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Association of abdominal visceral adiposity and thigh sarcopenia with changes of arteriosclerosis in haemodialysis patients

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Abstract

Background. In haemodialysis (HD) patients, abdominal visceral fat is accumulated while lean body mass is decreased irrespective of their body mass indexes (BMI). However, it is poorly understood which changes of fat and muscle masses are more associated with changes of arteriosclerosis. We aimed at examining the associations of abdominal visceral fat and thigh muscle masses with markers of arteriosclerosis in chronic HD patients in a cross-sectional fashion.

Patients and Methods. We measured abdominal visceral fat mass area (AVFA), abdominal subcutaneous fat mass area (ASFA), thigh muscle area (TMA) and TMA standardized for femoral shaft area (TMA/FSA) by computed tomography (CT) in 161 HD patients (age: 61 ± 11 years, time on HD: 12 ± 10 years, male/female = 113/48, non-

diabetes/diabetes = 127/34). We also investigated carotid artery intima-media thickness (CA-IMT) using the ultrasound instrument, and brachial-ankle pulse wave velocity (baPWV), cardio-ankle vascular index (CAVI) and ankle-brachial pressure index (ABI) using the waveform device (CAVI-VaSera VS-1000).

Results. AVFA was significantly and positively related to CA-IMT in both non-diabetic ($r = 0.23$, $P < 0.05$) and diabetic HD patients ($r = 0.38$, $P < 0.05$). There was a significant and positive correlation between AVFA and hs-CRP in all patients ($r = 0.26$, $P < 0.01$). ASFA was also significantly correlated with CA-IMT ($r = 0.53$, $P < 0.01$) in diabetic HD patients. TMA/SFA ratio was negatively associated with CA-IMT ($r = -0.21$, $P < 0.05$), while positively with ABI ($r = 0.28$, $P < 0.01$) in non-diabetic patients. TMA/SFA ratio was inversely related to baPWV ($r = -0.41$, $P < 0.01$) and CAVI ($r = -0.41$, $P < 0.05$) in diabetic HD patients. Multiple regression analysis revealed that AVFA was a significant determinant of CA-IMT. TMA/AFA was also significantly associated with CA-IMT, baPWV, CAVI and ABI.

Conclusion. Accumulated abdominal visceral fat is associated with CA-IMT. In addition, reduced thigh muscle mass area is independently related to CA-IMT, baPWV, CAVI and ABI, suggesting that sarcopenia in the leg is closely associated with systemic changes of arteriosclerosis in HD patients.

Keywords: abdominal visceral fat; arterial stiffness; carotid artery IMT; haemodialysis; thigh muscle

Introduction

Changes of body composition such as decreased muscle mass volume and increased fat mass volume are observed in patients with chronic kidney disease (CKD) [1,2]. By using computed tomography (CT), Odamaki *et al.* [1] demonstrated that abdominal visceral fat mass area (AVFA) adjusted by body mass index (BMI) was significantly higher, while abdominal subcutaneous fat mass area (ASFA) adjusted by BMI was rather lower in non-diabetic haemodialysis (HD) patients when compared with the age-matched control subjects. A decrease in abdominal muscle area is also observed in HD patients when compared with the age-matched healthy controls in each sex [2].

Recently, increased fat mass is reported to be associated with arteriosclerotic changes. Increased AVFA is independently associated with carotid artery intima-media thickness (CA-IMT) and carotid plaque area in healthy [3] and type 2 diabetes subjects [4]. Abdominal obesity is also associated with carotid-femoral pulse wave velocity (PWV) in the elderly [5].

Lower muscle is also associated with arteriosclerotic markers in the general population. Femoral muscle area is a strong determinant of ankle-brachial pressure index (ABI) [6]. Calf circumference is inversely related to carotid plaques in elderly subjects [7]. Reduced thigh muscle area (TMA) is also associated with brachial-ankle PWB (baPWV) in middle-aged to elderly men [8].

In CKD patients, most studies have demonstrated that higher BMI may be related to lower all-cause and cardiovascular mortality [9,10]. However, BMI does not differentiate between fat and muscle mass. So, it remains to be fully determined which changes of fat and muscle masses are associated with arteriosclerotic changes in HD patients.

The main aim of the present study was to evaluate more in detail the causative association of arteriosclerotic changes with fat and muscle masses in CKD patients requiring HD. We assessed abdominal adiposity and femoral muscle area by CT scan and tested whether these anthropometric parameters are associated with several markers of arteriosclerosis, including CA-IMT, carotid artery plaques, baPWV, cardio-ankle vascular index (CAVI), ABI and the percentile of aortic calcification area (%ACA).

Materials and methods

Subjects

We first enrolled 215 patients who had been undergoing regular HD in a single dialysis centre (Maruyama Hospital, Hamamatsu, Japan). We excluded totally the 54 patients who had not given their consensus, who were older than 80 years, who had been suffering from advanced cancer or who did not undergo all measurements. So, in total, we included 161 patients. The diagnosis of cardiovascular disease (CVD) (history of myocardial infarction, angina pectoris, stroke or peripheral arterial disease) or diabetes mellitus (DM), the presence of traditional major cardiovascular risk factors and drug prescription were recorded from the medical charts and analysed. The study was approved by the ethics committee of the institution. All patients gave their consent to participate in the study.

All patients had been subjected to regular HD for 4–5 h three times per week at a blood flow rate of 180–250 mL/min. All patients used bicarbonate dialysate (30 mEq/L, Kindaly AF-2P, Fuso, Osaka, Japan) at a dialysate flow rate of 500 mL/min. No bacteria or pyrogen was detected in the dialysate fluid obtained by reverse osmosis. Using an endotoxin removal filter, the endotoxin concentration in dialysate was below 0.05 EU/mL with a Limulus amoebocyte lysate assay (Wako Junyaku endotoxin measurement kit, Tokyo, Japan).

