Association of visceral fat thickness with carotid atherosclerosis and inflammation in peritoneal dialysis patients

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Association of visceral fat thickness with carotid atherosclerosis and inflammation in peritoneal dialysis patients

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<TABLE OF CONTENTS>

LIST OF FIGURES

LIST OF TABLES

ABSTRACT

Association of visceral fat thickness with carotid atherosclerosis and inflammation in peritoneal dialysis patients

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Background:

Patients with advanced chronic kidney disease (CKD) requiring maintenance dialysis have a significantly higher risk of cardiovascular mortality. In general population, anthropometric measurements of central obesity such as high body mass index (BMI), waist circumference (WC), and waist-to-hip ratio (WHR) are associated with increased cardiovascular mortality. However, the association between obesity and clinical outcomes in patients with peritoneal dialysis (PD) is conflicting. The aim of this study was to investigate whether visceral fat thickness had predictive role in carotid atherosclerosis determined by carotid intima-media thickness (cIMT) in PD patients.

Methods:

A cross-sectional study was undertaken in 88 prevalent PD patients between February 2010 and July 2010. BMI, WC, and WHR were measured as anthropometric indices of obesity. Visceral fat thickness (VFT) and subcutaneous fat thickness (SFT) were determined by sonographic measurement of abdominal fat. cIMT was measured as a surrogate marker of atherosclerosis. Carotid atherosclerosis was defined as cIMT ≥ 1 mm.

Results:

The mean age was 53.3 ± 11.8 years and the mean duration of PD was 63.6 months. Fifty-four patients (61.4%) were male and 22 patients (25%) were diabetes. The mean cIMT was 0.76 ± 0.26 mm, and the prevalence of carotid atherosclerosis was 20.4% (18/88). Patients with carotid atherosclerosis had significantly higher WC (89.4 ± 9.9 vs. 83.7 ± 7.8 cm, p = 0.033), higher WHR (0.94 ± 0.05 vs. 0.91 ± 0.05, p = 0.038), and higher VFT (42.5 ± 15.1 vs. 32.2 ± 8.9 mm, p <0.001) compared to patients without carotid atherosclerosis. In univariate analysis, VFT [Odds ratio (OR) = 1.085, 95% Confidence interval (CI): 1.032-1.14, p = 0.001], WHR (OR = 1.105, 95% CI: 1.033-1.218, p = 0.043), BMI (OR = 1.24, 95% CI: 1.029-1.494, p = 0.024), and WC (OR = 1.085, 95% CI: 1.016-1.158, p = 0.014) were significant risk factors of carotid atherosclerosis. However, multivariate logistic regression analysis revealed VFT was a single independent factor associated with carotid

atherosclerosis after adjustment of demographic and biochemical parameters (OR = 1.089, 95% CI: 1.021-1.161, p = 0.009). Moreover, VFT remained as an independent risk factor of carotid atherosclerosis in multivariate logistic regression analysis for comparison of relative independent association of obesity indices with carotid atherosclerosis (OR = 1.095, 95% CI: 1.004-1.194, p = 0.04). The respective areas under the receiver operating characteristic curve (AUC) of VFT was higher than the AUCs of all other parameters (VFT; AUC 0.705, p=0.007). When the patients were divided into three groups according to VFT, patients with high VFT tertile showed higher inflammatory markers such as high sensitivity C-reactive protein and fibrinogen, and higher insulin resistance compared to other groups.

Conclusion:

The main finding of this study is VFT, not SFT, is more predictive for carotid atherosclerosis than all other obesity indices in PD patients. Although WC and WHR showed significant relationships with carotid atherosclerosis in univariate analysis, VFT measured by abdominal ultrasonography was an independent risk factor of carotid atherosclerosis after adjustment for confounding variables. Therefore, sonographic measurement of VFT could be useful to stratify the risk of cardiovascular outcomes in PD patients.

Key words: visceral fat thickness, carotid intima-media thickness, atherosclerosis, peritoneal dialysis

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I. INTRODUCTION

In general population, a high body mass index (BMI; in kg/m^2) is associated with increased cardiovascular and all-cause mortalities[1,2]. In contrast, inverse association between BMI and survival rates has been reported in end-stage renal disease (ESRD) patients on hemodialysis[3-5]. The term 'reverse epidemiology' has been adopted to describe this paradoxical inverse association between BMI and mortality in dialysis patients[6]. However, the association between BMI and clinical outcomes in patients

treated with peritoneal dialysis (PD) is conflicting[7-10].

Anthropometric measurements of central obesity such as waist-to-hip ratio (WHR) and waist circumference (WC) are more predictive for cardiovascular mortality in general population[11,12]. Furthermore, several studies have shown that high WHR and WC are associated with an increased risk of cardiovascular mortality in chronic kidney disease (CKD) as well as dialysis patients[12,13]. However, WHR is influenced by gluteal muscle and peripheral fat[14], and WC does not differentiate between visceral and subcutaneous fat[14]. Therefore, there might be substantial variations on predicting the degree of central obesity in PD patients.

