Prevalence of Arterial Stiffness and Associated Factors in Thai Patients with Chronic Kidney Disease and Kidney Transplant Recipients

Prasert Thanakitcharu MD*,
Yanasar Jitsuparat MD*, Boonthum Jirajan MD*

** Division of Nephrology, Department of Medicine, Rajavithi Hospital, College of Medicine, Rangsit University, Bangkok, Thailand*

Background: *Patients with chronic kidney disease (CKD), end-stage renal disease (ESRD) with dialysis, and kidney transplant (KT) recipients are associated with increased cardiovascular (CV) morbidity and mortality. Arterial stiffness is a major non-traditional risk factor of CV disease, and increased aortic pulse wave velocity (PWV), the gold standard for arterial stiffness assessment, may predict CV morbidity and mortality in these patients.*

Objective: *The purpose of the present study was to evaluate the prevalence of arterial stiffness in pre-dialysis CKD, ESRD with dialysis patients and KT recipients, and associated factors that exacerbate the condition in order to serve as evidence to search for appropriate therapeutic options.*

Material and Method: *This was a cross-sectional study of 169 patients including cases of pre-dialysis CKD stages 3-5, ESRD with hemodialysis (HD), continuous ambulatory peritoneal dialysis (CAPD), kidney transplant (KT) recipients and healthy volunteers. Central blood pressure (BP) and aortic PWV were assessed using the SphygmoCor® CPV Pulse Wave Velocity system (AtCor Medical, Sydney, Australia). Increased arterial stiffness was defined as aortic PWV of $\geq$12 m/s.*

Results: *The prevalence rates of arterial stiffness in pre-dialysis CKD, HD, CAPD patients, KT recipients and normal controls were 53.1%, 68.8%, 64.7%, 38.9% and 5.7% respectively, and the mean aortic PWVs were 12.7$\pm$2.2, 13.5$\pm$2.8, 13.4$\pm$2.8, 11.3$\pm$1.8 and 9.5$\pm$1.7 m/s respectively ($p<0.001$). The factors associated with arterial stiffness determined by univariate analysis were older age, diabetes, CKD, HD, CAPD, KT recipients, higher brachial and central BP, higher serum phosphate, and calcium-phosphate products. A multivariate model showed that only HD, KT recipients, older age and higher central mean arterial pressure (MAP) were independently associated with increased arterial stiffness, with adjusted odds ratio (95% confidence interval) of 17.71 (2.39-131.04), 9.29 (1.46-59.09), 1.09 (1.05-1.14), and 1.11 (1.06-1.16) respectively.*

Conclusion: *Arterial stiffness was markedly raised in all groups of CKD patients with an overall prevalence of 56%. The highest prevalence of arterial stiffness was found in ESRD patients treated with HD and CAPD. It was shown that the associated factors that independently increased arterial stiffness were HD patients, KT recipients, older age and higher central MAP.*

Keywords: *Arterial stiffness, Cardiovascular disease, Pulse wave velocity, Chronic kidney disease, End stage renal disease, Dialysis, Kidney transplantation*

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Chronic kidney disease (CKD) is currently a major worldwide healthcare problem with a rising incidence and prevalence. It eventually leads to end-stage renal disease (ESRD) and requires some form of renal replacement therapies. It has been widely acknowledged that cardiovascular (CV) morbidity and mortality is greatly increased in patients with CKD, especially those with ESRD. There has been a 20- to 30-fold increase in cardiovascular disease (CVD) in patients with ESRD, and even milder stages of CKD are associated with excess CV risk[1]. Some traditional factors associated with CVD such as diabetes mellitus, hypertension, and dyslipidemia are major determinants for the development of CKD, and they also contribute to the progression of kidney disease long before ESRD is reached[2]. In addition, the impact of non-traditional risk factors of CVD morbidity in CKD patients is also important. Among these, the closely-related factors

Correspondence to:
Thanakitcharu P, Division of Nephrology, Department of Medicine, Rajavithi Hospital, 2 Phyathai Road, Rajathewi, Bangkok 10400, Thailand.
Phone: +66-2-3548180 ext. 5101, Fax: +66-2-3548188
E-mail: prasertthan@hotmail.com

appear to be endothelial dysfunction, vascular calcification and arterial stiffness.

Arterial stiffness of large arteries results in several important clinical consequences which include raised systolic blood pressure (BP), increased pulse pressure, left ventricular hypertrophy and reduced coronary perfusion[3]. It seems that arterial stiffness may have an impact on outcomes of various stages of CKD patients either before or after they receive renal replacement therapies. Even slight renal dysfunction may be associated with increased arterial stiffness; moreover, arterial stiffness will progressively increase as renal function deteriorates[4]. ESRD patients treated by dialysis have much stiffer arteries, and this has been identified as a major determinant of poor CV survival in ESRD[5]. Conversely, it has been reported that kidney transplantation leads to a decrease in arterial stiffness when compared with that of dialysis patients[6,7].

Early research explored multiple methods for assessing arterial stiffness and led to a consensus that aortic (carotid-femoral) pulse wave velocity (PWV) is the 'gold standard' for the evaluation of arterial stiffness[8]. Several studies have confirmed that increased PWV is an independent risk factor for CV events and for mortality in populations with and without CKD[9]. A recent meta-analysis of 17 studies that involved over 15,000 patients showed that arterial stiffness measured as PWV is a strong predictor of future CV events and all causes of mortality[10].

The frequency of arterial stiffness in Thai CKD patients remains unclear, and assessment of arterial stiffness in these patients using measurement of aortic PWV has not yet been widely studied in a Thai population. Therefore, the purpose of the present study was to evaluate the prevalence of arterial stiffness, by means of aortic PWV, in Thai patients with pre-dialysis CKD stage 3-5, ESRD patients treated either with hemodialysis (HD) or continuous ambulatory peritoneal dialysis (CAPD), and kidney transplant (KT) recipients; an additional aim was to identify the risk factors associated with increased arterial stiffness in this population. Hopefully, the findings of the present study will provide an estimate of the disease burden and further, serve as evidence which can be utilized in searching for appropriate therapeutic options to lessen the degree of arterial stiffness in these patients.

