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Increased prevalence of peripheral arterial disease in patients with obese sarcopenia undergoing hemodialysis

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Abstract. Background peripheral arterial disease (PAD) is a common complication in patients undergoing dialysis, which reduces the quality of life and increases the risk of mortality. Recent literature has documented an association between increased visceral fat (VF) content and a proatherogenic factors in end-stage renal disease. The present study investigated the prevalence of PAD in patients undergoing hemodialysis. PAD was determined as an ankle-brachial index <0.9. Additionally, VF content was determined using multiple frequency bioelectrical impendence analysis. The nutritional status of the patients was evaluated by subjective global assessment and endothelial function was measured by ultrasonographic brachial artery flow-mediated dilatation. Patients divided into two groups (malnourished and non-malnourished) with two further subgroups in each (high VF and low VF content). The prevalence of PAD was identified to be significantly higher in patients with a high VF mass compared with a low VF mass in non-malnourished patients. PAD was significantly more common in malnourished patients compared with non-malnourished patients ($P<0.01$). The presence of PAD in patients undergoing hemodialysis was identified to be significantly correlated with age, diabetes mellitus (DM) status VF content, malnutrition, serum albumin level, diastolic blood pressure and log C-reactive protein levels. Furthermore, logistic regression analysis determined that age, DM, VF content and malnutrition were significant independent risk factors for PAD in patients undergoing hemodialysis. In conclusion, the results of the present study indicated that obesity and malnutrition act synergistically to increase the risk of PAD in patients undergoing dialysis.

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Introduction

Peripheral arterial disease (PAD) is an atherosclerotic process that manifests in the lower extremities, which is a common complication of end-stage renal disease (ESRD) (1,2) and results in a reduced quality of life (3), in addition to an increased risk of mortality (4-6). While PAD is likely an important marker of the cardiovascular status, it has not been researched as thoroughly as coronary artery disease and its pathogenesis in patients undergoing dialysis is not well understood (7).

Malnutrition is frequently observed in patients with ESRD (8) and is associated with inflammation and atherosclerotic complications (9,10). Malnutrition, assessed by subjective global assessment (SGA) (11), has also been associated with indirect cardiovascular risk markers, including carotid intima-mediated thickness (12) and patient mortality (13).

There has been an epidemiological rise of obesity in the general population worldwide; the incidence of obesity is also increased in those undergoing dialysis, including those with ESRD (14). Patients with ESRD and obese sarcopenia, defined as a high visceral fat (VF) content, have particularly poor outcomes (15). Furthermore, a previous study has associated visceral fat (VF) accumulation in patients with ESRD with proatherogenic hyperlipidemia and inflammation (13). However, it remains unclear how nutritional status affects the development of PAD in patients undergoing dialysis.

The present observational and cross-sectional study analyzed the presence of PAD in patients undergoing hemodialysis using ankle-brachial index (ABI) and body composition measurements.

Patients and methods

Patient selection. A total of 210 patients with ESRD undergoing hemodialysis at the Outpatient Clinic of the Division of Nephrology of Tianjin Medical University General Hospital (Tianjin, China) were analyzed during a single outpatient visit between January and October 2015. The mean age of the patients included in the present study was 60 years old, with 52% females and 48% males. Patients undergoing hemodialysis for <3 months or patients unwilling or unsuitable for measurement by bioelectrical impedance analysis; for example, due to significant cognitive impairment, inability to walk, joint replacement or the presence of a cardiac pacemaker, were excluded. The ethical committee of Tianjin Medical University General Hospital approved the present study and written informed consent was obtained from all patients.

ABI measurement. ABI was measured as described by Feigelson *et al* (16). An ABI was calculated for each leg and the lowest value was used to group patients according to the presence (ABI <0.9) or absence (ABI ≥0.9) of PAD.

SGA for malnutrition. A dedicated dietician performed a SGA for malnutrition. The SGA method included six subjective assessments, of which three were based on the patient's history (weight loss, presence of anorexia and vomiting) and three were based on the physician's grading (muscle wasting, presence of edema and loss of subcutaneous fat) (17). On the basis of these assessments, the patients' were divided into non-malnutrition or malnutrition groups, as described previously (17).