Visceral fat is more metabolically active and associated with inflammation, insulin resistance, and atherosclerosis[15]. Sonographic measurement of visceral fat has been reported as a reliable method to estimate visceral fat, as effective as computed tomography and magnetic resonance imaging[16-18]. To date, the influence of visceral fat on cardiovascular disease in PD patients has never been elucidated. Therefore, the main aim of this study was to investigate whether sonographic measurement of visceral fat had an additional role in assessing atherosclerosis compared with other obesity indices in PD patients. Secondly, I investigated the relationship between visceral fat and various biochemical markers, which reflected role of chronic inflammation in the development of atherosclerosis.

II. MATERIALS AND METHODS

1. Subjects

A cross-sectional study was undertaken in 88 prevalent PD patients. Patients enrolled from a single outpatient dialysis center at Yonsei University Health System in Seoul, Korea between February 2010 and July 2010. Patients were excluded if they met the following criteria; younger than 18 years, active infections during the last 3 months before enrollment, a history of malignancy or other chronic inflammatory diseases, or less than 3 months of PD duration. This study was performed after the approval of the Institutional Review Board. All participants gave written informed consent.

2. Demographic and biochemical data assessment

Demographic data were obtained by a well-trained examiner using a questionnaire. Venous blood was taken from all study patients after a 12-hour overnight fast. Serum total cholesterol, high-density lipoprotein (HDL)-cholesterol, triglyceride, and low-density lipoprotein (LDL)-cholesterol concentrations were measured by an autoanalyzer with enzymatic colorimetric method (Hitachi 7150; Hitachi, Tokyo, Japan). High sensitivity C-reactive protein (hs-CRP) levels were determined using BN II analyzer (Dade Behring, Newarkand, DE) by a latex-enhanced immunoephelometric method. Fibronogen concentrations in citrated plasma were measured by a modified

clot rate assay using a Pacific Hemostasis Assay Set (Humlersville, NC, USA). Insulin resistance was assessed by using the homeostasis model assessment (HOMA-IR) equation, as follows: HOMA−IR = [fasting insulin (in microunits per milliliter) x fasting serum glucose (in millimoles per liter)/ 22.5]

3. Anthropometric measurements

Anthropometric indices were measured in the morning after complete emptying of overnight dialysate. To reflect the actual situation, usual overnight dialysate volume and glucose concentrations were not changed for this study. Patients were weighed with light clothing and height was measured with no shoes. BMI was calculated as weight/height^2 (kg/m^2). WC was measured at the narrowest point between the 12th rib and iliac crest. Hip circumference (HC) was the widest circumference between iliac crest and greater trochanters of femur. WHR was calculated as WC/HC. These anthropometric measurements were obtained by a single skilled nurse in the PD unit.

4. Sonographic measurements

All sonographic measurements of abdominal fat thickness and carotid intima-media thickness (cIMT) were performed by a single trained medical doctor using a LOGIQ α ultrasound (GE Medical Systems, Milwaukee, WI, USA).

Subcutaneous fat thickness (SFT) and visceral fat thickness (VFT) were measured in the region of 1 cm above the umbilicus using 10 MHz linear-array probe and 3.5 MHz convex-array probe, respectively. Patients were examined at the expiratory phase of quiet respiration and application of the transducer on the body surface was done without undue pressure. SFT was defined as the maximal thickness of fat tissue layer between the skin-fat interface and the linea alba. VFT was defined as the distance between the anterior wall of the aorta and the posterior aspect of the rectus abdominis muscle perpendicular to the aorta. The relative intra-observer technical error of measurement for the SFT was between 1.5% to 2.5% and 1% to 1.8% for the VFT. cIMT was measured in the prone position with the head extended and turned to the oppose direction. Both carotid arteries, carotid bulb, and internal carotid arteries were examined by 2 different longitudinal projections. cIMT was defined as the distance between the leading edges of the lumen interface and the media-adventitia interface at the far wall. The value of cIMT was expressed as an average of the maximal cIMT on both carotid arteries. Carotid atherosclerosis was defined as cIMT $\geq$ 1.0 mm in accordance with previous studies[19,20].

5. Statistical analysis

Data are expressed as means ± standard deviation, or count and percentage for categorical variables. Spearman's rank correlation coefficients were calculated

to examine the associations between cIMT and other variables. To compare the differences in characteristics according to the presence of carotid atherosclerosis (cIMT $\geq$ 1 mm), Student *t test* or Mann-Whitney *U* test for continuous variables and χ^2 test for categorical variables were performed. Multivariate logistic regression analysis was used to examine the independent association between anthropometric indices, sonographic VFT, and carotid atherosclerosis. Analysis was performed separately for each index with adjustment of traditional risk factors and known variables on prior univariate test. Consecutive logistic regression models were constructed to compare relative independent association of obesity indices with carotid atherosclerosis. Receiver operating characteristic (ROC) curves for each index were configured to examine predictive value for carotid atherosclerosis. Various biochemical markers for inflammation and insulin resistance according to VFT category were compared by ANOVA. Statistical analysis was performed with the Statistical Package for the Social Sciences (SPSS) for windows, version 18.0 (Chicago, IL, USA).

