Current Medical Science
DOI https://doi.org/10.1007/s11596-018-1937-7 38(4):727-733,2018

Ultrasound Assessment of Intima-media Thickness and Diameter of Carotid Arteries in Patients Undergoing Hemodialysis or Renal Transplantation*

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Summary: Renal transplant (RT) recipients have a high risk of developing cardiovascular diseases. However, the effects of renal transplantation on the development of arteriosclerosis have been controversial. The carotid intima-media thickness (CIMT) and diameter (CD) are important indicators of vascular remodeling and arteriosclerosis. In this study, 31 patients with hemodialysis (HD), 31 RT recipients and 84 age- and gender-matched control subjects were enrolled. Their CIMT and CD were measured by ultrasonic radiofrequency tracking, and the linear regression models and *Z* test were used to identify the progression of arteriosclerosis and the risk factors. Compared with HD group, RT group had significantly lower CIMT and CD. CIMT was found to be associated with age, body weight, resistance index and diastolic velocity, while CD was associated significantly with age, body weight, pulsatility index, end diastolic velocity and diastolic blood pressure (DBP), respectively. The correlation curves between CIMT and age showed the slopes of curves were decreased successively in control, RT and HD groups, and the curves between CD and age showed the slopes were decreased in order of RT > control > HD groups. It was concluded that CIMT and CD were significantly correlated with age in RT and moderately with age in HD patients. RT could reduce the progress of arteriosclerosis in patients with end-stage renal disease.
Key words: ultrasonic radiofrequency tracking; renal transplantation; arteriosclerosis; carotid intima-media thickness; age

The optimal treatment method for end-stage renal disease (ESRD) is renal transplantation (RT). Patients undergoing RT have a higher probability of survival and a better quality of life than those receiving blood dialysis[1]. Cardiovascular diseases are the major complications following RT. The cardiovascular risk factors, such as arteriosclerosis, hemodialysis, hypertension, diabetes, hypercholesterolemia and inflammation, play pivotal roles in the occurrence of cardiovascular diseases in renal allograft recipients[2]. Recent studies on RT found that the changes in hemodynamics after closure of the dialysis fistula along with age are main contributors to arteriosclerosis, which directly impacts the renal graft survival[3].

The carotid intima-media thickness (CIMT)

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*The research was supported by Shanghai Science and Technology Committee Fund (No. 15411969100, No. 16411969300), Interdisciplinary Program of Shanghai Jiao Tong University (No. YG2015MS28), Shanghai Health and Family Planning Commission Fund (No. 201440290, No. 201640043), Three-year Plan for Clinical Skills and Innovation in Municipal Hospitals (No. 16CR3105B), and Technology Transfer Project of Science & Technology Department, Shanghai Jiao Tong University School of Medicine (No. ZT201710, No. ZT201711).

and diameter (CD) are important indicators of arteriosclerosis and independent predictors of cardiovascular events[4]. A number of studies revealed that these surrogate endpoints are worsened in patients with ESRD[5]. Yet, there are few studies to assess whether RT could alleviate arteriosclerosis and lead to arterial remodeling[6]. Recently, a novel method for precisely measuring CIMT and CD using ultrasonic radiofrequency technique is developed with advantages of simplicity, noninvasion and excellent reproducibility[6]. This technique has been utilized to evaluate the arteriosclerosis of carotid arteries in RT patients by our research group[7].

The aim of this study was to measure the changes of the CIMT and CD using high resolution ultrasound in patients with ESRD who were on dialysis therapy or underwent RT and to explore their correlation with cardiovascular risk factors.

1 MATERIALS AND METHODS

1.1 Ethics

The study was approved by the Ethics Committee of Shanghai General Hospital, Shanghai Jiao Tong University, China. Written informed consent was obtained from all participants. The purpose of the research was explained to every prospective participant and they voluntarily participated in the study. This study was descriptive, and no attempts were made to modify any therapeutic strategy.

