (g/L)	143.3 ± 12.2	142.9 ± 11.4	141.7 ± 11.5	143.5 ± 11.6	0.4753
Hematocrit (%)	43.5 ± 3.3	43.4 ± 3.0	43.0 ± 3.1	43.7 ± 3.1	0.2652
Mean corpuscular volume (fL)	86.3 ± 1.6	89.7 ± 0.9	91.9 ± 1.0	95.3 ± 1.7	<0.0001
Mean corpuscular hemoglobin (pg/cell)	28.4 ± 0.9	29.6 ± 1.0	30.2 ± 0.9	31.3 ± 1.2	<0.0001
Mean corpuscular hemoglobin concentration (g/L)	329.2 ± 8.6	329.5 ± 9.6	329.1 ± 8.2	328.5 ± 10.7	0.8080
Visceral fat area index (cm^2/kg/m^2)	4.2 ± 2.4	4.0 ± 2.3	4.0 ± 2.3	3.8 ± 2.3	0.3908
IMAT index (cm^2/[kg/m^2])	0.09 ± 0.10	0.09 ± 0.08	0.11 ± 0.09	0.10 ± 0.09	0.3696
Total SMI (cm^2/[kg/m^2])	5.7 ± 1.2	5.8 ± 1.3	5.7 ± 1.1	5.8 ± 1.1	0.8520
NAM index (cm^2/[kg/m^2])	4.3 ± 1.4	4.3 ± 1.4	4.2 ± 1.2	4.3 ± 1.2	0.9615
LAM index (cm^2/[kg/m^2])	1.4 ± 0.4	1.5 ± 0.4	1.4 ± 0.4	1.5 ± 0.4	0.1759
Total SMD (HU)	42.3 ± 7.1	42.3 ± 7.3	42.1 ± 6.5	42.2 ± 7.0	0.9838
Sarcopenia	67 (38.3)	68 (38.9)	69 (39.2)	53 (30.1)	0.2305
Visceral obesity	88 (50.3)	78 (44.6)	74 (42.1)	72 (40.9)	0.2933
Sarcopenic obesity	50 (28.6)	36 (20.6)	44 (25.0)	36 (20.5)	0.2178

For men, quartile (Q)1: <88.62; Q2: 88.62–91.349; Q3: 91.350–93.74; and Q4: >93.74 fL; for women, Q1: <87.58; Q2: 87.58–89.92; Q3: 89.93–92.15; and Q4: >92.15 fL. †Values were analyzed after log transformation.

Table 2 | Results from adjusted multiple regression analyses

	Visceral fat area index		IMAT index		Total SMI		NAM index		LAM index		Total SMD	
	β	*P*-value	β	*P*-value	β	*P*-value	β	*P*-value	β	*P*-value	β	*P*-value
MCV, adjusted model 1	−0.160	<0.0001	−0.069	0.0338	0.103	<0.0001	0.111	<0.0001	−0.054	0.1216	0.133	<0.0001
MCV, adjusted model 2	−0.176	<0.0001	−0.077	0.0233	0.100	0.0001	0.115	<0.0001	−0.076	0.0381	0.152	<0.0001
MCV, adjusted model 3	−0.112	0.0005	−0.059	0.0883	0.055	0.0279	0.064	0.0130	−0.043	0.2376	0.103	0.0009
MCV, adjusted model 4	−0.107	0.0007	−0.058	0.0910	0.053	0.0341	0.061	0.0166	−0.042	0.2566	0.099	0.0012

Model 1: adjusted for age and sex. Model 2: adjusted for model 1 covariates plus smoking status, drinking status and exercise status. Model 3: adjusted for model 2 covariates plus the prevalence of hypertension, dyslipidemia, diabetes mellitus, albumin, estimated glomerular filtration rate and C-reactive protein levels. Model 4: adjusted for model 3 covariates plus hemoglobin level. IMAT, intermuscular adipose tissue; LAM, low-attenuation muscle; MCV, mean corpuscular volume; NAM, normal-attenuation muscle; SMD, skeletal muscle density; SMI, skeletal muscle index.

obesity and sarcopenic obesity are shown in Table 3. In model 4, MCV as a continuous variable and the highest MCV quartile were independently associated with the prevalence of sarcopenia or visceral obesity. Indeed, MCV as a continuous variable (OR 0.94, 95% CI 0.88–1.01; $P = 0.0758$) and highest MCV quartile (OR 0.54, 95% CI 0.29–1.01; $P = 0.0539$) tended to be independently associated with the prevalence of sarcopenic obesity, although it did not reach statistical significance.