Material and Method

Patients

A cross-sectional, comparative study was conducted over a period of 9 months, from April 2015 to December 2015, at the Department of Medicine of Rajavithi Hospital in Bangkok, Thailand. We enrolled patients with pre-dialysis CKD stage 3-5, ESRD patients receiving HD or CAPD, KT recipients, and normal healthy volunteers who had no history of any kidney disease, diabetes mellitus or hypertension. Subjects were consecutively enrolled using the following inclusion criteria: (1) age ≥18 years; (2) pre-dialysis CKD patients who were categorized in stage 3-5 according to the NKF-K/DOQI classification; (3) stable renal function (less than 10% change of estimated glomerular filtration rate, eGFR) for at least 3 months in pre-dialysis CKD patients; (4) stable ESRD patients who had been receiving chronic HD or CAPD for at least 3 months; (5) KT recipients who had been stable for at least 3 months; and (6) normal healthy volunteers who had no history of any kidney disease and had the following characteristics: BP <140/90 mmHg, fasting plasma glucose <126 mg/dl, eGFR >90 ml/min/1.73 m^2 and without proteinuria. Patients were excluded when any of the following criteria was met: (1) pregnancy; (2) any intercurrent illness that could potentially have an effect on BP; (3) severe obesity; (4) conditions that lead to reduction or variation of cardiac output which result in inaccurate assessment of aortic PWV including aortic stenosis, severe impaired left ventricular function and atrial fibrillation; (5) patients with high-grade stenosis of carotid artery and carotid sinus syndrome.

Written informed consent was obtained from all patients, including normal volunteers. They were scheduled for their testing appointment after receiving verbal and written descriptions of the study protocol which was reviewed and approved by the Ethical Committee of Rajavithi Hospital (No. 018/2558).

Methods

The clinical data were obtained from the patients' history and medical records. Their demographic characteristics, which included age, gender, co-morbid diseases, smoking habits, dialysis vintage, and post-KT duration. Each subject enrolled in the present study was weighed with a digital scale, and standing height was measured using a linear height scale. For chronic HD patients, dry body weight was used. Body mass index (BMI) was calculated using the conventional Quetelet formula (kg/m^2).

Biochemical parameters

Blood samples were drawn in the fasting condition from all patients and normal controls for

assessment of fasting plasma glucose, hemoglobin (Hb) A1c, blood urea nitrogen (BUN), serum creatinine, calcium and phosphate, intact parathyroid hormone (iPTH), lipid profile, and high-sensitivity C-reactive protein (hs-CRP). For chronic HD patients, all blood samples were collected before the dialysis sessions. Estimation of the GFR was calculated using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation which is currently accepted as the most accurate method of measurement[11].

Measurement of central blood pressure, aortic PWV and augmentation index[4,12]

For determination of central BP, aortic PWV, and augmentation index (AIx), the SphygmoCor® CPV system (AtCor Medical Inc., Sydney, Australia), which is regarded as the gold standard for non-invasive assessment of central vascular pressures and aortic PWV, was used. To maximize the accuracy and reproducibility of aortic PWV, the measurements were performed according to the proposed recommendations[13,14]. Brachial artery systolic and diastolic BP were measured preferentially at the right arm or the non-AV fistula arm of HD patients using a validated automatic sphygmomanometer. Pulse pressure (PP) was the difference between systolic (SBP) and diastolic blood pressure (DBP). Mean arterial pressure (MAP) was calculated by the formula: DBP + PP/3. There were two phases in operating the SphygmoCor® system: in the first phase, pulse wave analysis, measurements were obtained of the brachial and central BP readings together with the AIx from the apparatus; in the second phase, measuring the PWV which is the time interval between pulse pressure waves at the carotid and femoral arteries, an appropriate blood pressure cuff was placed around the right upper thigh after which the distance traveled by the flow wave between the carotid and femoral arteries at the level of the inguinal ligament and the inguinal ligament to the upper border of the blood pressure cuff were measured and recorded, and then a pencil-type hand-held tonometer probe was used to obtain pressure waveforms. Aortic PWV was obtained by calculating the distance divided by the time delay computed by the SphygmoCor® software.

Definition of arterial stiffness and augmentation index

Aortic (carotid-femoral) PWV is considered the 'gold standard' modality for evaluation of arterial stiffness[8]. Increased arterial stiffness is defined by the aortic PWV of $\geq$12 m/s which was proposed in the 2007 ESH/ESC hypertension guidelines[15]. This cut-off point is consistent with findings by Blacher et al[16] which showed a PWV of $\geq$12 m/s to have a significantly negative prognostic impact on the survival of ESRD patients.

Augmentation index (AIx) is accepted as a measure of the enhancement of central aortic pressure by a reflected pulse wave. It is a measure of wave reflection and arterial stiffness, and it is a ratio calculated from the BP wave form. It is defined as the ratio of augmentation pressure (AP) to pulse pressure (PP): AIx = AP/PP, where AP is the difference between the forward wave and reflected wave, and PP is the difference between the central SBP and DBP. Higher values occur with stiffer vessels due to the greater reflection of the pulse wave distally[17].

Statistical analysis

Using a 2-sided type 1 error ($\alpha = 0.05$), 80% power, sample size estimation based on testing two independent proportions[18] was performed to determine the sample size in the present study. The prevalence of arterial stiffness as reported by Blacher et al[19] and Wang et al[4] were used as the reference values for CKD patients (P1 = 0.64) and normal controls (P2 = 0.27) respectively. Sample sizes of 32 subjects for each CKD group and normal controls were considered adequate to test between two independent proportions. Continuous and categorical variables were expressed as mean values $\pm$ standard deviation and number (percent) respectively. One-way ANOVA was employed to compare quantitative variables among the 5 groups of subjects. For multiple comparisons, Scheffe's method was used because of the unequal sample sizes in each group. Comparisons of continuous variables between patients with and without arterial stiffness were done by unpaired t-test or Mann-Whitney U test as appropriate. Chi-square test or Fisher's exact test was used to test the difference in qualitative variables. Binary logistic regression was performed to identify the independent risk factors associated with arterial stiffness, and a *p*-value of less than 0.05 was considered statistically significant. All statistical analyses were obtained using SPSS for Windows version 17.0.