1.2 Subjects

The observational, cross-sectional, single-center study was carried out from May 2016 to March 2017. A total of 62 patients with ESRD participated in the study. They were divided into hemodialysis (HD) group (n=31, male:female = 20:11, age: 28 to 68 years with a mean age of 59.3 years) and RT group (n=31, male:female = 22:9, age: 30 to 72 years with a mean age of 57.9 years). For HD patients, the average dialysis duration was 24 months (range: 1–94 months) while for RT patients, the average post-RT time was 108 months (range: 12–264 months). The relevant clinical information of both HD and RT patients was extracted from the Renal Transplant Database of Shanghai General Hospital. The criteria of enrollment were based on considerations of matching of age, gender, duration of the disease and other risk factors between HD and RT patients. Patients with infection, active inflammation, autoimmune disease, malignancy, heart failure, atrial fibrillation, and acute coronary syndrome were excluded from the study. Eighty-four age- and gender-matched volunteer subjects without nephropathy were enrolled as a normal control group (male:female = 55:29, age: 31 to 72 years with a mean age of 58.1 years). Both patients and control subjects underwent CIMT and CD measurements with high resolution ultrasound.

1.3 General Procedures

A standardized questionnaire and the database were used for each subject to obtain subjects' information regarding cardiovascular risk factors, including hyperlipidemia, hypertension, diabetes and family history of cardiovascular diseases. Subjects' body weight, height, body mass index (BMI) and blood pressure were measured, while blood samples were tested for fasting blood glucose (FBG), triglyceride (TG), total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and hemoglobin A1c (HbA1c). Estimated glomerular filtration rate (eGFR) was calculated using the 4-variable Modification of Diet in Renal Disease Study group equation[8]. Parathormone (PTH) concentrations were measured with the ELISA method (Diagnostic System Laboratories, USA) (normal range: 15–65 pg/mL).

1.4 Ultrasound Imaging of Carotid Arteries

Ultrasound measurements of CMMT and CD were performed using high resolution ultrasound system (Mylab Twice, ESAOTE Medical Systems, Italy) with 4–13 MHz linear array transducers by two investigators (Li ZJ and Du LF, with 16 and 30 years of experience in diagnostic ultrasound, respectively) in a double blind fashion. The ultrasound system equipped with software could automatically and quantificationally estimate the CIMT and CD using radiofrequency technique (RFQIMT) (fig. 1).

The methods of ultrasound imaging used in this study were described previously[9, 10]. The common carotid arteries on both sides were measured in longitudinal planes and the reference points of measurement were 1.5 cm from the carotid bifurcation. The borderlines of lumen/intima and the media/adventitia were tracked in real-time during six cardiac cycles using imaging processing software (RFQIMT). Differences between these 2 borderlines of interfaces were calculated along a line orthogonal to the arterial wall. Single values were obtained from pixel-to-pixel measurements on neighboring lines perpendicular to the vertical line, then were averaged and expressed as the mean value for that segment. For each patient, the mean CIMT and CD were computed as the average CIMT and CD from both sides[11].

In addition, hemodynamic parameters, i.e., peak systolic velocity (Vmax), end diastolic velocity (EDV), mean flow velocity (MFV), velocity time integral (VTI), artery systolic/diastolic ratio (S/D=Vmax/EDV), resistance index [RI = (Vmax – EDV)/Vmax] and pulsatility index [PI = (Vmax – EDV)/MFV] of carotid arteries were acquired and recorded using conventional Doppler ultrasound technique. For statistical analysis, the measurement results from two observers with values of less than 5% difference were combined and calculated to obtain a mean value of CIMT and CD. In case of the difference greater than 5% between the two observers, discrepancies of the CIMT or CD values were determined by consensus of all investigators.