In model 3, RBC count, hemoglobin, hematocrit or mean corpuscular hemoglobin levels were independently associated with the prevalence of sarcopenia, whereas mean corpuscular hemoglobin concentration levels were not. In the same model, RBC count, hemoglobin, hematocrit or mean corpuscular hemoglobin concentration levels were independently associated with the prevalence of visceral obesity, whereas mean corpuscular hemoglobin levels were not. In the same model, RBC count, hemoglobin or hematocrit levels were independently associated with the prevalence of sarcopenic obesity, whereas mean corpuscular hemoglobin or mean corpuscular hemoglobin concentration levels were not.

After adjustment for age, sex, smoking status, drinking status, exercise status, hypertension, dyslipidemia, albumin, estimated glomerular filtration rate, CRP and hemoglobin levels, MCV as a continuous variable was independently associated with the prevalence of sarcopenia (OR per 1.0 increase 0.89, 95% CI 0.81–0.98; $P = 0.0149$) or visceral obesity (OR 0.89, 95% CI 0.80–0.98; $P = 0.0176$) in subjects with normal glucose levels. In the same model, MCV was not associated with the prevalence of sarcopenia, visceral obesity, or sarcopenic obesity in subjects with prediabetes. In the same model, MCV was independently associated with the prevalence of sarcopenia (OR, 0.37; 95% CI, 0.13.0.69; $P = 0.0003$) or sarcopenic obesity (OR 0.68, 95% CI 0.46–0.93; $P = 0.0132$) in participants with diabetes.

DISCUSSION

The present study has three principal survey results. First, even after full adjustment, MCV was related to the VFA index. Second, MCV was related to total SMI, NAM index and total SMD. In other words, MCV was related to both muscle quality and quantity. Third, MCV was related to the prevalence of sarcopenia or visceral obesity. Taken together, contrary to our prior hypothesis, we observed that a lower MCV was related to unfavorable body composition, leading to metabolic abnormalities in the participants without anemia and with normal MCV levels.

Table 3 | Adjusted odds ratios and 95% confidence intervals for the prevalence of sarcopenia, visceral obesity and sarcopenic obesity

	Sarcopenia		Visceral obesity		Sarcopenic obesity	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
MCV, per 1.0 fL increment						
Model 1	0.89 (0.85–0.94)	<0.0001	0.89 (0.84–0.94)	<0.0001	0.90 (0.85–0.95)	0.0002
Model 2	0.90 (0.85–0.95)	<0.0001	0.88 (0.83–0.93)	<0.0001	0.90 (0.85–0.95)	0.0002
Model 3	0.93 (0.88–0.98)	0.0086	0.91 (0.86–0.97)	0.0022	0.94 (0.88–1.00)	0.0659
Model 4	0.93 (0.88–0.98)	0.0097	0.91 (0.86–0.97)	0.0046	0.94 (0.88–1.01)	0.0758
MCV quartiles						
Model 1						
Q1	1.00		1.00		1.00	
Q2	0.67 (0.42–1.08)	0.1007	0.56 (0.34–0.92)	0.0207	0.46 (0.27–0.77)	0.0033
Q3	0.62 (0.38–0.99)	0.0460	0.43 (0.26–0.71)	0.0009	0.54 (0.32–0.90)	0.0177
Q4	0.34 (0.20–0.56)	<0.0001	0.37 (0.22–0.62)	0.0001	0.37 (0.21–0.63)	0.0003
Model 2						
Q1	1.00		1.00		1.00	
Q2	0.69 (0.42–1.11)	0.1279	0.55 (0.34–0.91)	0.0186	0.46 (0.27–0.78)	0.0037
Q3	0.65 (0.40–1.06)	0.0841	0.43 (0.26–0.72)	0.0013	0.54 (0.32–0.92)	0.0244
Q4	0.36 (0.21–0.60)	<0.0001	0.35 (0.20–0.60)	0.0001	0.37 (0.20–0.64)	0.0004
Model 3						
Q1	1.00		1.00		1.00	
Q2	0.76 (0.45–1.26)	0.2861	0.63 (0.37–1.06)	0.0836	0.51 (0.28–0.91)	0.0227
Q3	0.87 (0.52–1.47)	0.6119	0.55 (0.31–0.95)	0.0330	0.80 (0.45–1.43)	0.4506
Q4	0.48 (0.28–0.84)	0.0095	0.49 (0.28–0.87)	0.0153	0.55 (0.29–1.01)	0.0558
Model 4						
Q1	1.00		1.00		1.00	
Q2	0.76 (0.46–1.27)	0.3046	0.65 (0.38–1.11)	0.1124	0.51 (0.28–0.92)	0.0252
Q3	0.92 (0.54–1.54)	0.7438	0.62 (0.35–1.09)	0.0997	0.86 (0.48–1.55)	0.6259
Q4	0.48 (0.27–0.83)	0.0089	0.49 (0.27–0.88)	0.0170	0.54 (0.29–1.01)	0.0539