Blood sampling and laboratory examinations

Blood samples were drawn from the arterial site of the arteriovenous fistula at the start of each dialysis session after the 2-day interval. Serum electrolytes, urea nitrogen, creatinine, albumin, cholesterol and triglyceride were measured by standard laboratory techniques using an autoanalyser. Intact parathyroid hormone (PTH) was determined by immunoradiometric assay. Highly sensitive C-reactive protein (hs-CRP) was measured by latex photometric immunoassay (Wako Junyaku, Tokyo, Japan). BMI was calculated dividing dry weight (kg) by body height $(m)^2$.

Measurements of muscle and fat areas by CT

Axial CT images of the abdomen were obtained at the level of the third lumbar spine just before an HD session. The thickness of a slice was 10 mm. The radiographic images were digitally scanned for analysis by a personal computer. ASFA and AVFA were measured with use of the public domain planimetry programme, The National Institutes of Health IMAGE (written by Wayne Rasband, The National Institutes of Health, Bethesda, MD, USA). We diagnosed the patients as having visceral fat obesity if AVFA exceeded 100 cm^2 [11].

TMA was determined at the midpoint of a line extending from the superior birder of the patella to the greater trochanter of the femur. We standardized TMA divided by femoral shaft area (TMA/FSA ratio) to avoid the influence of body size, which is shown as a strong determinant of muscle volume [12]. TMA/FSA ratio < 10.0 is reported to well reflect malnourished status, while those with a value of > 13.0 indicate well nourishment in HD patients [12]. We also assessed %ACA by measuring the calcified area of scanned abdominal aorta [13].

Measurements CA-IMT

CA-IMT is a well known predictor of mortality in HD patients [14]. In this study, we investigated the bilateral carotid arteries in longitudinal projections using the ultrasound instrument (Hitachi EUB7000HV, Tokyo, Japan) in a supine position. The examination included sections of ~2–3 cm of common carotid artery just below the carotid bulb. The IMT was defined as the distance between the leading edge of the first echographic line (lumen-intima interface) and the second echographic line (media-adventitia interface) of the far wall. Plaque was defined as IMT larger than 1.0 mm. Mean and maximal CA-IMT at the 2-cm width of the posterior wall without plaque formation were calculated automatically. We also measured the maximal diameter of plaque at both common carotid arteries. IMT ultrasound studies were performed by the same investigator who was blinded to the patient's clinical and laboratory data.

Measurements of ABI, baPWV and CAVI

Recently, baPWV and ABI were shown as predictors of mortality in HD patients [15]. CAVI has been developed as a new index of arterial stiffness to overcome the influence of systemic blood pressure during measurement [16]. In this study, we measured baPWV, CAVI and ABI in supine position at rest for at least 10 min. We applied cuffs at the four extremities and monitored electrocardiogram and heart sounds during the measurement. PWV from the heart to the ankle was obtained by calculating the superficial path lengths from the elbow to the suprasternal notch (Da) and from the suprasternal notch to the femur to the ankle (Db) based on anthropometric data for the Japanese population. We measured the time interval between the initial increase in brachial and tibial waveforms (Ta) and obtained baPWV as follows: baPWV = (Db − Da) / Ta.

CAVI is calculated using the formula: $a\,[\rho / \Delta P[\ln \mathrm{Ps} / \mathrm{Pd}]\mathrm{ca\text{-}PWV2}] + b$ (a,b, constant; ρ, blood density; ΔP, difference in systolic and diastolic pressure; Ps, systolic pressure; Pd, diastolic pressure; PWV, heart-ankle pulse wave velocity) [15].

All measurements and calculations were made together and automatically in CAVI-VaSera VS-1000 (Fukuda Denshi Co, Ltd, Tokyo, Japan). We repeatedly measured these parameters at both legs in each patient and expressed those as the means. Referred ranges of these markers in control subjects are baPWV lower than 14.0 m/s, CAVI <8.0 and ABI from 0.9 to 1.2 [15,16].

Statistical analysis

Values were expressed as the means ± standard deviation (SD). The Chi-square test was used for categorical variables including gender, underlying kidney disease, prevalence of CVD and smoking habits. Univariate correlations between anthropometric parameters with laboratory variables were tested using Spearman rank correlation coefficient for continuous variables. Differences between two groups were analysed by an unpaired Student *t*-test following the analysis of variance (ANOVA). One-way factorial ANOVA was conducted using Bonferroni/Dunn test.

We divided all patients into the three tertiles according to their AVFA and AMA/FSA ratio [AVFA:AVFA <40 (n = 55), 40≤ AVFA <100 (n = 54), AVFA ≥100 cm^2 (n = 52), AMA/FSA ratio: AMA/FSA ratio <8.6 (n = 54), 8.6≤ AMA/FSA ratio <10.4 (n = 53), AMA/FSA ratio ≥10.4 (n = 54)] and compared mean CA-IMT between groups.

We examined the determinants of CA-IMT, PWV, CAVI and ABI with multiple stepwise regression analysis. We analysed the following clinical and laboratory parameters: age, time on HD, diabetes, serum calcium, phosphorous, albumin, total cholesterol, HDL cholesterol, triglyceride, haemoglobin, intact PTH, log-transformed hs-CRP, mean arterial pressure (MAP), AVFA, ASFA and TMA/SFA ratio. Since CRP was highly skewed, we naturally log-transformed those before analysis. All statistical calculations were performed with StatView 5J software (SAS Institute, USA).

Results

Clinical profiles

Table 1 presents characteristics of the study population. The average age was 61 ± 11 years, with a mean time on HD for 12 ± 10 years. The underlying kidney diseases were chronic glomerulonephritis (n = 89), diabetic nephropathy (n = 34), polycystic kidney disease (n = 10), benign nephrosclerosis (n = 5), malignant hypertension (n = 3), others (n = 11) and unknown (n = 9).