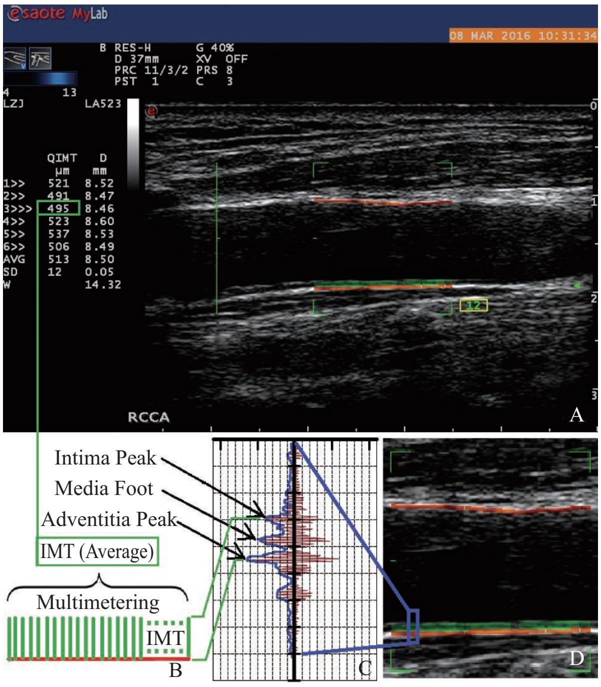

Fig. 1 Measurement of CIMT and CD using ultrasonic radiofrequency tracking technique
A: analysis of CIMT and CD using ultrasound system equipped with related software; B: assessment of multipoint intima-media thickness (IMT) on segmental carotid artery; C: ultrasonic radiofrequency (RF) signal diagram for single IMT point; D: magnification of the region of interest

1.5 Statistical Analysis

Interobserver agreement [intraclass correlation coefficient (ICC) for CIMT and CD] was calculated on the basis of preconsensus data. Results are presented as percentages for categorical data and analyzed by χ^2 test or Fisher's exact test as appropriate. Continuous normally distributed variables are expressed as means ± SD and compared with the one-factor analysis of variance analysis, and least significant difference method was adopted to compare differences between the groups. Non-normally distributed data, such as cumulative time on dialysis or time in hemodialysis, were expressed as median and interquartile range and analyzed by Mann-Whitney *U* test. The Kolmogorov-Smirnov test was used to check normal distribution. Bivariate correlations between study variables were calculated by Spearman's rank correlation coefficients. Subsequently, variables whose association with the carotid morphological parameters achieved statistical significance (i.e. $P<0.05$) and other factors that might affect arterial morphology (age, BMI, and metabolic and hemodynamics parameters) were entered into a stepwise multiple linear regression model to determine independent predictors of vascular parameters. The changes of CIMT and CD with age were analyzed by linear regression models, and the slopes of curves were compared using *Z* test. The analyses were performed with SPSS 13.0 (SPSS, USA) on a personal computer. The threshold of statistical significance was defined as $P<0.05$.

2 RESULTS

2.1 Clinical Characteristics

Clinical characteristics and laboratory results of all three groups are given in table 1. The patients and controls were matched very well in age and genders. The BMI in HD and RT groups was not statistically different from that in the control group ($P>0.05$). The three cohorts had comparable baseline clinical and biochemical characteristics as well as medical management (table 1).

2.2 Interobserver Agreement

As measured by the two observers, the median values of CIMT were 505 μm (IQR, 397–599 μm) and 526 μm (IQR, 421–594 μm), respectively, while the median values of CD were 7.8 mm (IQR, 6.8–8.5 mm) and 7.9 mm (IQR, 6.9–8.5 mm), respectively. The preconsensus measurements had a good ICC of 0.92 for CD [95% confidence interval (CI): 0.90, 0.93] and an excellent ICC of 0.95 for CIMT (95% CI: 0.94, 0.98).