For men, quartile (Q)1: <88.62; Q2: 88.62–91.349; Q3: 91.350–93.74; and Q4: >93.74 fL; for women, Q1: <87.58; Q2: 87.58–89.92; Q3: 89.93–92.15; and Q4: >92.15 fL. Model 1: adjusted for age and sex. Model 2: adjusted for model 1 covariates plus smoking status, drinking status and exercise status. Model 3: adjusted for model 2 covariates plus the prevalence of hypertension, dyslipidemia, diabetes mellitus, albumin, estimated glomerular filtration rate and C-reactive protein levels. Model 4: adjusted for model 3 covariates plus hemoglobin level. CI, confidence interval; MCV, mean corpuscular volume; OR, odds ratio.

The present study provides some support to previous investigations. First, Cazzola *et al.*[13] showed that athletes undergoing regular and adequate training had higher MCV than sedentary individuals. Second, several studies in individuals with chronic kidney disease, heart failure or in a non-anemic healthy population showed that higher MCV levels were associated with mortality or heart failure, which was the main outcome of the studies[6,7,14]. However, these studies showed that a higher MCV was associated with lower BMI, glycated hemoglobin, cholesterol, triglyceride or uric acid levels, and a lower prevalence of diabetes mellitus, dyslipidemia and hypertension[6,7,14]. Third, Sun *et al.*[15] showed that a low MCV predicts a high risk of instent restenosis. Taken together, it seems plausible that a lower MCV is associated with lower muscle quality, lower muscle quantity, sarcopenia or visceral obesity in individuals without anemia and normal MCV levels.

There are several potential mechanisms that might explain the present findings. First, obesity is associated with an increase in inflammation, which is related to an increase in oxidative stress. Indeed, oxidative stress is associated with RBC shrinkage, and inflammation itself is a leading cause of microcytosis[16]. In addition, sarcopenia is associated with reactive oxygen and nitrogen species[17]. The disproportion between reactive oxygen and nitrogen species production and these anti-oxidant defenses causes oxidative stress[17]. Sportsmen undergoing sufficient training had made better anti-oxidant conditions, along with a more fluid membrane status of RBCs[13]. Second, MCV might be a biomarker of cell dehydration, shrinkage or swelling. The crystal osmotic pressure regulates erythrocyte volume, and increased crystal osmotic pressure might induce erythrocyte shrinkage and lower MCV[6]. Arginine vasopressin secretion increases with increasing crystal osmotic pressure, which is associated with lower MCV levels. Higher fasting arginine vasopressin levels are related to diabetes and obesity, because of the effectiveness of arginine vasopressin on adrenocorticotropic hormone and cortisol release[18]. In contrast, cell swelling causes anabolic effects, and the stimulation of glycogen synthesis, and decreases proteolysis[19]. A study reported that the decrement of crystal osmotic pressure promoted lipolysis and counteracted proteolysis[20].