The prevalence of AVFA greater than 100 cm^2 was significantly higher in male than in female (37.2 vs 20.8%, P < 0.05). AVFA and ASFA were significantly lower in patients taking angiotensin-converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB) (n = 52) than in those not taking (n = 109) (AVFA: 57.5 ± 53.7 vs 95.0 ± 71.0 cm^2, ASFA: 137.1 ± 65.6 vs 107.7 ± 54.2 cm^2, P < 0.01).

Correlations between body composition and nutritional parameters

AVFA was significantly and positively correlated with serum creatinine (P < 0.01), triglyceride (P < 0.01), prealbumin (P < 0.05) and TMA (P < 0.01) in all patients (Table 2). AVFA was also positively associated with log-transformed hs-CRP (P < 0.01), though negatively with HDL cholesterol (P < 0.01). ASFA was significantly and inversely correlated with age (P < 0.05) and time on HD (P < 0.05). A significant association was found between ASFA and LDL cholesterol and prealbumin (P < 0.05). There was a significant and negative relationship between TMA/FSA ratio and age and time on HD (P < 0.01). TMA/FSA ratio was also positively associated with nutritional parameters such as serum creatinine, albumin and prealbumin (P < 0.01).

Associations of anthropometric CT measurements with markers of arteriosclerosis

AVFA was significantly and positively correlated with mean CA-IMT in non-diabetic (r = 0.23, P < 0.05) and in diabetic HD patients (r = 0.38, P < 0.05), respectively (Figure 1). ASFA was significantly and positively correlated with mean CA-IMT (r = 0.53, P < 0.01) in diabetic HD patients (Figure 1). There was a significantly greater mean and maximal CA-IMT in patients with AVFA higher than 100 cm^2 than that <100 cm^2 both in non-DM and DM groups (Figure 2). In contrast, AVFA (r = 0.08, P = 0.39) and ASFA (r = 0.01, P = 0.95) were not associated with maximal plaque diameter in all patients.

TMA did not associate with CA-IMT both in non-diabetic and diabetic patients. However, TMA/FSA ratio was significantly and inversely associated with mean CA-IMT in non-diabetic patients (r = −0.21, P < 0.05) (Figure 3).

TMA/FSA ratio was also significantly and negatively correlated with baPWV (P < 0.05), CAVI (P < 0.05) and ABI (P < 0.01) in all patients (Table 3). TMA/FSA ratio was associated with ABI (P < 0.01) in non-diabetic patients. In diabetic patients, TMA/FSA ratio was related to baPWV and CAVI (P < 0.05). There was no relation between TMA/SFA ratio and %ACA in all patients.

When the patients were divided into the three groups according to their AVFA and TMA/FSA ratio, mean level of CA-IMT was the most prominent in the group with the top tertile of AVFA (≥100 cm^2) and the bottom tertile of TMA/

Table 1. Characteristics of the patients with and without DM

	All	Non-DM	DM	Non-DM vs DM
n	161	127	34	
Age (years)	61 ± 11	64 ± 10	60 ± 11	0.09
HD vintage (years)	12 ± 10	13 ± 10	6 ± 8	<0.01
Male/female	113/48	85/42	28/6	0.09
ACEI/ARB (%)	32	24	62	<0.01
CVD history (%)	20	17	35	<0.05
Smoker (%)	21	21	23	0.87
Laboratory parameters				
Creatinine (mg/dL)	12.18 ± 3.12	12.43 ± 3.17	11.24 ± 2.75	<0.05
Calcium (mg/dL)	9.0 ± 0.9	9.1 ± 0.9	8.9 ± 0.8	0.50
Phosphorous (mg/dL)	5.7 ± 1.5	5.8 ± 1.6	5.5 ± 1.4	0.44
Intact PTH (pg/mL)	235 ± 207	245 ± 220	200 ± 144	0.27
Total cholesterol (mg/dL)	154 ± 37	156 ± 37	145 ± 39	0.13
LDL-C (mg/dL)	95 ± 33	96 ± 33	92 ± 31	0.49
HDL-C (mg/dL)	49 ± 15	51 ± 15	44 ± 14	<0.05
Triglyceride (mg/dL)	108 ± 62	108 ± 62	103 ± 55	0.71
Albumin (g/dL)	3.7 ± 0.3	3.7 ± 0.3	3.7 ± 0.3	0.83
Prealbumin (mg/dL)	29 ± 8	29 ± 8	27 ± 8	0.17
Hs-CRP (mg/L)	6.5 ± 20.4	5.9 ± 17.8	8.8 ± 28.3	0.47
Haemoglobin (g/dL)	10.8 ± 1.2	10.9 ± 1.2	10.4 ± 1.4	<0.05
Anthropometric parameters				
BMI (kg/m^2)	20.7 ± 2.8	20.6 ± 2.7	21.0 ± 3.2	0.49
AVFA (cm^2)	83.3 ± 68.2	81.4 ± 65.9	90.4 ± 76.6	0.49
ASFA (cm^2)	127.8 ± 63.6	127.1 ± 62.7	130.1 ± 67.7	0.81
AVFA/ASFA ratio	0.62 ± 0.38	0.62 ± 0.38	0.62 ± 0.39	0.97
TMA (cm^2)	180.8 ± 57.4	181.8 ± 59.7	177.0 ± 48.3	0.67
TMF/FSA ratio	9.7 ± 3.2	9.8 ± 3.3	9.3 ± 2.6	0.39
Markers of arteriosclerosis				
Systolic BP (mm Hg)	138 ± 28	132 ± 26	158 ± 29	<0.01
Diastolic BP (mm Hg)	80 ± 14	80 ± 15	81 ± 12	0.62
Pulse pressure (mm Hg)	58 ± 21	53 ± 16	77 ± 302	<0.01
Mean IMT (mm)	0.63 ± 0.12	0.63 ± 0.11	0.66 ± 0.13	0.10
Maximal IMT (mm)	0.80 ± 0.16	0.80 ± 0.16	0.82 ± 0.16	0.42
Prevalence of plaque (%)	68.9	74.0	58.8	0.09
Plaque diameter (mm)	2.8 ± 1.5	2.8 ± 1.4	2.7 ± 1.7	0.80
baPWV (m/s)	14.0 ± 2.1	13.7 ± 2.6	15.3 ± 2.7	<0.01
CAVI	9.1 ± 2.4	8.6 ± 2.0	10.8 ± 3.0	<0.01
ABI	1.05 ± 0.16	1.06 ± 0.15	1.00 ± 0.21	0.11
%ACA (%)	29 ± 23	29 ± 24	29 ± 22	0.94