2.3. Ultrasound Measurements of Carotid Arteries

CIMT was significantly increased in HD group when compared with control group (561.9±147.7 *vs*. 529.7±131.8 μm, $P<0.05$), and it was significantly decreased in RT group as compared with HD group but not with control group (480.5±90.3 μm, $P<0.05$ RT *vs*. HD group; $P>0.05$ RT *vs*. control group). The CD value was significantly higher in HD group than that in RT and control groups (8.6±0.8 mm for HD group, 7.9±0.8 mm for RT group and 7.50±1.0 mm for control group; $P<0.05$). However, there was no statistical difference in the CD value between the RT group and control group ($P>0.05$). Additionally, the hemodynamic parameters including peak systolic velocity, PI and S/D ratio were dramatically decreased in the RT group as compared with control group, while the VTI, EDV, MFV and RI were not significantly different between the HD and RT groups. The detailed analysis of carotid structure and hemodynamics is shown in table 2.

2.4 Correlation of CIMT and CD with Risk Factors

The multiple linear regression analysis (table 3) showed that both CIMT and CD were positively correlated with independent factors age, RI and EDV. After adjustment for covariates, it was found that the cumulative time on dialysis was positively correlated with CIMT and CD in both HD and RT groups. The multiple stepwise regression analysis demonstrated

Table 1 Baseline characteristics of the three groups

Variables	Control (*n*=84)	HD (*n*=31)	RT (*n*=31)	*P* values
Age (years)	58.1±19.9	59.3±17.9	57.9±14.3	0.141
Male, *n* (%)	55 (65)	20 (65)	22 (71)	0.317
Body mass index (kg/m^2)	26.2±4.5	26.0±5.5	24.2±3.5	0.083
Time in predialytic CKD (months)	–	70 (1–148)	73 (1–216)	0.351
Cumulative time on dialysis (months)	–	24 (1–94)	26 (1–104)	0.561
Hypertension, *n* (%)	11 (12)	28 (90)†	25 (80)†	0.039
Diabetes mellitus, *n* (%)	11 (13)	9 (28)†	8 (27)†	0.025
Dyslipidemia, *n* (%)	4 (5)	2 (6)	2 (6)	0.676
Smokers, *n*	4	3	1	0.07
Systolic blood pressure (mmHg)	119.3±15.8	146.9±21.3†	145.8±13.5†	<0.001
Diastolic blood pressure (mmHg)	77.1±8.3	86.9±13.5†	94.3±8.6†‡	<0.001
Glycosylated hemoglobin A1c (%)	4.6 ±0.7	4.7 ±0.7	4.9±0.6	0.156
Total cholesterol (mmol/L)	6.0±1.2	4.9±1.2	4.5±0.8	0.322
Triglycerides (mmol/L)	1.4±0.7	1.9±0.9	1.4±0.3	0.345
Low-density lipoprotein (mmol/L)	3.1±0.9	2.7±0.9	2.3±0.6	0.224
High-density lipoprotein (mmol/L)	1.2±0.3	1.3±0.3	1.4±0.3	0.432
Fasting blood glucose (mmol/L)	5.3±1.1	4.6±0.6	4.9±0.7	0.245
eGFR (mL/min/1.73 m^2)	69.3±20.5	8.3±24.0†	8.4±22.8†	<0.001
Ca (mmol/L)	2.39±0.10	2.40±0.14	2.33±0.19	0.422
P (mmol/L)	1.33±0.12	1.79±0.24†	1.39±0.56$^#$	0.003
PTH (pg/mL)	35±26	127±20†	39±22‡	0.050
ACEI use, *n* (%)	5 (6)	17 (56)†	20 (64)†	0.038
Calcium channel antagonist, *n* (%)	4 (5)	16 (50)†	10 (32)†	0.032
Diuretics, *n* (%)	4 (5)	12 (40)†	6 (18)$^{†#}$	0.042
Beta-blockers, *n* (%)	4 (5)	12 (40)†	8 (25)$^{†#}$	0.036
Statin use, *n* (%)	15 (18)	11 (35)†	10 (33)†	0.046

$^*P$<0.05, $^†P$<0.01 *vs*. control group; $^\#P$<0.05, $^‡P$<0.01 *vs*. HD group. Data were presented as mean (SD) or *n* (%).