The clinical relevance regards the diagnostic utility of MCV, as a provisional new marker of lower muscle quality, lower muscle quantity, sarcopenia and visceral obesity, that can be measured easily in the clinical laboratory and applied in medical practice. For the individuals who are generally considered healthy, the interesting concept of a role for MCV in unfavorable body composition holds great promise for the development of new preventive measures. However, the cross-sectional nature of the present study does not permit determination of causality. Indeed, it did not show whether MCV was a surrogate or predictable marker for clinical outcome. Therefore, large prospective studies are required to better assess the relationship between MCV levels and clinical outcome.

The present study had four limitations. First, the research participants were only Japanese. Racial characteristics are a significant factor of variation in body composition, and Western individuals have more muscle mass and less body adipose tissue compared with Asian individuals with the same BMI[21]. Therefore, generalizations to other races must be carried out with care. Second, we did not rule out the possibility of bone marrow malfunction, and did not measure factors affecting RBC size, such as thyroid function, iron, folic acid and vitamin B_{12} levels. Therefore, we excluded individuals with anemia or with abnormal MCV. Indeed, MCV was not related to white blood cell count, which was related to bone marrow function. Third, we did not propose a cut-off value of MCV for the prevalence of sarcopenia or visceral obesity, because MCV is associated with age. Our result is also in line with previous findings; indeed, in our unadjusted model, there were no significant differences across the MCV quartiles in terms of body composition parameters. However, in the age-adjusted model, MCV was related to several body composition parameters. Finally, we discussed possible underlying mechanisms regarding the association of MCV and body composition parameters. However, there are no data showing such mechanisms in the present study. Therefore, additional research is required to support the present findings.

In individuals without anemia and with normal MCV levels, a lower MCV was associated with unfavorable body composition, including lower muscle quality, lower muscle quantity, sarcopenia and visceral obesity.

DISCLOSURE

Yoshitaka Hashimoto has received grants from Asahi Kasei Pharma, and honoraria from Mitsubishi Tanabe Pharma Corp. and Novo Nordisk Pharma Ltd. outside of the submitted work. Michiaki Fukui has received grants from Takeda Pharma Co. Ltd., Sanofi K.K., Kissei Pharma Co. Ltd., Mitsubishi Tanabe Pharma Corp, Astellas Pharma Inc., Nippon Boehringer Ingelheim Co. Ltd., Daiichi Sankyo Co. Ltd., MSD K.K., Sanwa Kagagu Kenkyusho Co., Ltd., Kowa Pharma Co. Ltd., Kyowa Kirin Co., Ltd., Sumitomo Dainippon Pharma Co., Ltd., Novo Nordisk Pharma Ltd., Ono Pharma Co. Ltd., Eli Lilly Japan K.K., Taisho Pharma Co., Ltd., Teijin Pharma Ltd., Nippon Chemiphar Co., Ltd., Johnson & Johnson K.K. Medical Co., Abbott Japan Co. Ltd. and Terumo Corp.; and received honoraria from Teijin Pharma Ltd., Arkray Inc., Kissei Pharma Co., Ltd., Novo Nordisk Pharma Ltd., Mitsubishi Tanabe Pharma Corp., Sanofi K.K., Takeda Pharma Co. Ltd., Astellas Pharma Inc., MSD K.K., Kyowa Kirin Co. Ltd., Sumitomo Dainippon Pharma Co. Ltd., Daiichi Sankyo Co. Ltd., Ono Pharma Co. Ltd., Sanwa Kagaku Kenkyusho Co. Ltd., Nippon Boehringer Ingelheim Co., Ltd., Taisho Pharma Co., Ltd., Bayer Yakuhin, Ltd., AstraZeneca K.K., Mochida Pharma Co. Ltd., Abbott Japan Co. Ltd., Eli Lilly Japan K.K., Medtronic Japan Co. Ltd. and Nipro Corp. outside the submitted work. The sponsors were not involved in the study design or the collection, analysis and interpretation of the data. Furthermore, the sponsors were not involved in the writing or decision to submit the article for

publication in the manuscript. The authors, their immediate families and any affiliated research foundations have not received any financial payments or other benefits from any commercial entity related to the participants of this article. The authors are affiliated with a department financially supported by pharmaceutical companies and declare that they have not received any funding for this study, and this affiliation does not alter their adherence to the journal policies on sharing data and materials. The other authors declare no conflict of interest.