Abbreviations: DM, diabetes mellitus; HD, haemodialysis; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CVD, cardiovascular disease; PTH, parathyroid hormone; Hs-CRP, highly sensitive C-reactive protein; BMI, body mass index; AVFA, abdominal visceral fat area; ASFA, abdominal subcutaneous fat area; TMA, thigh muscle area; FSA, femoral shaft area; BP, blood pressure; IMT, \intima-media thickness; baPWV, brachial-ankle pulse wave velocity; CAVI, cardio-ankle vascular index; ABI, ankle-brachial pressure index; %ACA, percentile of aortic calcification area. Data are expressed as means ± standard deviation. Referred control ranges are baPWV lower than 14.0 m/s, CAVI <8.0 and ABI from 0.9 to 1.2 [15,16].

FMA ratio (<8.6) (0.72 ± 0.09 mm, $n = 14$). In contrast, mean CA-IMT was the lowest in the group with the bottom tertile of AVFA (<40 cm^2) and the highest tertile of TMA/FMA ratio (≥10.4) (0.55 ± 0.11 mm, $n = 17$) (Figure 4).

Determinants of markers of arteriosclerosis

Multiple stepwise regression analysis revealed that mean CA-IMT was independently associated with AVFA and TMA/FSA ratio (Table 4). TMA/FSA ratio was also independently correlated with baPWV, CAVI and ABI. In contrast, all of the anthropometric parameters did not associate with %ACA.

Discussion

In this study, we found that increased AVFA was independently associated with CA-IMT both in non-diabetic and diabetic HD patients. ASFA was also positively correlated with CA-IMT in diabetic patients. TMA/FSA ratio, an indicator of muscle mass volume [2,12], was significantly and positively correlated with baPWV, CAVI and ABI in all patients, and it also correlated with CA-IMT in non-diabetic patients. When the patients were divided into the three groups according to their AVFA and TMA/FSA ratio, mean CA-IMT was most increased in the group with the top tertile of AVFA and the lowest tertile of TMA/FSA ratio. These findings suggest that both increased abdominal visceral adiposity and sarcopenia in the leg are independently associated with arteriosclerotic changes in HD patients.

It has been reported that AVFA is associated with CA-IMT, insulin resistance, and lipid abnormalities in HD patients [17–22]. Yamauchi *et al.* [17] first demonstrated that a higher AVFA is associated with greater carotid arteriosclerotic changes in 77 non-diabetic HD patients. They showed that carotid artery plaque score was positively cor-

Table 2. Correlation between AVFA and ASFA and clinical parameters in all non-diabetic and diabetic patients

Characteristics	All (n = 161)		Non-DM (n = 127)		DM (n = 34)	
	AVFA	ASFA	AVFA	ASFA	AVFA	ASFA
Age	0.00	−0.20*	−0.01	−0.20*	0.00	−0.21
Time on HD	−0.04	−0.18*	−0.03	−0.22*	0.00	−0.04
Creatinine	0.28**	0.17*	0.31**	0.22*	0.26	−0.01
Albumin	−0.06	0.01	−0.04	0.04	−0.13	−0.12
Total cholesterol	0.09	0.26**	0.16	0.37**	−0.11	−0.10
HDL cholesterol	−0.31**	−0.06	−0.32**	−0.02	−0.29	−0.21
LDL cholesterol	0.17*	0.28**	0.23**	0.38**	−0.08	−0.10
Triglyceride	0.38**	0.22**	0.45**	0.26**	−0.15	0.06
Prealbumin	0.19*	0.19*	0.25**	0.25**	0.01	0.00
Log-transformed hs-CRP	0.26**	0.09	0.30**	0.05	0.10	0.18
Haemoglobin	0.18*	0.05	0.26**	0.07	−0.02	0.01
TMA	0.22**	0.28**	0.16	0.26**	0.47**	0.40*
TMA/FSA ratio	0.15	0.28**	0.08	0.28**	0.45**	0.31

Abbreviations: AVFA, abdominal visceral fat area; ASFA, abdominal subcutaneous fat area; TMA, thigh muscle area; FSA, femoral shaft area; HD, haemodialysis; Hs-CRP, highly sensitive C-reactive protein. Univariate correlations between anthropometric parameters with laboratory variables were tested using Spearman rank correlation coefficient for continuous variables. An asterisk and two asterisks denote $P < 0.05$ and $P < 0.01$, respectively.

related with AVFA. Visceral adiposity is also a predictor of carotid-femoral PWV in peritoneal dialysis (PD) patients [18]. A close association of ASFA with insulin resistance [19–21] and increased CA-IMT [22] has been demonstrated in HD patients.