Results

Patient characteristics

During this 9-month cross-sectional study, a total of 169 CKD patients and normal controls were consecutively enrolled. These included 32 pre-dialysis

CKD stage 3-5 patients, 32 HD patients, 34 CAPD patients, 36 KT recipients, and 35 normal controls. Their demographic characteristics and baseline laboratory data are shown in Table 1. The mean age of the pre-dialysis CKD patients (65.2±12.2 years) was significantly higher than those of the other groups, while patients receiving HD (57.8±16.5 years) or CAPD (56.3±13.3 years) were of similar age, and the youngest mean age was found in the group of normal controls (40.6±9.8 years) and KT recipients (45.6±12.2 years) and these were not significantly different from each other. Of the 134 CKD patients, 43 (32.1%) had diabetes mellitus. The numbers of patients with diabetes in the pre-dialysis CKD (40.6%), HD (34.4%), and CAPD (50.0%) groups were significantly higher than in KT recipients (5.6%). The HbA1c level in CAPD patients seemed to be higher than in other groups, but without statistical significance. The serum phosphate levels in HD (5.4±1.6 mg/dl) and CAPD (4.9±1.7 mg/dl) patients were similar, but significantly higher than those of other groups. Ca x P products were highest in the HD (48.5±14.8 mg^2/dl^2) and CAPD patients (42.6±15.5 mg^2/dl^2) and were significantly higher than in other groups. The iPTH levels were also highest in HD (661±1,021 pg/ml) and CAPD subjects (317±360.1 pg/ml). There were no significant differences in hs-CRP levels among all groups. The dialysis vintage in HD patients was significantly higher than in CAPD ones (74.2±61.2 vs. 25±21.7 months, $p<0.001$) but similar to post-transplant duration in KT recipients (87.9±56.5 months).

Cardiovascular risk factors and PWV

Table 2 depicts vascular parameters and demonstrates that the central SBP and PP were significantly lower than the brachial pressures in all groups. In contrast, the central DBP was significantly higher than the brachial pressure in pre-dialysis CKD, HD patients and KT recipients, and showed a tendency to be higher in CAPD. The central MAPs were slightly lower than brachial MAPs in all groups, but mostly without significant difference. The aortic PWV values were highest in HD (13.5±2.8 m/s), CAPD (13.4±2.8 m/s) and pre-dialysis CKD patients (12.7±2.2 m/s) but without significant difference among these 3 groups. The aortic PWV in KT recipients (11.3±1.8 m/s) was significantly lower than in the HD and CAPD groups, but not different from pre-dialysis CKD and still higher than normal controls (9.5±1.7 m/s). There were no significant differences in AIx among all groups. Using Spearman correlation, there was a significant inverse correlation between eGFR in pre-dialysis CKD patients and their aortic PWV ($r = -0.554$, $p<0.001$), and there was also a significant correlation between dialysis vintage/post-transplant duration and aortic PWV ($r = 0.340$, $p<0.001$), but there were no differences between these two parameters in separate groups: for HD ($r = 0.186$, $p = 0.309$), CAPD ($r = -0.103$, $p = 0.560$), and KT recipients ($r = -0.082$, $p = 0.636$).

The overall prevalence of arterial stiffness in all groups of CKD patients was 56.0% (75 of 134 patients). The highest prevalence was revealed in HD patients (68.8%), followed by the CAPD (64.7%) and pre-dialysis CKD groups (53.3%). The prevalence of arterial stiffness in KT recipients (38.9%) was significantly lower than in the other groups of CKD patients (Fig. 1).

Associated factors of arterial stiffness

Univariate analysis (Table 3) showed that the factors associated with arterial stiffness included older age, diabetes, higher SBP and MAP, wider PP, patients with pre-dialysis CKD, HD, and CAPD, but not KT recipients. The laboratory variables that were associated with arterial stiffness were higher BUN and creatinine, higher phosphate and Ca x P product, but not iPTH levels or lipid profiles.

Subanalysis regarding the diabetic condition revealed that there were statistically significant differences in aortic PWV, AIx and increased arterial stiffness between patients with diabetes and those without it (Table 4).

Multivariate analysis (Table 5) demonstrated that the only independent factor significantly associated with arterial stiffness were HD (OR = 17.7; 95% CI: 2.39-4-131.04, $p = 0.005$), KT recipients (OR = 9.3; 95% CI: 1.46-59.09, $p = 0.018$), age (OR = 1.1; 95% CI: 1.05-1.14, $p<0.001$) and central MAP (OR = 1.1; 95% CI: 1.06-1.16, $p<0.001$).

Discussion

Prevalence of arterial stiffness

In recent years, many studies have focused on the role of arterial rigidity in the development of CV diseases, and it has been shown that stiffening of arteries is associated with increased CV mortality and morbidity in CKD and ESRD patients[20]. Only aortic (carotid-to-femoral) PWV, which is a marker of arterial stiffness, has been shown to have predictive value for morbidity and mortality[21]. The optimal threshold PWV has been reported to be 9-10 m/s[21-23]. Using the definition of increased arterial stiffness as aortic PWV of, ≥12 m/s[15], Blacher et al[16] showed the

Table 1. Baseline demographic characteristics in normal controls and various groups of CKD patients (n = 169)