Body composition analysis. The body composition was measured by bioelectrical impendence analysis (BIA) using an MC-190 Multifrequency Body Composition Indicator (Tanita Corporation, Tokyo, Japan), with patients measured whilst standing and without shoes and socks, according to the manufacturer's protocol. This device uses multifrequency (5, 50 and 250 kHz) BIA technology and has eight tactile electrodes, of which four are in contact with the palm and thumb of each hand, while the other four are in contact with the feet. The total fat and VF levels are determined by a proprietary equation developed by the manufacturer. Patients in the malnutrition and non-malnutrition groups were divided into high VF and low VF subgroups based upon whether their VF level was above or below the median, respectively, which was calculated separately for males and females.

Flow-mediated dilatation (FMD). Non-invasive endothelium-dependent FMD was measured for each patient after a 10 min rest period, in a supine position and with an empty stomach on a non-dialysis day. The brachial artery, without an artery-venous fistula, was visualized in a longitudinal section 15 cm above the antecubital fossa using a Acuson 128XP/10 Ultrasound Machine with a 7 MHz Linear Array Transducer (Siemens AG, Munich, Germany). The baseline brachial artery diameter was measured by automated wall tracking using a Sonoline G50 Digital Ultrasound system (Siemens) as described previously (18). Furthermore, a pneumatic cuff was then inflated to 50 mmHg above the systolic blood pressure (SBP) and kept on the forearm for 5 min to induce reactive hyperemia. The percentage change in the brachial artery diameter 1 min after cuff release compared with the baseline diameter was recorded as the FMD.

Demographic and clinical data collection. Previously diagnosed coronary artery disease (previous myocardial infarction, ischemia detected by cardiogram abnormality, a history of coronary artery bypass grafting or coronary stent implantation) or a history of cerebrovascular events was classified as cardiovascular or cerebrovascular disease (CVD). A history of smoking (current or former) was defined as a ≥1 pack-year if tobacco use based on patient interviews or chart documentation.

Statistical analysis. Statistical analysis was performed using SPSS software (version 15.0; SPSS, Inc., Chicago, IL, USA). Results for continuous variables are presented as the mean ± standard deviation and results for categorical variables are presented as percentages. The statistical significance of differences between the low and high VF groups (normal nutrition and malnourishment) were determined using a Student's t-test for comparison between two variables and one-way multivariate analysis of variance for continuous variables, while the χ^2 test was used for categorical variables. Bivariate (Pearson) correlation analysis was conducted to determine the association between PAD and other variables. Variables that were significantly correlated with PAD were selected for binary logistic regression analysis to determine the independent risk factors for PAD. P<0.05 (two-tailed) was considered to indicate a statistically significant difference.

Results

Clinicopathological characteristics of patients undergoing hemodialysis based upon their nutritional status and VF level. A total of 210 patients (mean age, 60 years old; 52% female and 48% male) were available for analysis in the present study. The baseline clinicopathological characteristics are summarized in Table I. Furthermore, patients with a high VF had a significantly higher body mass index (BMI) compared with those with a low VF, both in the malnutrition and non-malnutrition groups (both P<0.05) and the BMI of malnourished patients with a low VF was significantly lower compared with that of non-malnourished patients with a low VF (20±2 vs. 22±2.5 kg/m^2, respectively; P<0.05). As expected, the serum albumin level was significantly lower in the malnutrition group compared with the non-malnutrition groups, in patients with low VF and with high VF (both P<0.05). Additionally, SBP and diastolic blood pressure (DBP) was comparable between the groups, except that the DBP was significantly lower in patients with a high VF in the malnutrition group compared with the non-malnutrition group (69±10 vs. 78±10, respectively; P<0.05). In the present study, malnourished patients with a high VF content had worse endothelial dysfunction (by FMD) compared with patients with a low VF content. Moreover, in high VF group, malnourished patients showed decreased FMD than patients with normal nutrition.

Risk factors for PAD in patients undergoing hemodialysis. The prevalence of PAD was 28% across all patients included in the study and it was significantly higher among malnourished patients compared with non-malnourished patients (Fig. 1; P<0.01). However, non-malnourished patients with a high VF had a significantly higher prevalence of PAD compared with those with a lower VF content (29.5 vs. 12.5%, respectively; P=0.007). Furthermore, bivariate correlation analysis revealed that the age, diabetic mellitus (DM), VF, malnutrition, serum albumin level, DBP and log C-reactive protein (CRP) were significantly correlated with PAD (all P<0.05) and subsequent logistic regression analysis determined that age, DM, VF

Table I. Comparison of variables between the low and high VF mass groups in well-nourished and malnourished patients undergoing hemodialysis.

