Mean Platelet Volume and Its Relation With Arterial Stiffness in Patients With Normotensive Polycystic Kidney Disease

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Background: Autosomal-dominant polycystic kidney disease (ADPKD) demonstrates cardiovascular manifestations, such as hypertension, myocardial infarction, and increased carotid intimae-media thickness. These complications are the main cause of morbidity and mortality in patients with ADPKD. Platelet activation and arterial stiffness are important manifestations that independently predict cardiovascular events. In the present study, we aimed to investigate the relation between arterial stiffness, mean platelet volume (MPV), and highly sensitive C-reactive protein (hs-CRP) in patients with normotensive polycystic kidney disease.

Methods: We included 30 normotensive subjects with ADPKD with an estimated glomerular filtration rate (eGFR) of 60 mL or more per minute per 1.73 m^2, 30 normotensive subjects with ADPKD with eGFR from 30 to 60 mL/min per 1.73 m^2, and 30 healthy controls in our study. Pulse wave velocity (PWV), eGFR, spot urine protein-creatinine ratio, MPV, and hs-CRP levels were measured in all participants. In addition, transthoracic echocardiography and ambulatory blood pressure monitoring were performed.

Results: Age, sex, biochemical markers, eGFR, hemoglobin level, and platelet count were similar in the ADPKD subjects and the controls. There were significant differences in MPV (9.8 ± 0.7, 8.7 ± 0.8, and 8.0 ± 0.5 femtolitre; $P < 0.001$) and hs-CRP (6.8 ± 3.0, 5.3 ± 2.7, and 2.6 ± 0.52 mg/L; $P < 0.001$) in the groups. Additionally, PWV values were increased from healthy subjects to ADPKD patients who have decreased eGFR (5.5 ± 1.1, 8.8 ± 1.6, and 10.8 ± 1.2 m/s; P for trend <0.001). There were significant positive correlations between PWV and MPV ($r = 0.401$; $P = 0.002$) and hs-CRP ($r = 0.343$; $P = 0.007$) in the patients with ADPKD. Additionally, PWV was independently predicted by MPV ($\beta = 0.286$; $P = 0.007$), proteinuria ($\beta = 0.255$; $P = 0.001$), eGFR ($\beta = -0.479$; $P < 0.001$), and hs-CRP ($\beta = 0.379$; $P < 0.001$) in the patients with ADPKD. In addition, eGFR, as a sign of severity of disease, was independently predicted by MPV ($\beta = -0.325$; $P = 0.003$), PWV ($\beta = -0.471$; $P < 0.001$), and hs-CRP ($\beta = -0.269$; $P = 0.008$).

Conclusions: Our findings suggest that MPV and hs-CRP levels are associated with increased arterial stiffness in patients with early-stage ADPKD and those with late-stage ADPKD. Also, MPV and hs-CRP were independently associated with the severity of ADPKD.

Key Words: mean platelet volume, inflammation, polycystic kidney disease, arterial stiffness

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Autosomal-dominant polycystic kidney disease (ADPKD) is the most common hereditary disease, present in approximately 8% to 10% of patients with end-stage renal disease.[1] Autosomal-dominant polycystic kidney disease demonstrates cardiovascular manifestations, such as hypertension, myocardial infarction, and increased carotid intimae-media thickness, and these complications are the main cause of morbidity and mortality in patients with ADPKD.[2]

Arterial stiffness is an important manifestation that independently predicts cardiovascular events.[3–7] Arterial stiffness increases with age, hypertension, diabetes mellitus, atherosclerosis, and end-stage renal disease.[8] Several studies showed that increased arterial stiffness parameters are an independent predictor of the prognosis in hypertension, myocardial infarction, congestive heart failure, and atherosclerotic change in the arterial wall resulting from atherosclerosis.[6,7] Previous studies have demonstrated that chronic inflammatory diseases can deteriorate vascular function and can lead to increased arterial stiffness.[9,10] Impaired function of the aorta in the patients with ADPKD might be due to inflammation.[11] Elevated circulating levels of proinflammatory and inflammatory mediators may encourage the degradation of collagen and elastin content of the aortic intima and may thus contribute to impaired function of the aorta.