III. RESULTS

1. Demographic characteristics of subjects

Demographic characteristics of subjects are shown in Table 1. The mean age was 53.3 ± 11.8 years and the mean duration of peritoneal dialysis was 63.6 months. Fifty-four patients (61.4%) were male and twenty two patients (25%) were diabetes. The mean BMI was 23.0 ± 2.8 kg/m^2, the mean WC was 84.8 ± 8.5 cm, and the mean WHR was 0.92 ± 0.05. By sonographic measurement of abdominal fat, the mean SFT was 16.0 ± 4.9 mm and the mean VFT was 34.3 ± 11.2 mm. The mean cIMT was 0.76 ± 0.26 mm, and carotid atherosclerosis (cIMT ≥ 1 mm) was present in 18 patients (20.4%).

Table 1. Baseline characteristics of the subjects

Characteristics	*n* = 88
Age (years)	53.8 ± 11.8
Sex (Male : Female)	54 (61.4%) : 34 (38.6%)
History of smoking, *n* (%)	35 (39.8%)
Diabetes mellitus, *n* (%)	22 (25%)
Duration of peritoneal dialysis (months)	63.6 ± 62.1 (3-228)
Systolic blood pressure (mmHg)	133.5 ± 21.8
Diastolic blood pressure (mmHg)	74.9 ± 14.2
Anthropometric measurement	
Body mass index (BMI) (kg/m^2)	23.0 ± 2.8
Waist circumference (WC) (cm)	84.8 ± 8.5
Waist-to-hip ratio (WHR)	0.92 ± 0.05
Total cholesterol (mg/dL)	168.5 ± 36.1
HDL-cholesterol (mg/dL)	45.3 ± 28.0
LDL-cholesterol (mg/dL)	90.7 ± 28.6
Triglyceride (mg/dL)	120.5 ± 74.2
hs-CRP (mg/L)	4.4 ± 10.2
ESR (mm/hr)	54.4 ± 31.3
Fibrinogen (mg/dL)	391.0 ± 68.0
HOMA-IR	3.0 ± 3.1
Calcium (mg/dL) x Phosphate (mg/dL)	43.0 ± 12.8
Parathyroid hormone (pg/mL)	213.6 ± 273.0
Sonographic measurement	
Subcutaneous fat thickness (SFT) (mm)	16.0 ± 4.9
Visceral fat thickness (VFT) (mm)	34.3 ± 11.2
Carotid intima-media thickness (cIMT) (mm)	0.76 ± 0.26

Data are expressed as mean ± standard deviation or number of patients (percent).
HDL-cholesterol, high-density lipoprotein-cholesterol; LDL-cholesterol, low-density lipoprotein-cholesterol; hs-CRP, high sensitivity C-reactive protein (mg/L); ESR, erythrocyte sedimentation rate; HOMA-IR, homeostasis model assessment-insulin resistance

2. Association of demographic, biochemical, and obesity indices with cIMT

Table 2 showed the association of demographic, biochemical, and obesity indices with cIMT. There were significant positive correlations between cIMT and age ($r = 0.481$, $P < 0.001$), diabetes ($r = 0.276$, $p = 0.009$), hs-CRP ($r = 0.341$, $p < 0.001$), erythrocyte sedimentation rates (ESR) ($r = 0.254$, $p = 0.017$), and HOMA-IR ($r = 0.213$, $p = 0.046$). All anthropometric indices were significantly associated with cIMT. The association was the strongest for WC ($r = 0.353$, $p < 0.001$), intermediate for BMI ($r = 0.323$, $p = 0.002$) and the weakest for WHR ($r = 0.268$, $p = 0.012$). VFT ($r = 0.341$, $p < 0.001$) was significantly correlated with cIMT, but SFT did not show a significant correlation with cIMT.

Table 2. Spearman's correlation coefficients of cIMT with clinical parameters

Variables	correlation coefficient	*p*-value
Male sex	-0.165	0.125
Age	0.481	<0.001*
History of smoking	0.015	0.889
Diabetes mellitus	0.276	0.009†
Duration of peritoneal dialysis	0.105	0.34
Mean arterial blood pressure	0.105	0.34
Anthropometric measurement		
Body mass index (BMI)	0.323	0.002†
Waist circumference (WC)	0.353	<0.001*
Waist -to-hip ratio (WHR)	0.268	0.012‡
Total cholesterol	-0.186	0.083
HDL-cholesterol	-0.358	0.322
LDL-cholesterol	-0.08	0.461
Triglyceride	0.107	0.322
Log hs-CRP	0.341	<0.001*
ESR	0.254	0.017‡
Fibrinogen	0.205	0.055
HOMA-IR	0.213	0.046‡
Parathyroid hormone	-0.076	0.481
Sonographic measurement		
Subcutaneous fat thickness (SFT)	0.042	0.701
Visceral fat thickness (VFT)	0.341	<0.001*

* <0.001 ; † <0.01 ; ‡ <0.05

cIMT, carotid intima-media thickness; HDL-cholesterol, high-density lipoprotein-cholesterol; LDL-cholesterol,low-density lipoprotein-cholesterol; hs-CRP, high sensitivity C-reactive protein; ESR, erythrocyte sedimentation rate; HOMA-IR homeostasis model assessment-insulin resistance.