Table 2 Comparison of carotid ultrasound measures among the three groups

Variables	Control (*n*=84)	HD (*n*=31)	RT (*n*=31)	*P* values
Carotid intima-media thickness (μm)	529.7±131.8	561.9±147.7*	480.5±90.3$^#$	0.045
Carotid diameter (mm)	7.50±1.0	8.6±0.8†	7.9±0.8‡	<0.001
Velocity time integral (m)	0.2±0.1	0.2±0.1	0.2±0.1	0.250
Peak systolic velocity (cm/s)	64.4±19.9	56.6±20.3	49.9±14.5†	0.002
End diastolic velocity (cm/s)	16.27±6.5	17.5±10.5	15.9±7.3	0.702
Mean flow velocity (cm/s)	26.9±7.4	27.5±10.1	24.8±7.7	0.388
Pulsatility index	1.8±0.6	1.6±0.7*	1.4±0.4†	0.003
Resistance index	0.7±0.2	0.7±0.2	0.7±0.2	0.197
S/D ratio	4.3±1.2	4.1±2.1	3.4±0.9†	0.017

$^*P$<0.05, $^†P$<0.01 *vs*. control group; $^\#P$<0.05, $^‡P$<0.01 *vs*. HD group

that in all risk factors, age had the most significant effect on CIMT and CD (β=0.641 and β=0.513) in the three groups. The slopes of CIMT-age curves were successively reduced in control group, RT and HD groups (β=6.357, 4.63 and 2.914, respectively). The slopes of CIMT-age curves in RT and HD groups compared with control group were significantly reduced (Z=1.417, *P*=0.006 and Z=2.223, *P*<0.001, respectively). The CIMT-age slope rate was not statistically significantly different between the RT and HD groups (*Z*=1.038, *P*=0.723) (fig. 2). There was significant difference in the CD-age slope rate between HD and control groups (*Z*=1.677, *P*=0.002). However, the CD-age slope rate had no statistically significant difference between HD and RT groups (Z=1.693, *P*=0.911 and Z=0.372, *P*=0.416, respectively) (fig. 3).

Table 3 Multiple linear regression analysis of the association of CIMT and CD with cardiovascular risk factors

Variables	CIMT				CD			
	All subjects	Control	HD	RT	All subjects	Control	HD	RT
	β^a (β^b)	β^a (β^b)	β^a (β^b)	β^a (β^b)	β^a (β^b)	β^a (β^b)	β^a (β^b)	β^a (β^b)
Age	5.3 (0.64)‡	6.91 (0.84)‡	–1.40 (–0.19)†	2.38 (0.30)†	0.03 (0.51)‡	0.04(0.52)‡	–0.03 (–0.25)†	0.01 (0.09)†
Cumulative time on dialysis	/	/	0.39 (0.24)‡	1.81 (0.23)†	/	/	0.03 (0.17)†	0.03 (0.41)†
Pulsatility index	–56.36 (–0.21)	–101.42 (–0.37)	–197.74 (–1.14)	162.70 (0.78)	0.7 (0.41)†	0.27 (0.12)	0.12 (0.04)	0.46 (0.21)
Resistance index	650.35 (0.69)‡	662.43 (0.62)	246.21 (0.49)	–469.76 (–0.78)	–2.375 (–0.38)†	–2.37 (–0.27)	–1.27 (–0.15)	3.19 (0.51)
End diastolic velocity	11.25 (0.51)‡	10.84 (0.53)†	–2.96 (1.14)	–15.61 (–0.74)	–0.01(–0.06)	–0.02 (–0.09)	0.01 (0.05)	0.11 (0.48)
Mean flow velocity	–5.61 (–0.29)	–20.47 (–0.96)†	–9.67 (–0.70)	14.60 (0.74)	0.05 (0.37)†	–0.01 (–0.04)	0.02 (0.09)	–0.16 (–0.77)
Systolic blood pressure	–9.51 (–0.08)	–32.38 (–0.29)†	51.59 (0.90)	–37.73 (–0.46)†	0.01(0.01)†	0.11 (0.12)†	0.17(0.17)	0.06 (0.07)†