Highly sensitive C-reactive protein (hs-CRP), an acute phase of an inflammatory marker, might be associated with atherosclerosis, hypertension, and other cardiovascular and inflammatory diseases. Mean platelet volume (MPV), a determinant of platelet activation, is recognized as an independent risk factor of hypertension, myocardial infarction, and stroke.[12] In a previous study, Bath et al.[13] showed that increased platelet volume in patients with ADPKD may be a predictable marker of premature vascular disease and sudden cardiac death in patients with ADPKD. Whereas the relationship between PKD and arterial stiffness has been previously examined,[14] an association with ADPKD, pulse wave velocity (PWV), and platelet activation have not as yet been sufficiently evaluated in this population. In the present study, we aimed to investigate the relation between arterial stiffness and inflammation status in patients with normotensive polycystic kidney disease.

MATERIALS AND METHODS

Study Population

We conducted a prospective community-based cohort multicenter study of polycystic kidney disease. The following participants were excluded from analysis: those younger than 17 years and those older than 60 years, those with a history of myocardial infarction, diabetes mellitus, hypertension, and stroke. Finally, a total of 60 patients (a group with eGFR from 30 to 60 mL/min, n = 30; a group with eGFR ≥60 mL/min, n = 30) and 30 healthy controls consented to participate in the study. Subjects in the control group were chosen on age, sex, race,

weight, or health to match as many features of the ADPKD population being studied as possible.

The eGFR level was calculated using the Modification of Diet in Renal Disease (MDRD) formula: MDRD = 186 × [serum creatinine (mg/dL)]$^{-1.154}$ × (age)$^{-0.203}$. A correction factor of 0.742 was used for women.[15] The study was approved by the university ethics committee and local hospital review committee. All participants provided written informed consent.

Biochemical Measurements

Blood samples were taken from the upper arm with the subjects in a seated position to measure biochemical parameters in the morning after a 20-minute rest following a fasting period of 12 hours. Glucose level, creatinine level, and lipid profile were determined by standard methods. Tripotassium EDTA-based anticoagulated blood samples were drawn to measure MPV stored at 4°C and assessed by a Sysmex K-1000 (Block Scientific, Bohemia, NY) auto analyzer within 30 minutes of sampling. Highly sensitive C-RP was measured by using a BN2 model nephelometer (Dade-Behring, Marburg, Germany). The expected values for hs-CRP in our laboratory ranged from 0 to 3 mg/L.

Echocardiography

All participants were examined by Vivid 7 instruments (GE Medical Systems, Milwaukee, WI), with a 2.5-MHz transducer and harmonic imaging. The echocardiographic examination was performed by a cardiology specialist in the echocardiography laboratory at baseline. All echocardiographic examinations were performed according to the recommendations of the American Society of Echocardiography. Echocardiographic examinations were conducted in the left lateral decubitus position using parasternal long-short axis and apical views. At least 3 consecutive beats in sinus rhythm were recorded, and the average values were taken. The left ventricular (LV) end-diastolic dimension (LVEDD), LV end-systolic dimension, interventricular septal thickness (IVSd), and posterior wall thickness (LPWd) were measured from M-mode images of the left ventricle generated in the long-axis view with the cursor at the tip of the mitral valve leaflets. The LV ejection fraction (LVEF) was calculated using the formula: LVEF % = [LVEDV − LVESV] / LVEDV × 100. The left ventricular mass (LVM) was calculated using the formula: LVM = 0.8 × [1.04 ({IVSd + LVEDD + LPWd}^{3} − {LVEDD}^{3})] + 0.6 g.[16]