3. Comparison of variables according to the presence of carotid atherosclerosis

According to the presence of carotid atherosclerosis (cIMT ≥ 1 mm), subjects were divided into 2 groups. The mean age (61 ± 8.9 vs. 51.9 ± 11.8 years), and hs-CRP (13.5 ± 3.1 vs 3.1 ± 8.8 mg/L) and fibrinogen levels (422.5 ± 72.8 vs. 382.9 ± 64.8 mg/dL) were significantly higher, while HDL-cholesterol (48.3 ± 30.6 vs. 33.6 ± 7.0 mg/dL) was significantly lower in patients with carotid atherosclerosis. However, there were no differences in the proportion of diabetic patients (33.3% vs. 22.8%, p = 0.265) and smokers (44.4% vs. 38.5%, p = 0.788) between the two groups. The patients with carotid atherosclerosis showed significantly higher WC (89.4 ± 9.9 vs. 83.7 ± 7.8 cm, p = 0.033), WHR (0.94 ± 0.05 vs. 0.91 ± 0.05, p = 0.038), and VFT (42.5 ± 15.1 vs. 32.2 ± 8.9 mm, p <0.001). In contrast, no significant differences were depicted in BMI (24.4 ± 3.4 vs. 22.7 ± 2.5 kg/m^2, p = 0.056) and SFT (17.4 ± 5.8 vs. 15.7 ± 4.6 mm, p = 0.281).

Table 3. Clinical characteristics of patients with and without carotid atherosclerosis

Characteristics	With carotid atherosclerosis (cIMT ≥ 1 mm) (n = 18)	Without carotid atherosclerosis (cIMT < 1 mm) (n = 70)	*p*-value
Age (years)	61 ± 8.9	51.9 ± 11.8	<0.001*
Male, n (%)	14 (77.7%)	40 (57.1%)	0.174
History of smoking, *n* (%)	8 (44.4%)	27 (38.5%)	0.788
Diabetes mellitus, *n* (%)	6 (33.3%)	16 (22.8%)	0.265
Duration of peritoneal dialysis (months)	59.8 ± 54.6	64.6 ± 64.2	0.781
Anthropometric measurement			
BMI (kg/m^2)	24.4 ± 3.4	22.7 ± 2.5	0.056
WC (cm)	89.4 ± 9.9	83.7 ± 7.8	0.033‡
WHR	0.94 ± 0.05	0.91 ± 0.05	0.038‡
Total cholesterol (mg/dL)	167.5 ± 39.9	168.7 ± 35.4	0.904
HDL-cholesterol (mg/dL)	33.6 ± 7.0	48.3 ± 30.6	0.047‡
LDL-cholesterol (mg/dL)	92.8 ± 26.7	90.2 ± 29.3	0.722
Triglyceride (mg/dL)	150.8 ± 91.3	112.6 ± 67.7	0.051
hs-CRP (mg/L)	13.5 ± 3.1	3.1 ± 8.8	0.016‡
ESR (mm/hr)	62.8 ± 20.6	52.2 ± 33.3	0.202
Fibrinogen (mg/dL)	422.5 ± 72.8	382.9 ± 64.8	0.027‡
HOMA -IR	3.3 ± 2.7	2.9 ± 3.2	0.59
PTH (pg/mL)	188.8 ± 102.4	220.0 ± 302.0	0.667
Sonographic measurement			
SFT (mm)	17.4 ± 5.8	15.7 ± 4.6	0.281
VFT (mm)	42.5 ± 15.1	32.2 ± 8.9	<0.001*

* <0.001 ; † <0.01 ; ‡ <0.05

Data are expressed as mean ± standard deviation or number of patients (percent).

cIMT, carotid intima-media thickness; BMI, body mass index; WC, waist circumference; WHR, waist-to-hip ratio; HDL-cholesterol, high-density lipoprotein-cholesterol; LDL-cholesterol, low-density lipoprotein-cholesterol; hs-CRP, high-sensitivity C-reactive protein; ESR, erythrocyte sedimentation rate; HOMA-IR, homeostasis model assessment-insulin resistance; PTH, parathyroid hormone; SFT, subcutaneous fat thickness; VFT, visceral fat thickness.