	Controls (n = 35)	Pre-dialysis CKD (n = 32)	HD (n = 32)	CAPD (n = 34)	KT recipients (n = 36)	*p*-value
Age (year)	40.6±9.8[a]	65.2±12.2[b]	57.8±16.5[c]	56.3±13.3[c]	45.6±12.2[a]	<0.001
Gender (female)	33 (94.3)[a]	19 (59.4)[b]	16 (50)[b]	18 (52.9)[b]	14 (38.9)[b]	<0.001
BMI (kg/m^2)	25.2±4.8[a]	23.7±4.2[a]	21.3±3.3[b]	24.8±4.3[a]	23.3±3.7[a]	<0.001
DM	0 (0.0)[a]	13 (40.6)[b]	11 (34.4%)[b]	17 (50.0)[b]	2 (5.6)[a]	<0.001
Hemoglobin (g/dl)	12.8±1.1[a]	11.7±1.9[ac]	10.1±1.6[b]	11.0±1.7[bc]	12.2±1.8[ac]	<0.001
FBS (mg/dl)	91.8±8.1[a]	132.3±61.1[ab]	141.4±101.0[b]	111.7±41.8[ab]	98.9±23.5[a]	0.001
HbA1c (%)	5.5±0.5	6.3±1.6	6.1±1.8	8.9±19.3	5.7±0.7	0.472
BUN (mg/dl)	11.8±3.8[a]	28.3±14.3[b]	58.1±21.4[c]	49.0±16.5[d]	22.6±10.5[b]	<0.001
Creatinine (mg/dl)	0.7±0.2[a]	2.0±1.1[a]	9.4±2.9[b]	9.4±3.8[b]	1.6±0.8[a]	<0.001
eGFR (ml/min/1.73 m^2)	99.3±17.5[a]	34.5±13.9[b]	5.4±2.2[c]	5.6±2.3[c]	54.8±20.2[d]	<0.001
Calcium (mg/dl)	9.4±0.3[ab]	9.3±0.6[ab]	9.0±0.7[ac]	9.1±0.9[ab]	9.5±0.7[b]	0.015
Phosphate (mg/dl)	3.5±0.4[a]	3.7±0.7[a]	5.4±1.6[b]	4.9±1.7[b]	3.4±0.7[a]	<0.001
Ca x PO_4 product	33.1±4.7[a]	34.8±7.3[a]	48.5±14.8[c]	42.6±15.5[c]	32.4±5.9[a]	<0.001
iPTH (pg/ml)	43.5±12.8[a]	88.7±84.7[a]	661.4±1021.0[b]	317.0±360.1[c]	112.9±91.8[a]	<0.001
Total cholesterol (mg/dl)	199.5±37.3[a]	175.3±41.5[ab]	167.2±47.7[ab]	189.2±59.6[ab]	160.9±26.1[b]	0.002
Triglycerides (mg/dl)	109.5±49.1	130.0±82.3	136.0±79.3	171.1±141.6	128.5±69.7	0.076
HDL (mg/dl)	56.1±13.5	58.7±19.8	41.9±16.9	59.0±56.5	53.3±17.5	0.125
LDL (mg/dl)	134.9±30.6	104.8±38.3	107.6±39.7	125.2±38.7	100.1±23.6	<0.001
hs-CRP (mg/dl)	0.3±0.4	0.9±1.8	1.1±2.8	0.4±0.8	0.3±0.7	0.109
Dialysis vintage or post-transplant duration (months)	-	-	74.2±61.2[a]	25.0±21.7[b]	87.9±56.5[a]	<0.001

Values were depicted as mean ± SD and number (percent), *p*-value from One Way ANOVA.
[a,b,c] different characters mean significant differences between groups in multiple comparisons using Scheffe's method (significant difference defied by *p*-value of <0.05).
CKD = chronic kidney disease; HD = hemodialysis; CAPD = continuous ambulatory peritoneal dialysis; KT = kidney transplant

Table 2. Comparison of brachial and central blood pressure, and vascular parameters in various groups of CKD patients (n = 169)

Blood pressure (mmHg)	Controls (n = 35)	Pre-dialysis CKD (n = 32)	HD (n = 32)	CAPD (n = 34)	KT recipients (n = 36)	*p*-value*
Systolic						
Brachial	124.1±11.2[a]	142.1±22.5[b]	145.2±25.0[bc]	159.9±30.4[c]	138.9±15.7[ab]	<0.001
Central	111.9±12.3[a]	129.2±19.7[bc]	129.8±22.5[bc]	142.2±26.3[b]	125.9±14.9[ac]	<0.001
p-value**	<0.001	<0.001	<0.001	<0.001	<0.001	
Diastolic						
Brachial	77.1±8.4[a]	79.4±10.4[ab]	78.1±15.5[a]	87.7±16.8[b]	82.6±8.7[ab]	0.003
Central	77.3±9.6[a]	81.2±10.8[ab]	79.4±15.3[ab]	88.4±16.6[b]	84.7±9.0[ab]	0.003
p-value**	0.841	<0.001	<0.001	0.057	0.046	
Mean arterial pressure						
Brachial	92.8±8.8[a]	100.3±12.5[a]	100.5±15.7[a]	111.7±19.3[b]	101.3±9.4[a]	<0.001
Central	91.8±11.2[a]	100.3±13.2[ab]	99.8±15.8[ab]	109.9±19.5[b]	100.7±10.3[ab]	<0.001
p-value**	0.227	0.456	0.123	0.040	0.458	
Pulse pressure						
Brachial	46.9±6.9[a]	62.7±19.5[bc]	67.1±23.4[bc]	72.3±23.6[b]	56.7±14.3[ac]	<0.001
Central	34.3±6.8[a]	48.9±16.5[bc]	50.4±20.2[bc]	53.9±18.4[b]	41.3±11.1[ac]	<0.001
p-value**	<0.001	<0.001	<0.001	<0.001	<0.001	
Aortic PWV (m/s)	9.5±1.7[a]	12.7±2.2[bc]	13.5±2.8[b]	13.4±2.8[b]	11.3±1.8[c]	<0.001
Augmentation index (AIx) (%)	26.1±11.9	29.1±12.8	24.3±12.0	27.5±8.5	24.4±9.6	0.335
Prevalence of arterial stiffness	2 (5.7)[a]	17 (53.3)[bc]	22 (68.8)[b]	22 (64.7)[b]	14 (38.9)[c]	<0.001

Values were depicted as mean ± SD and number (percent)

* = A *p*-value between group from One Way ANOVA and [a,b,c] showing multiple comparisons using Scheffe's method, different characters mean significant difference between groups. Significant difference defied by *p*-value of <0.05