Pulse Wave Velocity

Pulse wave velocity was measured from simultaneous Doppler flow signals obtained from the right carotid and right femoral arteries with nondirectional transcutaneous Doppler flow probes (model 810A, 9.0- to 10-MHz probes, Parks Medical Electronics, Inc, Aloha, OR) in a quiet temperature-controlled room with subjects resting in supine position. Digitized data were enrolled by custom programming for subsequent analysis. All measurements were performed by a single operator blinded to the nature of each exposure. A minimum of 10 beats were averaged for each simultaneous recording site using the QRS for synchronization. Three separate runs were enrolled for each participant, and all usable runs were averaged. The distance between the carotid and femoral sampling sites was measured above the surface of the body with a metal tape measure. This was done to avoid overestimation of the distance portion of the PWV

TABLE 1. Clinical and Echocardiographic Features of Patients With ADPKD and Healthy Controls

Parameters	ADPKD eGFR Less Than 60 (n = 30)	ADPKD eGFR 60 or More (n = 30)	Healthy Controls (n = 30)	*P*
Clinical parameters				
Age	37 ± 8	35 ± 7	35 ± 10	0.135
Sex, female, n (%)	15 (50)	16 (53)	16 (53)	0.956
Serum glucose, mg/dL	93 ± 10	92 ± 10	93 ± 9	0.737
Hemoglobin, g/L	14.1 ± 1.9	14.3 ± 1.9	14.2 ± 2.0	0.346
Platelet count, ×1000/mm^3	243 ± 62	249 ± 65	251 ± 72	0.579
Total cholesterol, mg/dL	178 ± 34	174 ± 28	158 ± 43	0.085
HDL cholesterol, mg/dL	43 ± 10	43 ± 12	42 ± 6	0.898
LDL cholesterol, mg/dL	118 ± 21	107 ± 17	105 ± 20	0.092
Plasma triglyceride, mg/dL	148 ± 81	128 ± 104	104 ± 79	0.664
hs-CRP, mg/L	6.8 ± 3.0	5.3 ± 2.7	2.6 ± 0.5	**<0.001**
Proteinuria, g/d	0.7 ± 0.5	0.4 ± 0.2	0.2 ± 0.2	**<0.001**
MPV, femtolitre	9.8 ± 0.7	8.7 ± 0.8	8.0 ± 0.5	**<0.001**
PWV, m/s	10.8 ± 1.2	8.8 ± 1.6	5.5 ± 1.1	**<0.001**
BMI, kg/m^2	26 ± 4.4	27 ± 3.8	25 ± 3.8	0.262
Echocardiographic parameters				
LVEDD, mm	47.8 ± 7.8	46.7 ± 3.9	45.9 ± 5.5	0.125
Left ventricular end-systolic diameter, mm	30.7 ± 3.5	29.6 ± 3.7	29.4 ± 2.9	0.334
Interventricular septal diameter, mm	9.9 ± 2.1	9.7 ± 1.9	9.4 ± 1.1	0.149
Left ventricular posterior wall diameter, mm	9.2 ± 1.4	8.8 ± 1.2	8.7 ± 1.0	0.262
LVEF, %	64.6 ± 3.9	64.7 ± 5.9	65.4 ± 4.3	0.711
LVM, g	154.8 ± 48.9	152.9 ± 47.4	146.6 ± 45.5	0.626
Right ventricular end-diastolic diameter, mm	29.1 ± 3.7	28.1 ± 3.2	28.0 ± 2.9	0.096

Data are expressed as mean ± SD or median for normally distributed data and percentage (%) for categorical variables.

HDL indicates high-density lipoprotein; LDL, low-density lipoprotein; BMI, body mass index.

equation. The time differentials between the onset of flow at carotid and femoral (defined as foot of the pressure tracing at each site) sites were divided by the associated distance to produce flow velocity.