4. VFT as the most independent parameter associated with carotid atherosclerosis

In univariate analysis, VFT [Odds ratio (OR) = 1.085, 95% Confidence interval (CI): 1.032-1.14, p = 0.001], WHR (OR = 1.105, 95% CI: 1.033-1.218, p = 0.043), BMI (OR = 1.24, 95% CI: 1.029-1.494, p = 0.024), and WC (OR = 1.085, 95% CI: 1.016-1.158, p = 0.014) were significantly associated with carotid atherosclerosis. Multivariate logistic regression analysis was performed to evaluate the association of each parameter with carotid atherosclerosis. Table 4 shows BMI (OR = 1.242, 95% CI: 1.00-1.50, p = 0.048) and VFT (OR = 1.084, 95% CI: 1.027-1.145, p = 0.004) are independently related to carotid atherosclerosis with adjustment for sex and age. After adjustment for further variables (smoking history, diabetes, LDL-cholesterol, hs-CRP, fibrinogen), BMI lost the independent relationship and VFT remained as a single independent factor. Interestingly, the independent association of VFT with carotid atherosclerosis was still strong even after adjustment for the above variables (OR = 1.089, 95% CI: 1.021-1.161, p = 0.009). To compare relative independent association of anthropometric and sonographic parameters with carotid atherosclerosis, multivariate logistic regression analyses including all indices were performed. After adjustment of each parameter, VFT was the only parameter exhibiting an independent relationship with carotid atherosclerosis (OR = 1.083, 95% CI: 1.014-1.157, p = 0.017). Furthermore, independent relationship had been founded ever after

adjustment for confounders (OR = 1.095, 95% CI: 1.004-1.194, p = 0.04) (Table.5).

Table 4. Multivariate regression models for the associations of BMI, WC, WHR, SFT, and VFT with carotid atherosclerosis

	BMI (per kg/m^2)			WC (per cm)		
	OR	95% CI	p-value	OR	95% CI	p-value
Crude	1.24	1.029-1.494	0.024‡	1.085	1.016-1.158	0.014‡
Model 1	1.242	1.002-1.540	0.048‡	1.063	0.989-1.142	0.097
Model 2	1.252	0.981-1.597	0.071	1.047	0.96-1.134	0.261
	WHR (per 0.01)			SFT (per mm)		
	OR	95% CI	p-value	OR	95% CI	p-value
Crude	1.105	1.033-1.218	0.043‡	1.070	0.963-1.188	0.209
Model 1	1.058	0.952-1.175	0.297	1.128	0.992-1.283	0.067
Model 2	1.020	0.906-1.149	0.745	1.161	0.153-4.058	0.077
	VFT (per mm)					
	OR	95% CI	p-value			
Crude	1.085	1.032-1.14	0.001*			
Model 1	1.084	1.027-1.145	0.004†			
Model 2	1.089	1.021-1.161	0.009†			

* <0.001 ; † <0.01 ; ‡ <0.05
Model 1 : adjusted for age, sex.
Model 2 : adjusted for age, sex, smoking history (as categorical variables, smoker vs. non smoker), diabetes (as categorical variables, diabetes vs. non diabetes), low density lipoprotein-cholesterol, high sensitivity C-reactive protein, and fibrinogen.
BMI, body mass index; WC, waist circumference; WHR, waist-to-hip ratio; SFT, subcutaneous fat thickness; VFT, visceral fat thickness; OR, odds ratio; 95% CI, 95% confidence interval.

Table 5. Multivariate regression models for comparison of independent association of BMI, WC, WHR, SFT, and VFT with carotid atherosclerosis (forced entry of all obesity indices for comparison)

Crude			
	OR	95% CI	p-value
BMI (per kg/m^2)	1.05	0.657-1.679	0.838
WC (per cm)	1.059	0.853-1.315	0.602
WHR (per 0.01)	0.955	0.788-1.158	0.64
SFT (per mm)	0.926	0.789-1.087	0.345
VFT (per mm)	1.083	1.014-1.157	0.017‡

* <0.001 ; † <0.01 ; ‡ <0.05

Model 1			
	OR	95% CI	p-value
BMI (per kg/m^2)	1.154	0.676-1.972	0.599
WC (per cm)	0.975	0.776-1.226	0.831
WHR (per 0.01)	0.924	0.748-1.142	0.465
SFT (per mm)	0.995	0.819-1.209	0.962
VFT (per mm)	1.10	1.017-1.189	0.017‡

* <0.001 ; † <0.01 ; ‡ <0.05, Model 1 : adjusted for age, sex.