In the present study, we confirmed that AVFA is a significant indicator of CA-IMT both in non-diabetic and diabetic HD patients. ASFA was correlated with carotid arteriosclerosis in diabetic but not in non-diabetic patients. In contrast, abdominal adipose tissues did not associate with maximal

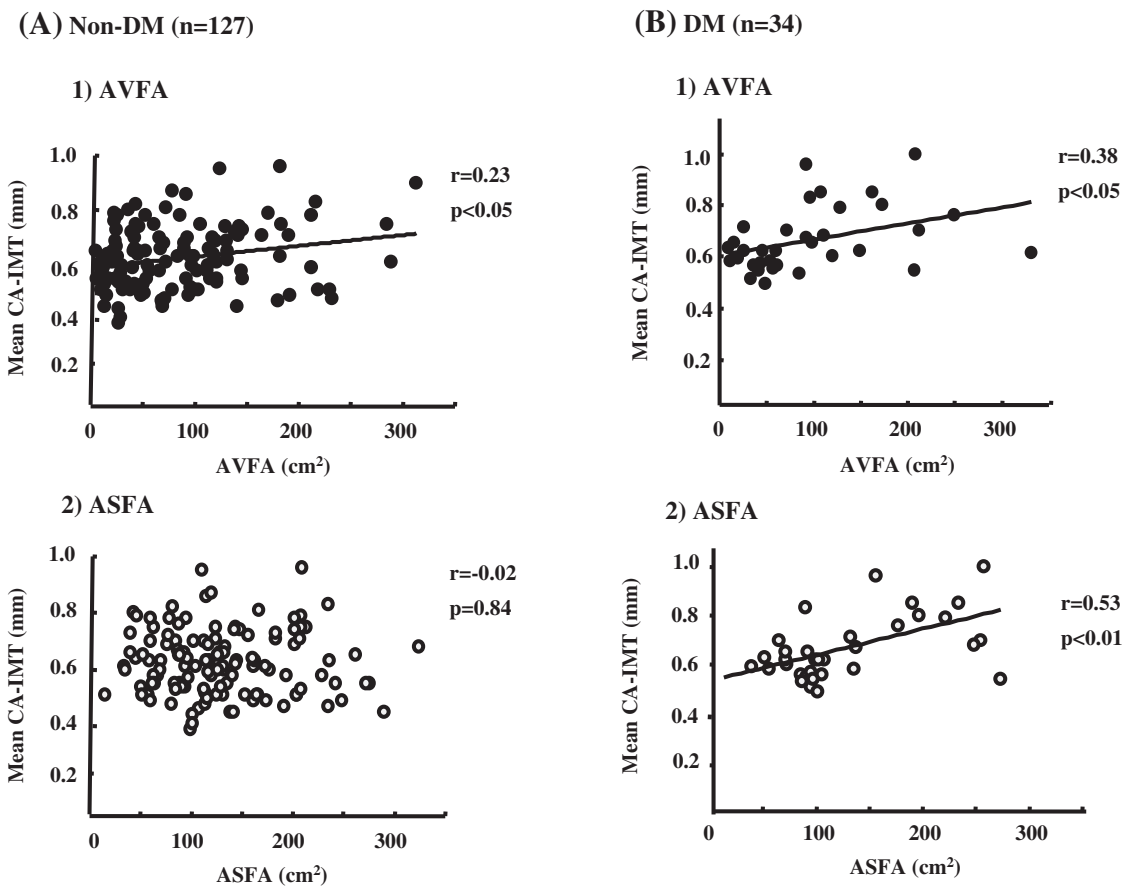

Fig. 1. Associations between abdominal subcutaneous and visceral fat mass and mean CA-IMT. AVFA was significantly and positively correlated with CA-IMT in non-diabetic (n = 127) and diabetic HD patients (n = 34). ASFA was also related to CA-IMT in diabetic patients. Abbreviations: DM, diabetes mellitus; AVFA, abdominal visceral fat mass area; ASFA, abdominal subcutaneous fat mass area; CA-IMT, carotid artery intima-media thickness.

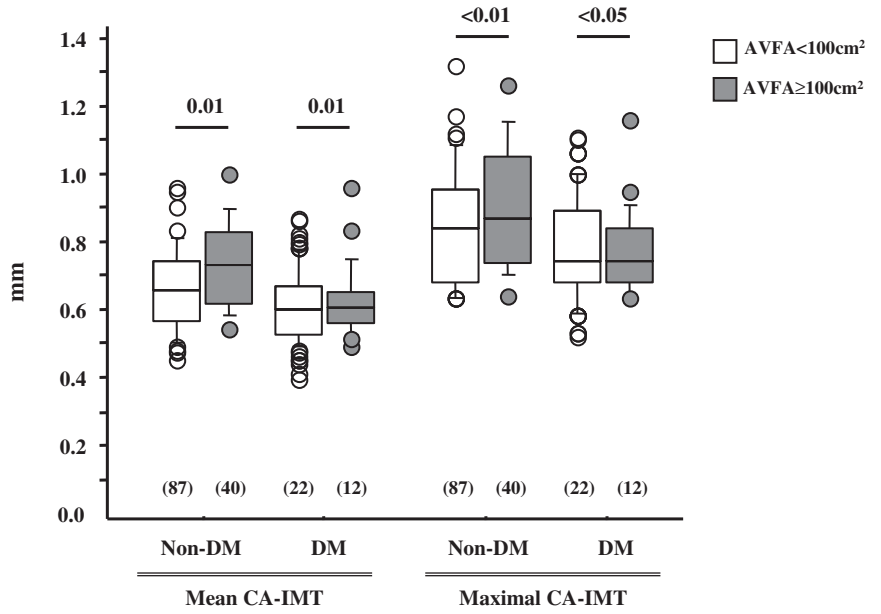

Fig. 2. Visceral adiposity and mean and maximal CA-IMT in non-diabetic and diabetic HD patients. Mean and maximal CA-IMT were significantly higher in both non-DM ($n = 127$) and DM ($n = 34$) patients with AVFA more than 100 cm^2 when compared with those <100 cm^2. Data are presented as box plots. Differences between the two groups were analysed following one-way ANOVA by Bonferroni/Dunn test. The number of the patients in each category was shown in parentheses. Abbreviations: DM, diabetes mellitus; AVFA, abdominal visceral fat mass area; CA-IMT, carotid artery intima-media thickness.