Ambulatory Blood Pressure Measurements

The 24-hour blood pressure monitoring was performed by the Del Mar Medical pressurometer Model P6 device (Del Mar Reynolds, Irvine, CA), and the results were assessed using its computer software. Measurements were conducted once every 15 minutes from 7 AM until 11 PM and once every 30 minutes from 11 PM until 7 AM. Evaluation was performed taking the mean values of day and night blood pressures into account. Hypertension was considered to be present if the systolic pressure was more than 140 mm Hg and/or diastolic pressure was more than 90 mm Hg or if the individual was taking antihypertensive medication.

Statistical Analysis

Continuous variables were tested for normal distribution by the Kolmogorov-Smirnov test. We report continuous data as mean and standard deviation or median. One-way analysis of variance and the Tukey post hoc test for multiple comparisons were used to compare healthy control subjects and patient groups. Categorical variables were summarized as percentages and compared with the χ^2 test. Pearson correlation coefficients were calculated to examine the degree of association between variables in the patients with ADPKD. $P < 0.05$ was considered as significant. Some of the variable differences between the groups may be a significant confounding factor interfering with the PWV and eGFR. Thus, we performed a multivariate linear regression analysis to determine the independent effects of variables on PWV and eGFR. A 2-tailed $P < 0.05$ was considered significant, All statistical analyses were performed using SPSS version 15 (SPSS, Inc, Chicago, IL).

RESULTS

The clinical biochemical data and renal function measurements of the ADPKD and control groups are shown in Table 1. Age, sex distribution, fasting glucose levels, and platelet count were similar among the groups. In addition, there were no significant differences in the serum lipid levels among the groups. However, there were significant differences in MPV (9.8 ± 0.7, 8.7 ± 0.8, and 8.0 ± 0.5 fl; $P < 0.001$), proteinuria (0.7 ± 0.5, 0.4 ± 0.2, and 0.2 ± 0.2 g/d), and hs-CRP (6.8 ± 3.0, 5.3 ± 2.7, and 2.6 ± 0.52 mg/L; $P < 0.001$) in the groups. Additionally, PWV values were increased from the healthy subjects to the patients with ADPKD who have decreased eGFR (5.5 ± 1.1, 8.8 ± 1.6, and 10.8 ± 1.2; P for trend <0.001; Table 1). Post hoc analysis of MPV, proteinuria, hs-CRP, and PWV values are illustrated in Figure 1, showing the significant differences in these basal characteristics among the 3 groups.

Left ventricular end-diastolic diameter, left ventricular end-systolic diameter, interventricular septal thickness, LPWd, LVEF, LVM, systolic pulmonary artery pressure, and right ventricular end-diastolic diameter were similar in all study groups (Table 1).