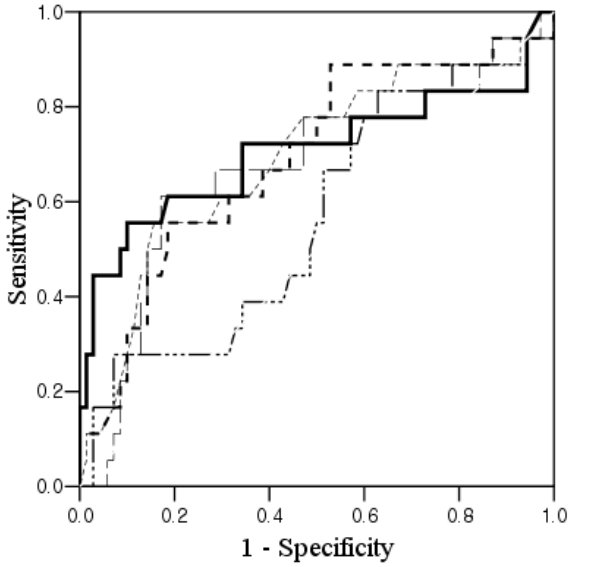
Model 2			
	OR	95% CI	p-value
BMI (per kg/m^2)	1.296	0.668-2.516	0.443
WC (per cm)	0.913	0.693-1.202	0.516
WHR (per 0.01)	0.908	0.719-1.146	0.415
SFT (per mm)	1.073	0.849-1.356	0.554
VFT (per mm)	1.095	1.004-1.194	0.04‡

* <0.001 ; † <0.01 ; ‡ <0.05, Model 2 : adjusted for age, sex, smoking history (as categorical variables, smoker vs. non smoker), diabetes (as categorical variables, diabetes vs. non diabetes), low density lipoprotein-cholesterol, high sensitivity C-reactive protein, and fibrinogen.
BMI, body mass index; WC, waist circumference; WHR, waist-to-hip ratio; SFT, subcutaneous fat thickness; VFT, visceral fat thickness; OR, odds ratio; 95% CI, 95% confidence interval.

5. ROC analysis for prediction of carotid atherosclerosis

To assess predictive value of different anthropometric indices for carotid atherosclerosis, ROC analyses were performed. The respective area under the ROC curve (AUC) of VFT was higher than the AUCs of all other parameters (VFT; AUC 0.705, p=0.007, BMI; AUC 0.691, p=0.013, WC; AUC 0.690, p=0.013, WHR; AUC 0.671, p=0.026, and SFT; AUC 0.563, p=0.408) and the estimated cut-off value of VFT was 39.1 mm. It provided a sensitivity of 61.2 % and specificity of 80.4% to predict carotid atherosclerosis (Figure 1).

Figure 1. Receiver operating characteristic (ROC) curve for VFT, BMI, WC, WHR, and SFT to predict carotid atherosclerosis



	AUC	p-value
VFT	0.705	0.007
BMI	0.691	0.013
WC	0.690	0.013
WHR	0.671	0.026
SFT	0.563	0.408

VFT, visceral fat thickness; BMI, body mass index; WC, waist circumference; WHR, waist-to-hip ratio; SFT, subcutaneous fat thickness; AUC, areas under the ROC curve.

6. Biochemical markers for inflammation and insulin resistance according to VFT.

The patients were divided into 3 groups according to the values of VFT and biochemical markers were compared among the three groups. Table 6 shows a significant trend for increasing value of hs-CRP, fibrinogen, and HOMA-IR across VFT tertiles. In the 3rd VFT tertile, hs-CRP, fibrinogen, and HOMA-IR were significantly higher compared with other groups.

Table 6. Inflammatory markers according to the tertiles of visceral fat thickness (VFT)

	VFT			
Characteristics	1st tertile (mean 22.7 mm)	2nd tertile (mean 33.0 mm)	3rd tertile (mean 46.8 mm)	p-value
ESR (mm/hr)	44.5 ± 20.8	58.4 ± 44.3	60.1 ± 22.0	0.113
hs-CRP (mg/L)	2.5 ± 6.5	4.4 ± 6.2	5.4 ± 8.4	0.047*
Fibrinogen (mg/dL)	372.1 ± 53.4	384.3 ± 71.4	415.6 ± 71.8	0.038*
HOMA-IR	2.1 ± 2.9	2.5 ± 2.2	3.0 ± 3.1	0.019*

* <0.05

ESR, erythrocyte sedimentation rate; hs-CRP, high sensitivity C-reactive protein; HOMA-IR, homeostasis model assessment –insulin resistance.

IV. DISCUSSION

This study demonstrated VFT, as a marker of central obesity, was independently associated with carotid atherosclerosis in PD patients. Although other anthropometric measurements of obesity, including WC, WHR, and BMI, showed independent relationships with cIMT in separate univariate analysis, after adjustment for confounders, VFT was a single independent predictor for carotid atherosclerosis in patients on PD.

In dialysis patients, malnutrition and weight loss are associated with high mortality rates, whereas there is a controversy about the association between obesity and mortality. The phenomenon of reverse epidemiology, which meant obesity and higher BMI were associated with low mortality rates in dialysis patients, was observed in many studies[2-5,21]. However, Beddhu et al.[22] showed that the protective effect of high BMI was limited to patients with normal or high muscle mass among 70,028 hemodialysis patients. Recent studies provided a concept of obese sarcopenia which meant high body mass with protein energy malnutrition and low muscle mass were associated with high mortality rates in ESRD patients. A Postrino's report supported this theory[12]. It revealed that WC was an independent predictor for cardiovascular mortality and BMI showed an inverse relationship with mortality[12].