** = A *p*-value within group (Brachialvs Central) from paired t-test

CKD = chronic kidney disease; HD = hemodialysis; CAPD = continuous ambulatory peritoneal dialysis; KT = kidney transplant; PWV = pulse wave velocity

Table 3. Comparison of associated factors of arterial stiffness by univariate analysis (n = 169)

	Arterial stiffness (n = 77)	No arterial stiffness (n = 92)	*p*-value
Age (years)	59.3±14.1	47.2±15.3	<0.001
BMI (kg/m^2)	23.2±4.1	24.1±4.4	0.185
DM	30 (39.0)	13 (14.2)	<0.001
Type			
Pre-dialysis CKD	17 (22.1)	15 (16.3)	<0.001
HD	22 (28.6)	10 (10.9)	<0.001
CAPD	22 (28.6)	12 (13)	<0.001
KT recipients	14 (18.2)	22 (23.9)	<0.001
Brachial BP (mmHg)			
Systolic pressure	155.6±23.7	130.4±18.7	<0.001
Diastolic pressure	83.7±13.7	78.8±11.7	0.013
MAP (mmHg)	107.7±14.5	95.9±12.9	<0.001
Pulse pressure	71.9±21.4	51.6±13.7	<0.001
Central BP (mmHg)			
Systolic pressure	139.2±21.0	117.9±17.3	<0.001
Diastolic pressure	85.7±13.4	79.4±12.1	<0.002
MAP	107.1±15.3	94.8±12.9	<0.001
Pulse pressure	53.9±18.5	38.4±11.3	<0.001
HbA1c (%)	6.9±11.7	6.0±11.6	0.491
BUN (mg/dl)	42.3±21.6	26.1±20.0	<0.001
Creatinine (mg/dl)	6.2±4.5	3.1±3.9	<0.001
Calcium (mg/dl)	9.3±0.6	9.2±0.8	0.235
Phosphorus (mg/dl)	4.5±1.5	3.9±1.2	0.015
Ca x PO_4 products	40.7±13.8	35.9±10.2	0.012
iPTH (pg/ml)	313.8±646.2	176.12±379.9	0.087
Total cholesterol (mg/dl)	179.1±44.0	177.7±47.4	0.845
Triglycerides (mg/dl)	138.9±108.0	129.9±65.4	0.524
HDL (mg/dl)	57.7±37.1	49.3±17.0	0.067
LDL (mg/dl)	113.6±39.4	115.5±34.3	0.730

Values were depicted as mean ± SD and number (percent)
CKD = chronic kidney disease; HD = hemodialysis; CAPD = continuous ambulatory peritoneal dialysis; KT = kidney transplant; BP = blood pressure; MAP = mean arterial pressure

consistency of this cut-off point in having a significant negative prognostic impact on the survival of ESRD patients. Therefore, the main finding of the present study is the observation that arterial stiffness, as assessed noninvasively by aortic PWV, was markedly increased in all groups of CKD patients with an overall prevalence of 56%. The highest incidence of increased arterial stiffness was found in patients receiving HD (68.8%) and CAPD (64.7%), followed by pre-dialysis CKD patients (53.3%) and KT recipients (38.9%), compared to 5.7% in normal controls (Table 2, Fig. 1).

Central blood pressure and augmentation index

Normally, there are two interrelated arterial functions: conduit function, for delivering adequate blood flow to tissues and organs; and cushioning or dampening function, for transforming cyclic high-flow and pressure oscillations in the aorta into continuous and low-pressure capillary flow[20], thereby limiting their transmission to microcirculation[24]. In a normal person, because of an increase in arterial stiffness moving away from the heart, there is a systolic amplification of brachial pressure[25] which normally causes the brachial systolic pressure to be slightly higher than the central systolic pressure.

When the arterial wall becomes stiffer and more resistant to distension, it causes an abrupt rise in systolic pressure during ventricular ejection with

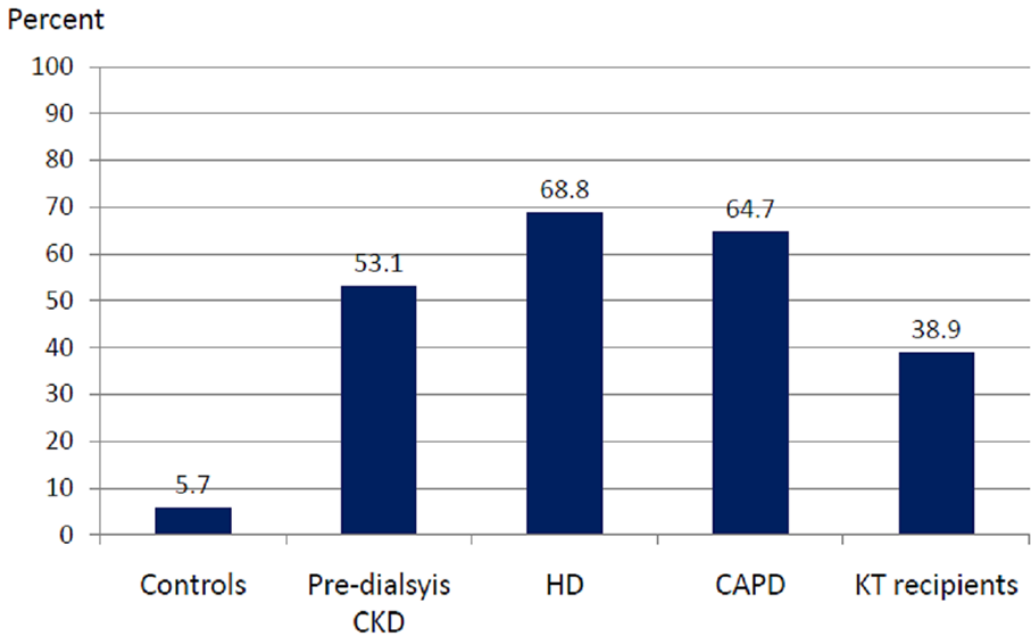

Fig. 1 Prevalence of arterial stiffness in CKD patients.
CKD = chronic kidney disease; HD = hemodialysis; CAPD = continuous ambulatory peritoneal dialysis; KT = kidney transplant.