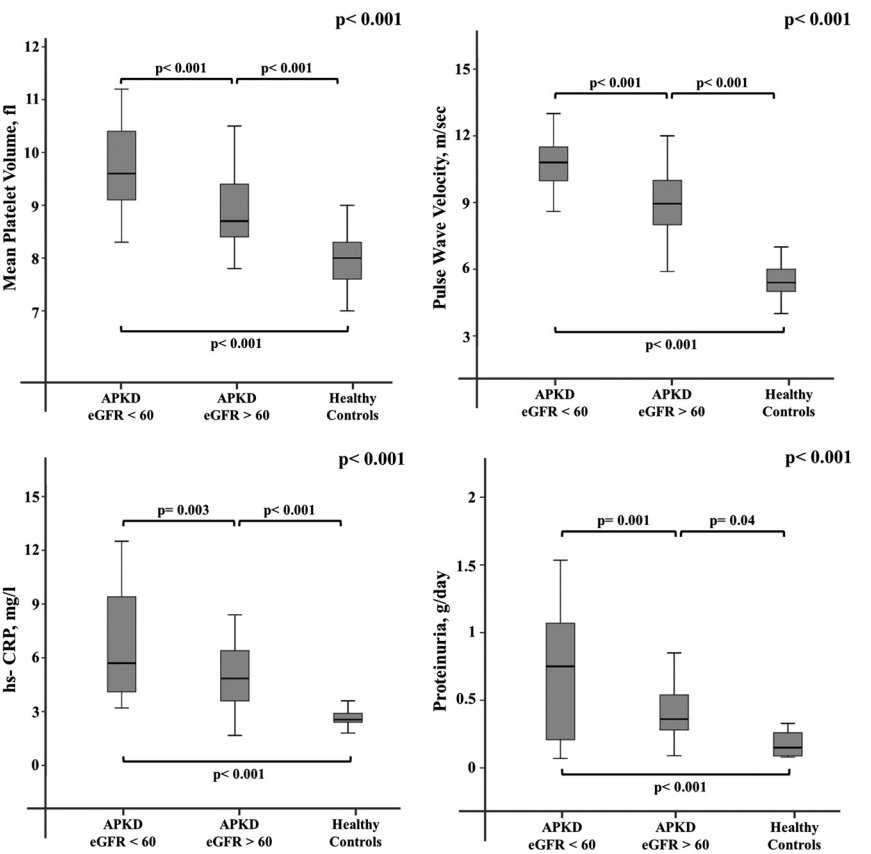

FIGURE 1. Box plot with whiskers from minimum to maximum values of MPV, PWV, hs-CRP, and proteinuria levels in the group with an eGFR of less than 60 mL/min, the group with an eGFR of 60 or more milliliters per minute, and the healthy subjects.

TABLE 2. Data From Ambulatory Blood Pressure Measurements of the Study Subjects

Parameters	ADPKD eGFR Less Than 60 (n = 30)	ADPKD eGFR 60 or More (n = 30)	Healthy Controls (n = 30)	*P*
Mean 24-h systolic BP, mm Hg	115.7 ± 8.8	115.2 ± 7.9	112.1 ± 6.8	0.074
Mean daytime systolic BP, mm Hg	119.1 ± 7.9	118.2 ± 8.2	115.6 ± 7.1	0.159
Mean nighttime systolic BP, mm Hg	111.1 ± 10.6	110.6 ± 9.3	107.9 ± 8.5	0.110
Mean 24-h diastolic BP, mm Hg	74.5 ± 6.2	73.5 ± 5.8	73.0 ± 5.1	0.424
Mean daytime diastolic BP, mm Hg	76.6 ± 7.1	75.9 ± 6.2	75.7 ± 6.0	0.726
Mean nighttime diastolic BP, mm Hg	70.7 ± 6.2	70.1 ± 4.9	69.8 ± 5.3	0.745
Mean 24-h mean BP, mm Hg	88.3 ± 6.6	87.4 ± 6.6	84.9 ± 6.6	0.139
Mean daytime mean BP, mm Hg	90.8 ± 6.9	90.0 ± 7.6	84.0 ± 6.3	0.322
Mean nighttime mean BP, mm Hg	84.2 ± 6.1	83.6 ± 6.8	82.5 ± 5.8	0.413

Data are expressed as mean ± SD or median for normally distributed data and percentage (%) for categorical variables.
BP indicates blood pressure.

As shown in Table 2, the 24-hour blood pressure monitoring was performed in all patients with and those without ADPKD. Hypertension was not observed in any of the study groups. In the patients with ADPKD, there were significant positive correlations between PWV and MPV ($r = 0.401$; $P = 0.002$), proteinuria ($r = 0.265$; $P = 0.041$), and hs-CRP ($r = 0.427$; $P = 0.001$). In addition, there was a significant correlation between MPV and hs-CRP ($r = 0.343$; $P = 0.007$; Fig. 2).