REFERENCES

1. Cruz-Jentoft AJ, Bahat G, Bauer J, *et al*. Writing Group for the European Working Group on Sarcopenia in Older People 2 (EWGSOP2), and the Extended Group for EWGSOP2. Sarcopenia: Revised European consensus on definition and diagnosis. *Age Ageing* 2019; 48: 16–31.
2. Arvandi M, Strasser B, Meisinger C, *et al*. Gender differences in the association between grip strength and mortality in older adults: results from the KORA-age study. *BMC Geriatr* 2016; 16: 201.
3. Roubenoff R. Sarcopenic obesity: the confluence of two epidemics. *Obes Res* 2004; 12: 887–888.
4. Wannamethee SG, Atkins JL. Muscle loss and obesity: the health implications of sarcopenia and sarcopenic obesity. *Proc Nutr Soc* 2015; 74: 405–412.
5. Myojo M, Iwata H, Kohro T, *et al*. Prognostic implication of macrocytosis on adverse outcomes after coronary intervention. *Atherosclerosis* 2012; 221: 148–153.
6. Hsieh YP, Chang CC, Kor CT, *et al*. Mean corpuscular volume and mortality in patients with CKD. *Clin J Am Soc Nephrol* 2017; 12: 237–244.
7. Ueda T, Kawakami R, Horii M, *et al*. High mean corpuscular volume is a new indicator of prognosis in acute decompensated heart failure. *Circ J* 2013; 77: 2766–2771.
8. Tennankore KK, Soroka SD, West KA, *et al*. Macrocytosis may be associated with mortality in chronic hemodialysis patients: a prospective study. *BMC Nephrol* 2011; 12: 19.
9. Tanaka M, Okada H, Hashimoto Y, *et al*. Relationship between metabolic syndrome and trunk muscle quality as well as quantity evaluated by computed tomography. *Clin Nutr* 2019; 39: 1818–1825.
10. Studenski SA, Peters KW, Alley DE, *et al*. The FNIH sarcopenia project: rationale, study description, conference recommendations, and final estimates. *J Gerontol A Biol Sci Med Sci* 2014; 69: 547–558.
11. Janssen I, Heymsfield SB, Ross R. Low relative skeletal muscle mass (sarcopenia) in older persons is associated with functional impairment and physical disability. *J Am Geriatr Soc* 2002; 50: 889–896.
12. Examination Committee of Criteria for 'Obesity Disease' in Japan; Japan Society for the Study of Obesity. New criteria for 'obesity disease' in Japan. *Circ J* 2002; 66: 987–992.
13. Cazzola R, Russo-Volpe S, Cervato G, *et al*. Biochemical assessments of oxidative stress, erythrocyte membrane fluidity and antioxidant status in professional soccer players and sedentary controls. *Eur J Clin Invest* 2003; 33: 924–930.
14. Yoon HJ, Kim K, Nam YS, *et al*. Mean corpuscular volume levels and all-cause and liver cancer mortality. *Clin Chem Lab Med* 2016; 54: 1247–1257.
15. Sun L, Zhang C, Ju Y, *et al*. Mean corpuscular volume predicts in-stent restenosis risk for stable coronary artery disease patients receiving elective percutaneous coronary intervention. *Med Sci Monit* 2019; 25: 3976–3982.
16. Muzyamba MC, Gibson JS. Effect of 1-chloro-2,4-dinitrobenzene on K+ transport in normal and sickle human red blood cells. *J Physiol* 2003; 547: 903–911.
17. Liguori I, Russo G, Curcio F, *et al*. Oxidative stress, aging, and diseases. *Clin Interv Aging* 2018; 13: 757–772.
18. Lorenzo I, Serra-Prat M, Yébenes JC. The role of water homeostasis in muscle function and frailty: a review. *Nutrients*. 2019; 11: 1857.
19. Häussinger D. The role of cellular hydration in the regulation of cell function. *Biochem J* 1996; 313: 697–710.
20. Keller U, Szinnai G, Bilz S, *et al*. Effects of changes in hydration on protein, glucose and lipid metabolism in man: impact on health. *Eur J Clin Nutr* 2003; 57: s69–s74.
21. Nakagami T, Qiao Q, Carstensen B, *et al*. DECODE-DECODA Study Group. Age, body mass index and type 2 diabetes-associations modified by ethnicity. *Diabetologia* 2003; 46: 1063–1070.