Variable	Non-malnourished		Malnourished		Significance
	Low VF (n=136)	High VF (n=32)	Low VF (n=20)	High VF (n=22)	
Age (years)	54±15	66±10	64±12	72±6	ABCD
Gender (male %)	56	50	23	41	B
DM (%)	28	45	30	63	AC
CVD (%)	12	35	18	33	A
Smokers (%)	27	42	10	27	NS
Dialysis duration (m)	13±18	17±21	15±18	11±13	NS
Height (cm)	160±9	160±8	155±8	159±8	B
Weight (kg)	57±9	67±10	47±8	61±10	ABCD
BMI (kg/m^2)	22±2.5	26±3	20±2	25±4	ABC
Alb (g/l)	39.9±6	39.6±4	36.8±4	35.6±4	BD
SBP (mmHg)	134±20	138±21	133±31	125±22	NS
DBP (mmHg)	80±15	78±10	75±13	69±10	D
TG (mmol/l)	2.4±1.7	2.8±1.8	2.5±1.6	2.9±2	NS
TC (mmol/l)	5.1±1.1	5.0±1	6.1±1.5	5.2±1.2	B
HDL (mmol/l)	1.2±0.3	1±0.2	1.4±0.4	1.1±0.3	ABC
LDL (mmol/l)	3±0.9	3±1	3.8±1.1	3±0.8	BC
Glu (mmol/l)	5.4±1.7	6.3±2.6	6.3±2.7	6.5±2	A
LnCRP	0.48±1.5	1.2±1.5	0.9±1.1	2.1±1.4	ACD
Ca (mmol/l)	2.3±0.4	2.4±0.3	2.2±0.4	2.5±0.3	NS
P (mmol/l)	1.6±0.4	1.5±0.4	1.4±0.5	1.5±0.4	NS
BUN (mmol/l)	23.5±6	21.5±5	19.7±7.5	18.6±7.3	AB
Scr (μmol/l)	918±288	880±277	749±352	792±263	B
KT/V (total)	1.8±0.5	1.8±0.6	1.9±0.4	1.8±1.8	NS
KT/V (renal)	0.5±0.6	0.4±0.7	0.4±0.4	0.3±0.3	NS
Fat (kg)	14±5	23±8	11±3	21±8	AC
Hb (g/l)	115±17	118±15	109±21	115±20	NS
Total fat (%)	24±8	33±10	24±7	31±14	AC
FMD (%)	8.6±5.5	7.3±3.6	8.6±4.5	4.6±2.4	CD
VF	7.2±3.3	12.8±3.5	5.6±2.2	12.5±3	ABC

A and C: Significant difference between low and high VF groups within the malnutrition or non-malnutrition groups. B and D: Significant difference between the malnutrition and non-malnutrition groups within low and high VF groups. NS, no significant difference between each group. DM, diabetic mellitus; CVD, cardiovascular or cerebrovascular disease; BMI, body mass index; Alb, serum albumin; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglyceride; TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LnCRP, log C-reactive protein; BUN, blood urea nitrogen; Scr, serum creatinine; KT/V, clearance of urine; Hb, hemoglobin; FMD, flow-mediated dilatation; VF, visceral fat.

content and malnutrition were independent risk factors for PAD (all $P<0.05$) (Table II).

Discussion

The present study revealed an association between nutritional status and VF content and the prevalence of PAD in patients undergoing hemodialysis. Malnourished patients with a high VF mass (obese sarcopenia) had the highest prevalence of PAD in the hemodialysis population of the present study. This is similar to the results of a previous study (15), which identified the detrimental effects of malnutrition in the presence of obesity by demonstrating that obese sarcopenia was associated with inflammation and increased mortality in ESRD patients.

Notably, increased VF was identified to be an independent risk factor for PAD in the present study. Although no previous studies, to the best of our knowledge, have explored the association between VF and PAD in patients with ESRD, it has been revealed that visceral obesity is associated with uremic dyslipidemia, inflammation and arterial stiffness (19), in addition to cardiovascular mortality (20) in patients with ESRD.

The underlying molecular mechanisms of the association between adiposity and CVD are not fully understood (21); however, it is well known that adipose tissue, in addition to

Table II. Univariate and multivariate analysis of selected variables and peripheral arterial disease patients undergoing hemodialysis.