The independence of multiple correlations was analyzed with multivariate linear regression analyses in the patients with ADPKD. Pulse wave velocity was independently predicted by MPV ($\beta = 0.286$; $P = 0.007$), proteinuria ($\beta = 0.255$; $P = 0.001$), eGFR ($\beta = -0.479$; $P < 0.001$), and hs-CRP ($\beta = 0.379$; $P < 0.001$) (Table 3). In addition, eGFR as a sign of severity of disease was independently predicted by MPV ($\beta = -0.325$; $P = 0.003$), proteinuria ($\beta = -0.211$; $P = 0.040$), PWV ($\beta = -0.471$; $P < 0.001$), and hs-CRP ($\beta = -0.269$; $P = 0.008$) (Table 4).

DISCUSSION

There are 3 major findings of this study. Arterial stiffness is increased in the ADPKD groups compared to the healthy controls, and both MPV and hs-CRP levels were increased and correlated with the severity of ADPKD.

Several studies showed that increased arterial stiffness parameters are an independent predictor in the prognosis of congestive heart failure, hypertension, myocardial infarction, and atherosclerotic change in the arterial wall resulting from atherosclerosis.[17,18] Therefore, arterial stiffness in the arteries has been reported to be the best predictor of cardiovascular morbidity and mortality in coronary artery disease.[19–21]

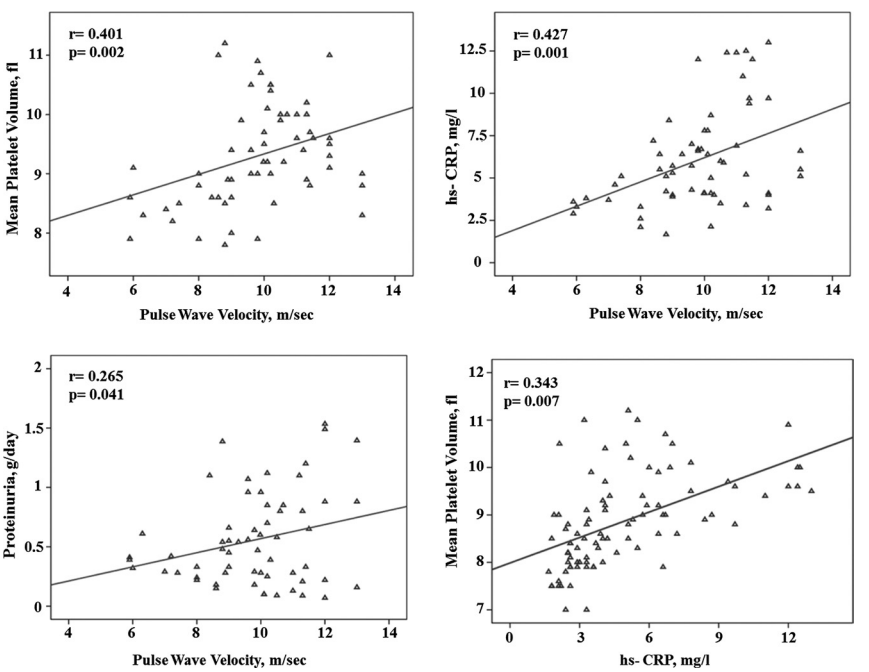

FIGURE 2. Correlations of PWV with MPV, hs-CRP, and proteinuria in all patients with ADPKD (the group with eGFR <60 mL/min and the group with eGFR ≥60 mL/min).

TABLE 3. Multivariate Linear Regression Analysis for PWV in Patients With ADPKD

	PWV		
Parameters	**Beta**	**Standard Error**	***P***
hs-CRP	0.379	0.071	**<0.001**
MPV	0.286	0.215	**0.007**
Proteinuria	0.255	0.489	**0.001**
eGFR	-0.479	0.016	**<0.001**

The original model included, hs-CRP, eGFR, SBP, DBP, glucose, total cholesterol, and plasma triglyceride.

Adjusted $r^2 = 0.695$.