The association between BMI and clinical outcomes in PD patients is not well established[22]. Johnson et al.[7] found that high BMI is associated with a

significant survival advantage in patients on PD. The largest epidemiologic study of nearly 46,000 PD patients also presented the survival rates of overweight and obese PD patients was higher[8]. In contrast, a study of Australia and New Zealand Dialysis and Transplant Registry (ANZDATA) showed that obesity at the start of PD was a significant risk factor for death and technique failure. In addition, mortality rates of underweight group (BMI < 20 kg/m^2) were the lowest[9]. Most of the previous studies concerning association between obesity and mortality have used BMI as a surrogate marker for excess weight in dialysis patients. However, BMI dose not differentiate between muscle and fat mass. Not only is BMI a poor anthropometric marker, but it also fails to provide any detailed information about the specific origin of the excess weight. Moreover, CKD is associated with decreased muscle mass and fluid imbalance. Since BMI is affected by fat, muscle mass and fluid status, lower BMI may reflect decreased fat (mostly subcutaneous), decreased muscle mass and fluid depletion. Collectively, in patients with CKD, BMI might not be ideal for anthropometric measurement of obesity[6].

WC and WHR are directly associated with all cause and cardiovascular mortalities in general population[11]. In addition, WHR was the strongest body size measure associated with myocardial infarction in the (INTERHEART) study, a world-wide extended case control study[24]. Odds ratio of myocardial infarction was significantly higher for each successive quintile of WHR, but

not BMI. Moreover, BMI lost substantial prognostic value in an analysis adjusting for WHR and others. Elsayed et al.[13] demonstrated that WHR, but not BMI, was associated with the development of CKD and cardiac events in CKD patients. However, it is well known that WC and WHR are not the direct measurements for the amount of abdominal fat and are not able to discriminate visceral and subcutaneous fat. Recent observational studies supported the discrepant association between WC and visceral adiposity[25,26]. High WC, as a consequence of excess subcutaneous fat, not visceral fat in severely obese men, did not increase metabolic complications[25]. In addition, visceral adiposity in patients with normal WC was significantly associated with the severity of coronary heart disease[27]. These data suggested that simple measurement of WC or WHR is not able to assess the quantity of visceral obesity. Therefore, direct measurement of visceral fat would be a more validate marker of central obesity. The standard quantification method of visceral adiposity is abdominal fat computed tomography scan. However, this method has some problems such as exposure to radiation and high cost. Several studies reported that ultrasonography was simple and accurate to measure visceral fat tissue[16-18]. In the present study, BMI, WC, WHR, and VFT were associated with carotid atherosclerosis in univariate analysis. However, only ultrasound measurement of VFT remained as a significant independent factor associated with carotid atherosclerosis after adjustment. Furthermore, when relative independent associations of obesity indices with

carotid atherosclerosis were compared, VFT showed the highest predictive value.

Abdominal obesity is largely caused by the accumulation of visceral fat, while peripheral obesity is mainly characterized by subcutaneous fat accumulation[6]. Central fat and peripheral fat may have different effect on metabolic disturbances and clinical events. Visceral fat is the most metabolically active fat store and key factor in the development of insulin resistance, type-2 diabetes, and atherosclerosis[15]. And it is also associated with inflammation and oxidative stress[28]. In contrast to central fat, peripheral fat may confer a protective effect on cardiovascular disease[14]. Ultrasonographic measurement of abdominal fat was consisted of VFT and SFT in this study. Interestingly, only VFT, not SFT, was independently associated with carotid atherosclerosis. This result elucidate each fat component may have different role in atherosclerosis and visceral fat is more important to the development of cardiovascular disease. As ultrasonographic measurement can differentiate visceral fat and subcutaneous fat, the results of the present study suggest VFT could be a more powerful tool to detect central obesity and atherosclerosis in PD patients.

Visceral fat is now recognized as an immune organ that secretes numerous immune modulatory factors[15]. In addition, it is a significant source of inflammatory signals that cause disturbance of the insulin-signaling pathway at relevant sites, such as liver, muscle, and adipose tissue[28]. Accumulating

evidence has shown that pro-inflammatory cytokines released from monocytes and adipocytes are elevated and induce inflammatory responses in obese mice and human subjects[29]. Chronic low grade inflammation as a non-traditional risk factor in dialysis patients has been proposed to be related to the development and progression of atherosclerosis[30]. It is well known that chronic inflammation is strongly associated with cardiovascular diseases in dialysis patients[31,32]. CRP as an inflammatory marker has been shown to be an independent predictor of the number of atherosclerotic plaques in carotid arteries in dialysis patients[30]. Correspondingly, high VFT was closely associated with high hs-CRP, fibrinogen levels, and HOMA-IR in the present study. These findings suggest that visceral fat is related to inflammation, insulin resistance, and atherosclerosis in accordance with the results of previous studies[28,30-32].