	Analysis type			
	Univariate		Multivariate	
Variable	R-value	P-value	Exp (β)	P-value
Age	0.304	<0.010	1.036	0.047
DM	0.242	<0.010	2.11	0.045
Visceral fat	0.211	<0.010	1.11	0.030
Malnutrition	0.277	<0.010	4.53	0.010
Alb	-0.170	0.014		
LnCRP	0.168	0.016		
DBP	-0.226	<0.010		

Univariate analysis was bivariate correlation analysis and multivariate analysis was logistic regression analysis. DM, diabetic mellitus; Alb, serum albumin; LnCRP, log C-reactive protein; DBP, diastolic blood pressure; Exp (β), odds ratio for each variable in multivariate regression.

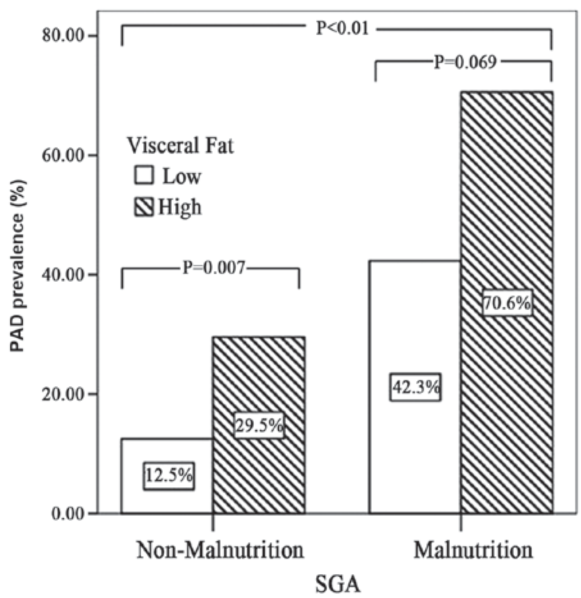

Figure 1. Prevalence of PAD in non-malnourished and malnourished patients with a low VF or high VF content undergoing hemodialysis. PAD, peripheral arterial disease; VF, visceral fat; SGA, subjective global assessment.

storing energy in the form of triglycerides, is a highly active endocrine tissue that secretes a large variety of cytokines, several of which are thought to be associated with cardiovascular disease (13). Furthermore, systemic inflammation is considered to be an important mediator of CVD in patients with ESRD, while VF has been identified to be positively correlated with low-grade inflammation in this patient group (22). In the present study, patients with a higher VF mass had significantly higher CRP levels, particularly if they were also malnourished. Similarly, levels of antiatherogenic high-density lipoprotein q43 known to be low in obese patients with ESRD (22) and the present study identified that patients with increased abdominal fat had a more atherogenic lipid profile.

A risk factor for PAD is endothelial dysfunction, which has previously been determined to be associated with obesity in non-uremic individuals (13). In the present study, malnourished patients with a high VF content had worse endothelial dysfunction. This confirms earlier reports of an association between fat content and FMD (13), in addition to between FMD and the adipokines, adiponectin, leptin and visfatin, in patients undergoing dialysis (13). The present study did not show an association between FMD and PAD prevalence, which is contrary to what previous studies have identified. However, the patients undergoing hemodialysis in the present study had several risk factors for PAD, including hypertension, dyslipidemia, malnutrition, obesity, diabetes, smoking, CRP level and CVD complications, which could contribute to a lower FMD independently of PAD (23).

The present study had a number of limitations, including that a causal relationship between PAD and obese sarcopenia could not be determined by a cross-sectional observation study and the estimation of the body composition of patients undergoing hemodialysis by BIA may not be as accurate as that of general subjects due to volume overload. In addition, the levels of atherogenetic adipokines, including leptin and adiponectin, were not tested in the present study.

In conclusion, obesity and malnutrition were demonstrated to have a synergistic effect on increasing the risk of PAD in patients undergoing hemodialysis. The association between a high VF content and increased risk of PAD has attracted the attention of nephrologists for cardiovascular disease detection and prevention, particularly due to the increasing prevalence of obesity in patients with ESRD (14). The present study presents an association between PAD and obese sarcopenia, which implies that some intervention is required to decrease the incidence of cardiovascular complications in patients with ESRD. Further studies are required to clarify whether improving nutritional status and decreasing visceral fat-mass may help to reduce cardiovascular complications in patients with ESRD.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

ST contributed to the study design and data analysis. KZ collected and analyzed data. PX contributed to the design and drafting of the manuscript, agrees to be accountable for all aspects of the work and gave final approval of the version to be published.

Ethics approval and consent to participate

The ethics committee of Tianjin Medical University General Hospital approved the present study and written informed consent was obtained from all patients.

Consent for publication

All patients provided written informed consent for publication.

Competing interests

The authors declare that they have no competing interests.

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