a: unstandardized coefficients; b: standardized coefficients. †P<0.05, ‡P<0.01

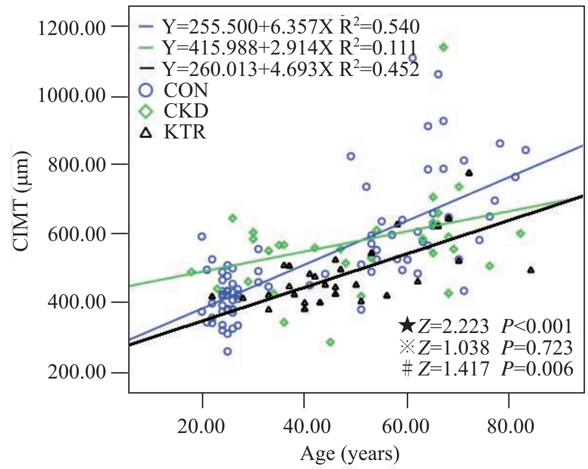

Fig. 2 Association of age with CIMT in the three groups
★control group *vs*. HD group; ※HD group *vs*. RT group; #control group *vs*. RT group

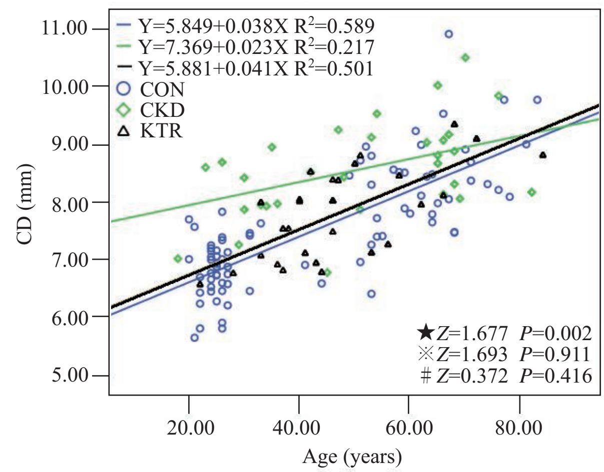

Fig. 3 Association of age with CD in the three groups
★control group *vs*. HD group; ※HD group *vs*. RT group; #control group *vs*. RT group

3 DISCUSSION

This observational study was designed to assess the morphological changes of carotid arteries in patients undergoing HD or RT. Theoretically, the hemodynamic changes after HD and RT would result in the alterations of vascular morphology and physiology. In this study, the vascular remodeling and mural changes of the carotid, which are reflected by CIMT and CD, were determined by high resolution ultrasound imaging with radiofrequency tracking technique. The results showed that CIMT and CD were significantly decreased in RT group as compared with HD group, indicating a partial recovery in the morphology of the carotid artery. The age, gender, serum biochemical parameters, diabetes mellitus, hypertension and history of medication, which contributed to arterial remodeling and stiffness, showed no significant difference among RT, HD and control groups. The duration of pre-hemodialytic chronic kidney disease and cumulative time on dialysis were also comparable between the RT and HD groups. This study attempted to evaluate the morphologic changes of the carotid artery using advanced ultrasound technique in patients receiving HD or RT.

3.1 Arterial Aging

Aging is significantly associated with the mechanical and geometric changes of the arterial trees[12]. Some studies had indicated that the age-related changes of the arterial remodeling mainly occurred in elastic arterial vessels (e.g. aorta and carotid artery), which were significantly accelerated by hemodialysis therapy[13]. In this study, the correlation between CIMT and age showed that the slopes of curves were decreased successively for control, RT, and HD groups. The similar trends between CIMT and age were also shown in the previous study[14]. The multivariate regression analysis demonstrated that the independent risk factors for CIMT and CD were age, blood pressure and hemodynamic parameters (such as PI, RI and EDV) in all the subjects. Previous studies had different findings in term of changes of CIMT in RT. At 1st year post-transplantation, the CIMT was increased. The post-transplant diabetes, triglycerides and higher vascular VCAM-1 protein level were related to it[15].