Inflammation may exert its adverse vascular effects by structural changes in the artery wall and, consequently, alterations in arterial elasticity. If inflammation is a marker for endothelial dysfunction, the relationship should be expressed through an inflammatory process in the wall of the conduit arteries that may exhibit cellular infiltration and thickening.[22,23] Inflammatory mediators can increase vascular stiffness contributing to endothelial dysfunction, which elevates smooth muscle tone, depresses endothelial flow-mediated dilation, worsens the response to vascular injury, affects angiogenesis, and promotes atherosclerotic plaque formation.[24] Such arterial wall structural changes would be expected to increase arterial stiffness or reduce arterial compliance via inflammation.[25]

With the growing understanding of the role of inflammation in the chronic kidney disease, studies have focused on hs-CRP as a marker of risk. We used the hs-CRP levels as a marker of inflammatory status in study population. Therefore, we planned to evaluate arterial stiffness with MPV and hs-CRP in normotensive patients with ADPKD and healthy controls.

C-reactive protein is a marker of inflammation status that is produced in response to acute injury, infection, or other inflammatory stimulus. Previous studies shown that hs-CRP is a strong predictor of future cardiovascular events.[26,27] We also demonstrated that hs-CRP reflects as a marker of inflammation in patients with ADPKD.[28]

Mean platelet volume correlates closely with platelet size and activity. Increased platelet activity is associated with increased platelet volume. Large platelets that contain denser granules are metabolically and enzymatically more active than small platelets.[29–32] There is also an established consensus about the relationship between inflammation and stimulation of platelets in the literature.[33,34] Mean platelet volume levels have been shown to reflect the inflammatory burden and disease activity in several diseases.[35,36] To the best of our knowledge, there are no data about direct link between pathogenesis of PKD and platelet indices, especially MPV, in the literature. However, there is an established relation between inflammatory status and ADPKD. Li et al.[37] showed that tumor necrosis factor alpha, an inflammatory cytokine, was shown in the cystic fluid of humans with ADPKD. Menon et al.[38] showed that systemic inflammation is evident early in ADPKD even with preserved kidney function. Heffernan et al.[39] demonstrated that vascular inflammation is evident in young normotensive patients with ADPKD with preserved renal function. In the present study, MPV levels were significantly higher in the patients with ADPKD and also increased with the severity of ADPKD. In addition, there was a significant correlation between each of the 3 parameters (MPV, hs-CRP, and PWV levels) with each other. We hypothesized that increased platelet activation in patients with ADPKD may contribute to an increase in vascular damage in the arterial wall and to impair arterial stiffness via inflammation mediators. The occurrence of inflammation induced platelet activation, and these activated platelets may cause release of cytokines resulting in arterial intimal thickening.[40,41] Therefore, high MPV levels in ADPKD groups seem to be related with some aspects of inflammation that stimulated by underlying ADPKD.

The major limitations of the current study are the small sample size and a cross-sectional design. The other limitation of this study is that we did not perform invasive methods to assess aortic elasticity and pulse pressure. Pulse wave velocity can be measured noninvasively,[42] and the technique has been found to be extremely reproducible, with replicate testing yielding a correlation of more than 0.80.[43] Additionally, the femoral pressure waveform may be difficult to record accurately in patients with metabolic syndrome, obesity, diabetes, and peripheral artery disease. In the presence of aortic, iliac, or proximal femoral stenosis, the pressure wave may be attenuated and delayed. Abdominal obesity, particularly in men, and large bust size in women can make distance measurements inaccurate. Another possible limitation of this study may be method of complete blood count measurement. Tripotassium EDTA-based anticoagulated blood samples were used to measure complete blood count parameters in our study. Most laboratories use EDTA for anticoagulation of whole blood before automated cell counting, but owing to platelet swelling, MPV values may increase with its use. Dastjerdi et al.[44] found that MPV can be measured accurately by using both methods of anticoagulation, EDTA, and citrate if analysis be performed within 1 hour of sampling. Macey et al.[45] also showed that the changes in MPV, which reflect platelet sphering and swelling, were greatest between 30 and 60 minutes in blood stored at ambient temperature. Whereas in our study, blood samples were analyzed within 5 minutes. Therefore, we had adequate confidence about the results of our study.