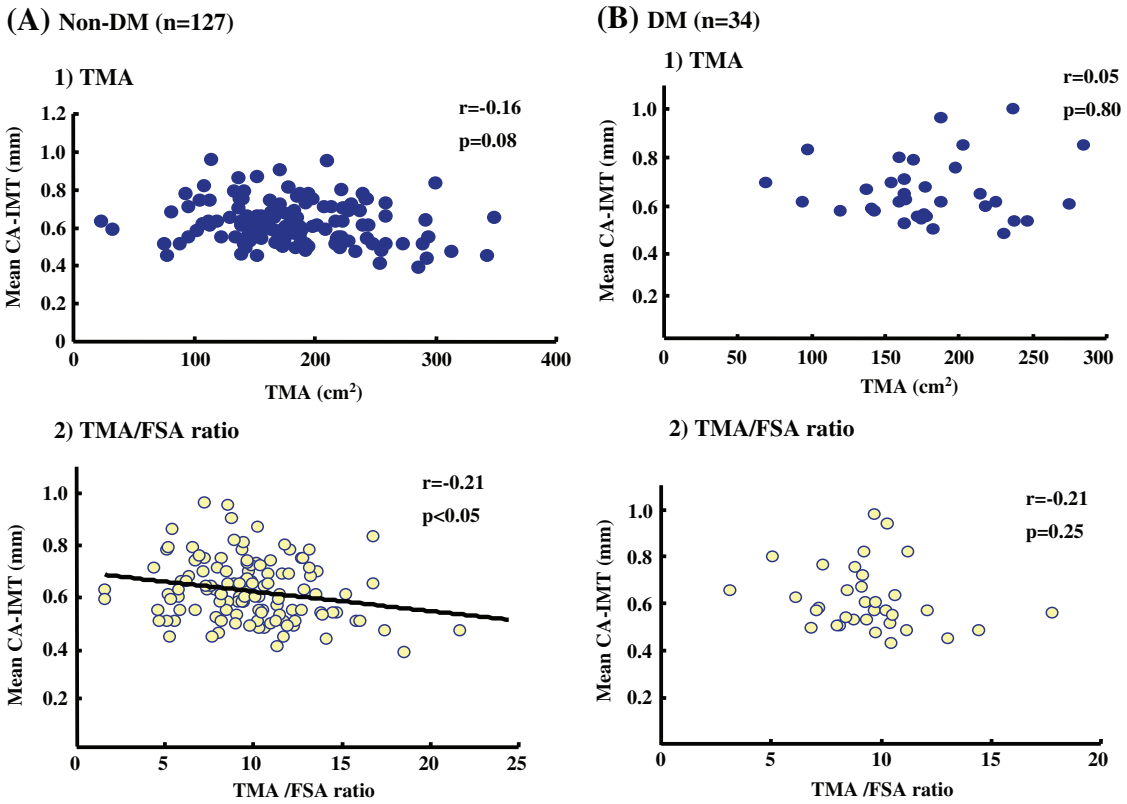

Fig. 3. Relationship between CA-IMT and thigh muscle mass area. TMA did not relate to CA-IMT both in non-diabetic ($n = 127$) and diabetic ($n = 34$) HD patients. TMA/FSA ratio was significantly and negatively correlated with CA-IMT in non-diabetic patients. Abbreviations: DM, diabetes mellitus; TMA, thigh muscle area; FSA, femoral shaft area; CA-IMT, carotid artery intima-media thickness.

Table 3. Association of body composition with markers of arteriosclerosis

(A) All patients (n = 161)

	baPWV	CAVI	ABI	%ACA
AVFA	−0.02 (0.85)	0.04 (0.68)	0.04 (0.70)	−0.00 (0.96)
ASFA	−0.01 (0.90)	0.08 (0.40)	0.02 (0.81)	−0.05 (0.57)
TMA	−0.18 (<0.05)	−0.09 (0.31)	0.19 (<0.05)	−0.12 (0.14)
TMA/FSA ratio	−0.19 (<0.05)	−0.20 (<0.05)	0.25 (<0.01)	−0.07 (0.43)

(B) Non-diabetic patients (n = 127)

	baPWV	CAVI	ABI	%ACA
AVFA	−0.08 (0.44)	0.03 (0.74)	−0.04 (0.68)	0.04 (0.69)
ASFA	−0.06 (0.56)	0.14 (0.18)	−0.09 (0.36)	−0.04 (0.70)
TMA	−0.18 (0.09)	−0.10 (0.35)	0.21 (<0.05)	−0.09 (0.33)
TMA/FSA ratio	−0.13 (0.20)	−0.14 (0.18)	0.28 (<0.01)	−0.01 (0.92)

(C) Diabetic patients (n = 34)

	baPWV	CAVI	ABI	%ACA
AVFA	0.04 (0.84)	−0.08 (0.71)	0.24 (0.23)	−0.06 (0.74)
ASFA	0.10 (0.62)	−0.09 (0.68)	0.32 (0.09)	−0.09 (0.62)
TMA	−0.24 (0.24)	−0.14 (0.52)	0.17 (0.42)	−0.28 (0.12)
TMA/FSA ratio	−0.41 (<0.05)	−0.41 (<0.05)	0.17 (0.40)	−0.33 (0.07)

Abbreviations: AVFA, abdominal visceral fat area; ASFA, abdominal subcutaneous fat area; TMA, thigh muscle area; FSA, femoral shaft area; baPWV, brachial-ankle pulse wave velocity; CAVI, cardio-ankle vascular index; ABI, ankle-brachial pressure index; %ACA, percentile of aortic calcification area. Univariate correlations between anthropometric parameters with laboratory variables were tested using Spearman rank correlation coefficient for continuous variables. Data and parenthesis represent correlation coefficients and P-values between the two groups.

plaque diameter. Thus, it follows from these findings that accumulated abdominal adipose tissue may play a greater role in intima-medial thickening than in the development of atherosclerotic plaques in HD patients, as shown previously in the general population [3].