This study has several limitations. One of the limitations is the absence of a definite ultrasonographic cutoff value to define carotid atherosclerosis and visceral obesity. Although many clinical factors such as diabetes and age can affect the values of cIMT, it has been regarded as a useful tool to detect atherosclerosis. Carotid atherosclerosis was defined as cIMT thickening (cIMT $\geq$ 1.0 mm) based on other studies[16-19]. Secondly, since this study was a cross-sectional observational study, the casual relationship between visceral obesity and cardiovascular prognosis is not able to clarify by the present study only. Lastly, as a relatively small number of patients were studied, these data should

be confirmed in a future large-scale prospective investigation.

Ⅴ. CONCLUSION

In conclusion, VFT on ultrasonographic measurement is independently associated with carotid atherosclerosis in PD patients. And it is also significantly correlated with inflammation. These findings suggest VFT would be a powerful marker of central obesity and a tool for prediction of atherosclerosis in patients with PD. Therefore, direct measurement of visceral fat thickness could be helpful to access the cardiovascular risk in PD patients.

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ABSTRACT (IN KOREAN)

초음파로 측정한 내장 지방과 경동맥 죽상 동맥 경화의 연관성

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배경:

투석을 받는 환자들은 일반 인구에 비하여 높은 심혈관계 질환 위험도를 갖고 있는 것으로 알려져 있다. 일반 인구에서는 높은 체질량 지수와 복부 지방을 반영한다고 알려진 허리 둘레, 허리-엉덩이 둘레 비율이 심혈관계 질환 사망률과 연관되어 있는 것으로 알려져 있다. 그러나 복막 투석 환자에서는 비만과 심혈관계 질환의 관계가 잘 정립되어 있지 않고 연구마다 다른 결과를 보이고 있다. 특히 복막 투석 환자에서 초음파로 측정한 내장 지방과 경동맥 죽상 동맥 경화와의 관계에 대해서는 보고된 바가 없어, 본 연구에서는 복막 투석 환자에서 초음파를 통해 측정한 내장

지방 두께가 경동맥 죽상 동맥 경화와 관련이 있는지를 확인하고, 다른 신체 계측 지표들과 비교했을 때에 경동맥 죽상 동맥 경화의 예측 지표로서의 우월성을 확인하고자 하였다.

방법:

2010년 2월부터 7월까지 88 명의 복막 투석 환자를 대상으로 단면적 연구를 시행하였다. 신체 계측을 실시하여 체질량 지수, 허리 둘레, 허리-엉덩이 둘레 비율을 측정하였으며, 초음파를 통하여 복부 지방과 경동맥 내막-중막 두께를 측정하였다. 복부 지방은 내장 지방 두께와 피하 지방 두께로 구분하였다.

결과:

대상자의 평균 나이는 53.3 ± 11.8 세였고, 남자가 54 명 (61.4%) 이었다. 평균 경동맥 내막-중막 두께는 0.76 ± 0.26 mm 였고, 경동맥 죽상 동맥 경화 소견은 (경동맥 내막-중막 두께 ≥1 mm) 18 명 (20.4 %) 에서 관찰되었다. 경동맥 죽상 동맥 경

화는 단변량 분석에서 내장 지방 두께 [OR (odds ratio) = 1.085, p = 0.001], 허리-엉덩이 둘레 비율 (OR = 1.105, p = 0.043), 체질량 지수 (OR = 1.24, p = 0.024), 허리 둘레 (OR = 1.085, p = 0.014)와 연관되어 있었다. 그러나 다변량 분석에서는 내장 지방 두께만이 경동맥 죽상 동맥 경화와 연관되어 있었다. (OR =1.089, 95% 신뢰 구간: 1.021-1.161, p = 0.009). 경동맥 죽상 동맥 경화를 예측하는 데에 있어, 신체계측 지표와 초음파로 측정한 지표들의 비교를 위해 시행한 다변량 분석에서도 내장 지방 두께만이 유의한 결과를 보였다 (OR = 1.095, 95% 신뢰구간: 1.004-1.194, p = 0.04).

결론 :

본 연구에서 복막 투석 환자에서 경동맥 죽상 동맥 경화를 가장 잘 예측할 수 있는 지표는 초음파로 측정한 내장 지방 두께였다. 이전의 다른 연구들에서 복부 지방과 연관이 있다고 알려진 허리 둘레와 허리-엉덩이둘레 비율은 본 연구에서는 다변량 분석 시 유의한 연관성을 보이지 않았다. 복막 투석 환자에서 비만과 관련된 신체 계측 지표들은 경동맥 죽상

동맥 경화를 예측할 수 없었으며, 초음파로 측정한 내장 지방 두께만이 경동맥 죽상 동맥 경화와 연관되어 있었다. 따라서 복막 투석 환자에서 초음파를 이용하여 내장 지방 두께를 직접적으로 측정하는 것이 경동맥 죽상 동맥 경화의 위험성을 판단하는 데에 도움이 될 것으로 사료된다.

핵심되는 말: 초음파 계측 내장 지방 두께, 경동맥 죽상 동맥 경화, 경동맥 두께, 복막 투석