We surmise that the discrepancy is due to the fact that these studies did not consider the influence of aging on the carotid artery which undergoes remarkable morphological and physiological changes, such as increasing stiffness, length, diameters, and wall thickness along with aging[16]. Our study attempted to include the age as an important factor for evaluation of CIMT and CD in patients with HD or RT.

3.2 CIMT

The precise measurement contributes to accurate assessment of the changes of CIMT and CD. In this study, advanced ultrasonic radiofrequency tracking technique was utilized to automatically measure the CIMT with 30–50 sampling points adopted in a 1–1.5 cm segment of the artery (fig. 1A and 1B). The values of CIMT were measured and calculated in a single cardiac cycle (fig. 1C and 1D) with a mean value obtained in 6 continuous cardiac cycles (fig. 1A). The measurement of the CIMT was obtained from high resolution ultrasound imaging using micrometer-scale value and the repeatability was excellent. In this study, the results showed that CIMT and CD were decreased in RT patients as compared with HD patients, although both groups had similar cumulative times of dialysis. Although affirmative conclusions cannot be drawn from this across-sectional comparison study, our results suggested that the vascular risk factors could be reduced and reversed by successful RT with improved metabolism and hemodynamic condition[17].

Our findings of CIMT in RT patients are consistent with those in previously published studies. De Lima *et al* noted a significant decrease of CIMT during 3 years of follow-up in 22 adult allograft recipients[18]. Suwelack *et al* found that a decrease of CIMT in post-RT patients was correlated with decreased blood pressure (BP)[19]. Notably, in our study, the CIMT in RT patients decreased significantly, and was close to the value of control subjects. The regression coefficient of CIMT with age was greater in RT patients than that in HD patients while no significant difference was found between RT and control subjects. These results suggested that the age effects on CIMT were even greater for RT patients than for HD patients. CIMT is affected by many factors such as age, BP, blood glucose, dyslipidemia[20], smoking, hemodynamics, inflammatory factors, and these factors have different impacts on CIMT[21]. After eliminating related risk factors, age seemed to be a major contributor to CIMT. Indeed, a 6-month follow-up study demonstrated that the CIMT increased with time in 26 cases of RT[22]. A study by Mark *et al* found that the CIMT was increased and associated with increased BP in 32 children post-RT (follow-up<1 year)[23]. The reasons of these discrepancies with our study may relate to different study population (adults *vs*. children) and follow-up periods.

3.3 CD

Arteriosclerosis is the most common cause of cardiovascular morbidity in hemodialysis patients[24]. Studies have shown that patients with HD have progressive changes in the walls of the arteries, which are evidenced by increased IMT and lumen diameter in the carotid and femoral arteries[25, 26]. In HD patients, A-V fistula results in high-volume hemodynamics and it accelerates vascular remodeling, especially for the right common carotid artery (CCA), which was demonstrated in our previous study[10]. In this study, the luminal diameter of carotid arteries in HD patients was greater than that in RT patients, which is due to HD-induced high-volume hemodynamic change and irreversible vascular dilation. Certainly, the vascular dilation has a potential risk of insufficient blood perfusion that would lead to organ damage. Thus, avoiding long-term HD could reduce vascular injuries and cardio-cerebral vascular events.

There were some limitations in this study. The sample was too small for cross-sectional analysis to determine the morphologic changes and characteristics of carotid arteries after RT. Longitudinal studies with large sample size are needed to evaluate the morphologic changes of carotid arteries and their association with cardiovascular factors (e.g., anemia, transplant time, etc.).

In conclusion, our study demonstrated that the changes of CIMT and CD were significantly correlated with age in RT patients and were moderately correlated with age in HD patients. RT could reduce the progress of arteriosclerosis in patients with ESRD.

Conflict of Interest Statement

The authors declare that there is no conflict of interest with any financial organization or corporation or individual that can inappropriately influence this work.

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(Received Aug. 12, 2017; revised April 10, 2018)