decreased diastolic pressure during diastolic runoff, resulting in wide pulse pressure. In addition, arterial stiffness also determines the propagation velocity of the pressure wave from the proximal aorta toward peripheral vessels: so-called pulse wave velocity (PWV)[26]. The arterial pressure wave generated in the aorta (forward or incident wave) is propagated to arteries throughout the body, causing slightly delayed reflected waves of forward pressure waves traveling back to the central aorta[27]. Arterial stiffening disrupts the normally desirable timing of the reflected waves. With increased PWV, the reflected waves return earlier, consequently impacting the central arteries during systole rather than diastole, amplifying aortic and ventricular pressures during systole, reducing aortic pressure during diastole and thus raising the central pressure approaching the brachial pressure[28]. The heart, kidneys, and major arteries supplying the brain are exposed to aortic rather than brachial pressure, and recent evidence suggests that, as a result, central pressure is more strongly related to future CV events than brachial pressure[29,30].

In the present study, the authors were able to confirm the systolic amplification of brachial pressure in normal controls which still persisted in all groups of CKD patients. However, the brachial and central BPs, including pulse pressure, in most CKD patients with the exception of KT recipients, were still significantly higher than those of normal controls (Table 2), despite receiving antihypertensive therapy. The central DBPs in most CKD patients were significantly higher than the corresponding brachial DBP. This could be the cause of increased central MAPs approaching the level of brachial MAPs.

Another cause of raised absolute aortic systolic pressure is increased AIx, which quantifies the extent of augmented pressure relative to the central pulse pressure and is also a marker of arterial stiffness[25]. In the present study, despite significant increases in central systolic pressure, the authors could not demonstrate any significant difference in AIx among all groups of CKD patients and normal controls.

Associated factors of arterial stiffness

Normal arterial aging is characterized by arterial enlargement, wall thickening, and stiffening, causing PWV increases with age of 0.06-0.12 m/s for each year of life[31]. This arterial remodeling is already observed in early-stage CKD[32] and occurs in parallel with GFR decline[33]. Age-related hardening is much more pronounced in the aorta and central arteries than in muscular-type peripheral ones[34]. In the present study,

Table 4. Comparison of aortic pulse wave velocity and arterial stiffness between diabetic and non-diabetic patients (n = 134)

	Diabetes (n = 43)	Non-diabetes (n = 91)	*p*-value
Aortic pulse wave velocity (m/s)	13.8±2.7	12.2±2.3	<0.001
Augmentation index (%)	29.1±10.5	25.0±10.9	0.044
Increased arterial stiffness	30/43 (69.8)	45/91 (49.5)	0.027

Values were depicted as mean ± SD and number (percent)

Table 5. Risk factors related to occurrence of arterial stiffness by multivariate analysis

	Crude OR (95% CI)	*p*-value	Adjusted OR (95% CI)	*p*-value
Type healthy	Reference		Reference	
Pre-dialysis CKD	18.70 (3.82-91.44)	<0.001	3.50 (0.52-23.45)	0.196
HD	36.30 (7.24-181.81)	<0.001	17.71 (2.39-131.04)	0.005*
CAPD	30.25 (6.16-148.51)	<0.001	5.30 (0.81-34.34)	0.08
KT recipients	10.50 (2.17-50.81)	0.003	9.29 (1.46-59.09)	0.018*
Age	1.05 (1.03-1.08)	<0.001	1.09 (1.05-1.14)	<0.001*
Central MAP	1.08 (1.03-1.09)	<0.001	1.11 (1.06-1.16)	<0.001*
Ca x PO_4 product	1.04 (1.00-1.06)	0.012	1.00 (0.96-1.04)	0.726
iPTH	1.00 (1.00-1.00)	0.124	1.00 (0.99-1.00)	0.550
LDL	0.99 (0.99-1.00)	0.725	1.01 (0.99-1.02)	0.120

OR = odds ratio; CI = confidence interval; CKD = chronic kidney disease; HD = hemodialysis; CAPD = continuous ambulatory peritoneal dialysis; KT = kidney transplant; MAP = mean arterial pressure; iPTH = intact parathyroid hormone; LDL = low density lipoprotein

it was shown that patients with pre-dialysis CKD and ESRD receiving HD and CAPD were much older than normal controls and KT recipients (Table 1); furthermore, increased age was one of the independent factors of arterial stiffness (Table 5). Besides the effects of aging, multiple factors which contribute to the pathogenesis of arterial stiffness/hardening in CKD and ESRD are associated with alterations of the intrinsic elastic properties of arterial walls, including fibroelastic intimal thickening, elastinolysis and increased collagen in the medial layer, calcification and hypertrophy of vascular smooth muscle cells[9]. These changes are influenced not only by non-specific factors, such as age, genetics, hypertension, diabetes, lipid abnormalities, inflammation, and/or common atherosclerosis, but also by parameters associated with the presence of uremia per se. Chronic kidney disease-mineral bone disorder (CKD-MBD) has been recognized as an important cause of vascular calcification associated with CKD. Mediators in the pathogenesis of CKD-MBD have been associated with arterial stiffness. Certainly, high serum phosphate was independently associated with high ankle-brachial index, a marker of peripheral arterial stiffness, in people with and without CKD recruited into the MESA study[35].

Several mentioned associated factors of arterial stiffness were confirmed by the present study. Using univariate analysis (Table 3), variables found to be significantly associated with risk of developing arterial stiffness included aging, diabetes, presence of CKD, ESRD, higher BP, serum creatinine, phosphate, and Ca x P products. However, the only four variables that remained significant according to multivariate analysis (Table 5), were HD patients, KT recipients, age and central MAP.

One major contributor to arterial stiffness which is also associated with an increased risk of death in ESRD patients is vascular calcification[36]. There is strong evidence to show that vascular calcification is closely associated with high serum calcium and phosphate levels[37]. Moreover, high serum phosphate levels are a major contributing factor of vascular medial

calcification, and clinical studies have shown that patients with the poorest phosphate control experience the most rapid progression of vascular calcification[38]. Therefore, the higher serum phosphate and Ca x P products in patients with increased arterial stiffness in the present study were likely to underlie the genesis of increased arterial stiffness through vascular calcification (not assessed in the present study).