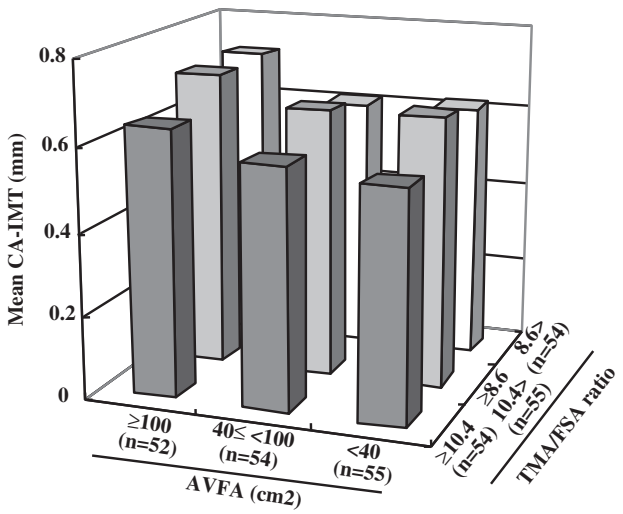

Fig. 4. Increased AFVA and reduced TMA/FSA ratio were independently associated with mean CA-IMT. When all patients were divided into the three groups according to their AVFA and TMA/FSA ratio, mean levels of CA-IMT were the most prominent in the group with the top tertile of AVFA (≥100 cm^2) and the bottom tertile of TMA/FMA ratio (<8.6) (0.71 ± 0.17 mm, n = 17). In contrast, mean CA-IMT was the lowest in the group with the bottom tertile of AVFA (<40 cm^2) and the highest tertile of TMA/FMA ratio (≥10.4) (0.55 ± 0.11 mm, n = 14). Abbreviations: CA-IMT, carotid artery intima-media thickness; AVFA, abdominal visceral fat mass area; TMA, thigh muscle area; FSA, femoral shaft area.

Recent investigations have suggested that a number of cytokines such as leptin, adiponectin, visfatin, tumour necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) are produced by adipose tissues [16,23]. Abdominal visceral adipose tissue is demonstrated to be more associated with serum CRP and IL-6 than subcutaneous adipose tissue in the general population [24]. A close relationship between obesity and oxidative stress and inflammation is shown in patients with moderate to severe chronic CKD [25]. Increased abdominal fat deposition is also related to serum CRP and IL-6 in HD patients [26]. Visceral and subcutaneous adipose tissues measured by magnetic resonance imaging are associated with serum level of ceruloplasmin, an acute-phase reactant, in prevalent HD patients [27]. A recent study [28] also demonstrated that abdominal obesity (waist circumference ≥94 cm) underlies a high risk of all-cause and CV mortality in HD patients. In this study, we found that AVFA was positively correlated with log-transformed hs-CRP. Because abdominal fat tissue expresses higher amounts of proinflammatory cytokines in patients with end-stage renal disease (ESRD) than in control subjects [29], accumulated adipose tissue could be an important and universal part of the overall systemic inflammatory reaction, thereby leading to advanced arteriosclerotic changes in HD patients.

Decreased muscle mass is associated with physiological and functional impairment, eventually leading to increased mortality in most common diseases and conditions [30]. Lower muscle mass at upper and lower limbs is independently associated with worse survival in HD patients [31,32]. Urinary creatinine excretion rate, an indirect marker of whole muscle volume, is strongly associated with mortality in general outpatients with stable coronary arterial disease [33]. Recently, mid-thigh muscle cross-sectional area ad-

Table 4. Multiple regression analysis predicting markers of arteriosclerosis in 161 haemodialysis patients

Variables	R^2	Standard regression coefficient	SE	F-to-remove	P value
Parameters for mean CA-IMT					
Age	0.08	0.28	7.20	13.36	<0.01
AVFA	0.07	0.27	43.96	12.56	<0.01
TMA/FSA ratio	0.05	−0.21	2.09	7.29	<0.01
HDL cholesterol	0.03	−0.16	10.15	4.22	<0.05
Parameters for baPWV					
MAP	0.33	0.57	0.56	59.34	<0.01
Age	0.22	0.46	0.34	33.17	<0.01
Diabetes	0.06	−0.24	0.01	7.61	<0.01
Total cholesterol	0.05	−0.23	1.25	6.42	<0.05
TMA/SFA ratio	0.04	−0.19	0.10	4.57	<0.05
Parameters for CAVI					
MAP	0.27	0.52	0.65	45.58	<0.01
Age	0.16	0.41	0.39	24.09	<0.01
Diabetes	0.14	−0.38	0.01	20.50	<0.01
TMA/SFA ratio	0.04	−0.20	0.11	5.23	<0.05
Creatinine	0.04	−0.20	0.12	4.97	<0.05
Parameters for ABI					
Age	0.06	−0.25	5.99	8.28	<0.01
TMA/FSA ratio	0.06	0.25	1.68	8.04	<0.01
Creatinine	0.03	0.18	1.69	4.21	<0.05
Parameters for %ACA					
Age	0.13	0.35	0.04	20.55	<0.01
Triglyceride	0.04	−0.19	0.22	5.24	<0.05
Time on HD	0.03	0.17	0.04	4.32	<0.05
Calcium	0.03	0.17	0.003	4.29	<0.05

Multiple stepwise regression analysis of variables including the followings: age, time on HD, diabetes, calcium, phosphorous, albumin, total cholesterol, HDL cholesterol, triglyceride, log-transformed C-reactive protein (CRP), intact parathyroid hormone, body mass index, mean arterial pressure (MAP), abdominal visceral fat area (AVFA), abdominal subcutaneous fat area (ASFA), thigh muscle area standardized for femoral shaft area (TMA/FSA ratio). Abbreviations: baPWV, brachial-ankle pulse wave velocity; CAVI, cardio-ankle vascular index; ABI, ankle-brachial pressure index; %ACA, percentile of aortic calcification area.

justed by body weight is shown as an independent predictor of baPWV in middle-age to elderly men [8]. In this study, we used the TMA/FSA ratio as a reliable marker to assess systemic muscle mass volume, because this ratio is well correlated with creatinine production in the spent dialysate [12] and estimated whole muscle mass volume calculated from creatinine kinetic model [34]. TMA is also negatively correlated with IL-6 and CRP in HD patients [35]. We first showed that TMA/FSA ratio was independently associated with CA-IMT, baPWV, CAVI and ABI, supporting a close association between reduced muscle mass and markers of arteriosclerosis in ESRD patients.