Diabetes mellitus has been recognized as an entity which increases arterial stiffness through pathologic changes in the vessel bed, and it is closely related to the progression of complications in diabetes. Oliveira Alvim et al[39] reported a prevalence of 33.0% of increased arterial stiffness in their diabetic patients. In the present study, diabetes mellitus was the major associated disease in pre-dialysis CKD (40.6%) and ESRD patients (34.4% in HD, 50% in CAPD) (Table 1), and the authors also demonstrated that diabetes was a significant associated factor of arterial stiffness (Table 3). Interestingly, subanalysis regarding the diabetic condition (Table 4) revealed that diabetic patients had significantly higher prevalence of increased arterial stiffness compared to non-diabetic patients (69.8% vs. 49.5%, $p<0.027$), with significantly higher aortic PWV and AIx; however, it could not be established as an independent factor of increased arterial stiffness by multivariate analysis.

Impact of renal function and dialysis modalities

There is a substantial body of evidence to confirm that arterial stiffness is a risk factor for both CV disease and progressive GFR decline in patients with CKD. Arterial stiffness results in greater transmission of fluctuations in pressure and exposure of smaller arteries in the brain and kidneys to higher SBP, and this in turn may aggravate microvascular damage in these two organs. Arterial stiffness resulting from CKD may, therefore, also contribute to the progression of CKD[40]. A large cohort study showed that measures of arterial stiffness are independently associated with a greater decline in eGFR over 5 years[41]. The present study was not designed to evaluate the direct association between arterial stiffness and GFR decline; however, it was able to show that there was a significant reverse correlation in moderate degree between eGFR in pre-dialysis CKD patients and their aortic PWV ($r = -0.554$, $p<0.001$).

Data from the dialysis population suggest that a relationship exists between severity of arterial calcification, long dialysis vintage and arterial stiffness[42,43]. In the present study, ESRD patients with dialysis (HD and CAPD) were shown to be important associated factors of increased arterial stiffness (Table 3) which was highest in patients with HD (68.8%) and CAPD (64.7%) with aortic PWVs of 13.5 ± 2.8 and 13.4 ± 2.8 m/s respectively (Table 2). It could also be shown that there was a significant correlation between dialysis vintage/post-transplant duration and aortic PWV ($r = 0.340$, $p<0.001$). The reasons which may explain the highest prevalence of arterial stiffness in dialysis patients are possibly the greater derangement of risk factors, including older age, a higher percentage of diabetes, more exposure of uremic milieu, higher serum phosphate and iPTH, and possibly higher degree of vascular calcification (not assessed). One would wonder whether there is any difference between the dialysis modalities. Chang et al[44] performed a comparative study on arterial stiffness and cardiac function between patients treated with HD and CAPD, and they found that HD patients had significantly increased arterial stiffness and severe diastolic dysfunction compared with CAPD patients. The reason that CAPD may be superior to HD for fluid and BP control is probably that CAPD provides better fluid control than HD presumably due to greater preserved residual renal function[45]. Volume overload increases arterial distension, eventually resulting in arterial stiffness, and this may explain the worse arterial stiffness in HD than in CAPD patients.

Impact of kidney transplantation

Following successful transplantation, arterial stiffness indices improve significantly[6,7]. It is believed that successful KT leads to elimination of uremic milieu, improvement in endothelial dysfunction, better control of hypervolemia and restoration of abnormal mineral metabolism[46]. All these favorable changes may lead to rapid aortic remodeling after KT. These postulations might be true and are compatible with the results of the present study. The prevalence of increased arterial stiffness in KT recipients from the present study was 38.9% which was lower than in pre-dialysis CKD and ESRD patients, but still higher than in normal controls. The aortic PWVs in KT recipients were significantly lower than in ESRD patients with dialysis, but not different from pre-dialysis CKD patients (Table 2). It is likely that KT recipients were much younger than the pre-dialysis CKD and ESRD patients, and almost all other associated factors of arterial stiffness improved after transplantation, including BP control, uremic milieu, and CKD-MBD parameters; furthermore, and importantly, the number of KT recipients with diabetes was quite low (5.6%). Surprisingly, the percentage of

KT recipients with arterial stiffness was lower than that of patients without it (18.2% vs. 23.9%, $p<0.001$) (Table 3). Risk factors of arterial stiffness assessment using multivariate analysis showed that the odds ratio of KT recipients (9.29; 95% CI: 1.46-59.09, $p = 0.018$) was much lower than that of HD patients (Table 5). In contrast, Strozecki et al carried out a longer KT follow-up (24-36 months) and found that arterial stiffness was higher in KT recipients[47], and the authors proposed that other mechanisms such as hypertension, lipid metabolism disturbances, and types of immunosuppressive therapy may promote progressive arterial stiffening[48].

The present study was limited by its cross-sectional design, as well as by the lack of information on patients' medication and assessment of vascular calcification, for which the causal-effect relationship was not well-explained. Therefore a further long-term study, including all related parameters, with some interventions should be considered.

Conclusion

The present study reported an overall prevalence of arterial stiffness in 56% of patients, with the highest prevalence in HD and CAPD patients. It was shown that the associated factors that independently increased arterial stiffness were HD patients, KT recipients, advancing age and higher central MAP. Screening methods to assess central BP and the degree of arterial stiffness by noninvasive measurement of aortic PWV could potentially be worthwhile in general clinical practice, as this may allow accurate risk stratification and provide more appropriate therapeutic options for these patients.

What is already known on this topic?

Arterial stiffness is common in CKD and ESRD patients, but conflicting data exists on kidney transplant recipients.

Arterial stiffness can be assessed non-invasively by aortic pulse wave velocity.

What this study adds?

Details of the prevalence of arterial stiffness in Thai patients with pre-dialysis CKD stage 3-5, ESRD patients receiving HD or CAPD and kidney transplant recipients.