There are several potential reasons why low muscle mass may be associated with arteriosclerotic changes in dialysis patients. Firstly, since TMA/FSA ratio was well correlated with serum albumin and prealbumin, low muscle mass in the thigh may reflect poor nutritional status. Secondly, skeletal muscle is the main site for insulin-mediated glucose disposal, so low muscle mass volume may be associated with insulin resistance. Thirdly, decreased muscle mass of the leg links to low physical activity, which may lead to the promotion of arteriosclerosis.

In this study, both increased visceral adiposity and decreased thigh muscle volume are independently associated with markers of arteriosclerosis independently of the confounding factors related to arteriosclerosis. Mean CA-IMT was increased most prominently in patients with the top tertile of AVFA ($\geq$100 cm^2) and the bottom tertile of TMA/FSA ratio (<8.6) (Figure 4). In this group, ABI was also lowest (0.97 ± 0.18), and baPWV was highest (14.9 ± 3.1 m/s) when compared with other groups (data not shown). An association of increased visceral adiposity and altered thigh muscle composition with intramuscular fat infiltration is observed in HD patients with sleep apnoea syndrome [36]. Protein wasting can also be present in obese patients and is associated with inflammation and poor survival in HD patients [37]. So, decreased muscle mass, increased visceral fat and arteriosclerosis may share a common pathway, i.e. chronic low-grade inflammation, and may interact with each other in ESRD patients.

Recently, Golledge *et al.* [38] showed a 6-fold increase in the odds of abdominal aortic calcification in the upper compared with the lower tertile of the visceral adipose tissue in 148 patients with peripheral arterial disease. However, a large community-based study [39] failed to show any association of abdominal subcutaneous and visceral adipose tissue with aortic calcification when adjusted for multivariate in the general population. In this study, AVFA, ASFA and TMA/FSA ratio did not associate with %ACA. In contrast, age and triglyceride became independent indicators of %ACA (Table 4), confirming that classical risk factors contribute to aortic calcification in HD patients.

In the present study, mean BMI (20.7 ± 2.8 kg/m^2) was much lower than those in North American and European countries. However, our mean of BMI is compar-

able to that (20.9 ± 3.2 kg/m^2) in Japanese HD patients in the Dialysis Outcomes and Practice Pattern Study (DOPPS) III [40]. In DOPPS III, the interactions between nutritional parameters on risk of death were almost identical among Europe, North America and Japan despite the substantial variations across countries. So, our results could be, for the most part, generalizable to maintenance HD patients.

There are several limitations to the present study. Firstly, its cross-sectional design of the study did not allow us to determine causality. Secondly, the relatively low number of patients in a single HD centre may not provide enough statistical power to avoid the existence of confounding variables. Finally, since we conducted CT scan before HD session, we could not completely exclude the influence of hydration state on CT anthropometrics.

Conclusion

In summary, we showed that abdominal visceral fat mass is associated with carotid intima-medial thickening in HD patients. Abdominal visceral adiposity is positively correlated with hs-CRP. Subcutaneous fatness also correlates with mean CA-IMT in diabetic patients. Furthermore, reduced thigh muscle mass area is related to baPWV, CAVI and ABI in addition to CA-IMT. Our findings suggest that TMA/FSA ratio may be a novel anthropometric marker to take into account when assessing arteriosclerotic changes in ESRD patients. Further prospective studies will be needed to test whether TMA/FSA ratio is useful in predicting progression of arteriosclerosis, cardiovascular events and mortality in CKD patients.

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Conflict of interest statement. None declared.

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Restless legs syndrome enhances cardiovascular risk and mortality in patients with end-stage kidney disease undergoing long-term haemodialysis treatment

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Abstract

Background. Restless legs syndrome (RLS) is a sensorimotor neurological disorder characterized by paraesthesia, dysaesthesia and the irresistible urge to move the legs especially at night. Its prevalence is much higher among dialysis patients at 12 to 62% compared to 3 to 9% in the general population. Here, we investigated the association between RLS and cardiovascular events risk and laboratory parameters in end-stage kidney disease (ESKD) patients on dialysis.

Methods. One hundred ESKD patients undergoing haemodialysis were enrolled in an 18-month prospective observational study. The main outcomes were the associations of RLS with new cardiovascular events and cardiovascular mortality.

Results. RLS affected 31% of the study population. It was associated with female gender, gradual reduction in residual diuresis, lower albumin (P = 0.039) and inflammation, but not the dialysis parameters Kt/V and URR. During observation, 47% of patients experienced new cardiovascular events (64.5% with and 39.1% without RLS; P = 0.019). New cardiovascular events increased with severity of RLS [intermittent (I-RLS) vs continuous (C-RLS)]. Mortality was 20.0% in all patients, 32.3% in those with and 14.5% in patients without RLS (P = 0.04). In patients with I-RLS, mortality was 23.8% compared to 55.6% in patients with C-RLS (P = 0.014). Multivariate analysis confirmed the relationship between RLS and mortality.

Conclusions. This study confirmed the high prevalence of RLS among dialysis patients and the associations between the severity of RLS and the risk of new cardiovascular events and higher short-term mortality.

Keywords: cardiovascular outcome; haemodialysis; mortality; restless legs syndrome