Confirmation that arterial stiffness improved after kidney transplantation.

Confirmation that the independent associated factors of arterial stiffness in Thai patients with pre-dialysis CKD and ESRD were hemodialysis, kidney transplantation, older age, and higher central mean arterial pressure.

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Potential conflicts of interest

None.

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ความชุกและปัจจัยที่มีความสัมพันธ์กับการแข็งตัวของผนังหลอดเลือดแดงในผู้ป่วยไตวายเรื้อรังและผู้ป่วยที่ได้รับการปลูกถ่ายไต

ประเสริฐ ธนกิจจารุ, ญานษา จิตสุภารัตน์, บุญธรรม จิระจันทร์

ภูมิหลัง: ภาวะไตวายเรื้อรังทั้งที่ได้รับและไม่ได้รับการบำบัดทดแทนไตรวมถึงผู้ที่ได้รับการปลูกถ่ายไต ต่างมีความสัมพันธ์กับอัตราการเกิดโรคและการเสียชีวิตจากโรคหัวใจและหลอดเลือด ซึ่งมีปัจจัยเสี่ยงสำคัญอย่างหนึ่งคือการแข็งตัวของผนังหลอดเลือดแดง ในปัจจุบันพบว่าการตรวจวัด aortic pulse wave velocity (PWV) เป็นเครื่องบ่งชี้มาตรฐานของการเกิดการแข็งตัวของผนังหลอดเลือดแดง ซึ่งอาจช่วยพยากรณ์ถึงอัตราการเกิดโรคและการเสียชีวิตจากโรคหัวใจและหลอดเลือดได้ในผู้ป่วยเหล่านี้

วัตถุประสงค์: ต้องการศึกษาถึงความชุกและปัจจัยที่มีผลต่อการเกิดการแข็งตัวของผนังหลอดเลือดแดงในผู้ป่วยไตวายเรื้อรัง ทั้งที่ได้รับและไม่ได้รับการบำบัดทดแทนไตและผู้ป่วยที่ได้รับการปลูกถ่ายไต

วัสดุและวิธีการ: เป็นการศึกษาแบบ cross-sectional study โดยมีผู้เข้าร่วมการศึกษาทั้งหมด 169 คน แบ่งเป็น 5 กลุ่ม คือ กลุ่มผู้ป่วยโรคไตวายเรื้อรังระยะที่ 3-5 ในระยะก่อนการฟอกเลือด กลุ่มผู้ป่วยโรคไตวายเรื้อรังระยะสุดท้ายที่ได้รับการบำบัดทดแทนไตด้วยการฟอกเลือด ด้วยเครื่องไตเทียมหรือการล้างไตทางช่องท้อง กลุ่มผู้ป่วยที่ได้รับการปลูกถ่ายไตและกลุ่มควบคุม ซึ่งเป็นอาสาสมัครที่มีสุขภาพดีทำการวัดความดันโลหิตส่วนกลางและ aortic PWV ด้วยเครื่อง SphygmoCor® CPV Pulse Wave Velocity system (AtCor Medical, Sydney, Australia) โดยกำหนดให้มีการแข็งตัวของผนังหลอดเลือดแดงเพิ่มขึ้นเมื่อมีค่า aortic PWV ≥12 เมตรต่อวินาที

ผลการศึกษา: การแข็งตัวของผนังหลอดเลือดแดงในกลุ่มผู้ป่วยโรคไตวายเรื้อรังระยะก่อนการฟอกเลือด กลุ่มที่ได้รับการบำบัดทดแทนไตด้วยเครื่องไตเทียมหรือการล้างไตทางช่องท้อง กลุ่มที่ได้รับการปลูกถ่ายไต และกลุ่มควบคุม มีความชุก ร้อยละ 53.1, 68.8, 64.7, 38.9 และ 5.7 ตามลำดับ โดยมีค่า aortic PWV เท่ากับ 12.7±2.2, 13.5±2.8, 13.4±2.8, 11.3±1.8 และ 9.5±1.7 เมตรต่อวินาทีตามลำดับ ($p<0.001$) เมื่อวิเคราะห์ถึงปัจจัย ที่มีผลต่อการแข็งตัวของผนังหลอดเลือดแบบตัวแปรเดียว พบว่ามีความสัมพันธ์กับกลุ่มผู้ป่วยโรคไตวายเรื้อรังในระยะก่อนการฟอกเลือด กลุ่มที่ได้รับ การบำบัดทดแทนไตด้วยเครื่องไตเทียมหรือการล้างไตทางช่องท้อง กลุ่มที่ได้รับการปลูกถ่ายไต อายุ โรคเบาหวาน ความดันโลหิตทั้งส่วนกลางและที่หลอดเลือด brachial สูง ระดับฟอสเฟตในเลือดสูง และค่าผลคูณของแคลเซียมและฟอสเฟตในเลือด แต่เมื่อนำมาวิเคราะห์ปัจจัยแบบหลายตัวแปร พบว่า อายุ ความดันโลหิตเฉลี่ยส่วนกลาง กลุ่มที่ได้รับการบำบัดทดแทนไตด้วยเครื่องไตเทียมและกลุ่มที่ได้รับการปลูกถ่ายไตเท่านั้น ที่เป็นปัจจัยที่มีความสัมพันธ์กับการแข็งตัวของผนังหลอดเลือดอย่างมีนัยสำคัญทางสถิติ

สรุป: การแข็งตัวของผนังหลอดเลือดแดงพบได้บ่อยในผู้ป่วยโรคไตเรื้อรังทุกกลุ่ม โดยมีความชุกโดยรวมร้อยละ 56 ซึ่งพบมากที่สุดในกลุ่มที่ได้รับการบำบัดทดแทนไตด้วยเครื่องไตเทียมและการล้างไตทางช่องท้อง และปัจจัยสำคัญที่มีผลต่อการแข็งตัวของผนังหลอดเลือดแดง คือ การบำบัดทดแทนไตด้วยเครื่องไตเทียม การปลูกถ่ายไต อายุ และความดันโลหิตเฉลี่ยส่วนกลาง