In conclusion, we demonstrated that MPV and hs-CRP levels are associated with increased arterial stiffness in normotensive patients with ADPKD and independently correlate with the severity of disease. Increased platelet activation and inflammatory response may contribute to a decrease in arterial elasticity in these patients. Therefore, MPV and hs-CRP levels are suggested as possible mechanistic factors to explain impaired useful explanation for impaired arterial stiffness, and they may be used to monitor the vascular status during the treatment period in the patients with ADPKD. In addition, therapeutic goals set in this regard may help decrease the risk of cardiovascular disease in these patients.

TABLE 4. Multivariate Linear Regression Analysis for eGFR in Patients With ADPKD

	eGFR		
Parameters	**Beta**	**Standard Error**	***P***
hs-CRP	−0.269	0.457	**0.008**
MPV	−0.325	1.492	**0.003**
Proteinuria	−0.211	3.190	**0.040**
PWV	−0.471	0.817	**<0.001**

The original model included, hs-CRP, eGFR, SBP, DBP, glucose, total cholesterol, and plasma triglyceride.

Adjusted $r^2 = 0.428$.

REFERENCES

1. Gabow PA. Autosomal dominant polycystic kidney disease. *Am J Kidney Dis*. 1993;22(4):511–512.
2. Fick GM, Johnson AM, Hammond WS, et al. Causes of death in autosomal dominant polycystic kidney disease. *J Am Soc Nephrol*. 1995;5(12):2048–2056.
3. Cameron JD, Jennings GL, Dart AM. Systemic arterial compliance is decreased in newly diagnosed patients with coronary heart disease: implications for prediction of risk. *J Cardiovasc Risk*. 1996;3(6): 495–500.
4. Nemes A, Forster T, Csanady M, et al. Indices of aortic distensibility and coronary flow velocity reserve in patients with different grades of aortic atherosclerosis. *Int J Cardiovasc Imaging*. 2004;20(4):271–277.
5. McGill HC Jr, McMahan CA, Malcom GT, et al. Effects of serum lipoproteins and smoking on atherosclerosis in young men and women. The PDAY Research Group. Pathobiological determinants of atherosclerosis in youth. *Arterioscler Thromb Vasc Biol*. 1997;17(1): 95–106.
6. Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. *J Am Coll Cardiol*. 2010;55(13): 1318–1327.
7. Laurent S, Boutouyrie P, Asmar R, et al. Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. *Hypertension*. 2001;37(5):1236–1241.
8. Blacher J, Guerin AP, Pannier B, et al. Impact of aortic stiffness on survival in end-stage renal disease. *Circulation*. 1999;99(18): 2434–2439.
9. Klocke R, Cockcroft JR, Taylor GJ, et al. Arterial stiffness and central blood pressure, as determined by pulse wave analysis, in rheumatoid arthritis. *Ann Rheum Dis*. 2003;62(5):414–418.
10. Wong M, Toh L, Wilson A, et al. Reduced arterial elasticity in rheumatoid arthritis and the relationship to vascular disease risk factors and inflammation. *Arthritis Rheum*. 2003;48(1):81–89.
11. Moyssakis I, Gialafos E, Vassiliou VA, et al. Myocardial performance and aortic elasticity are impaired in patients with ankylosing spondylitis. *Scand J Rheumatol*. 2009;38(3):216–221.
12. Kaya MG, Yarlioglues M, Gunebakmaz O, et al. Platelet activation and inflammatory response in patients with non-dipper hypertension. *Atherosclerosis*. 2010;209(1):278–282.
13. Bath PM, Saggar-Malik AK, Macdougall IC, et al. Original articles: increased platelet volume in patients with adult polycystic kidney disease. *Platelets*. 1995;6(6):336–339.
14. Borresen ML, Wang D, Strandgaard S. Pulse wave reflection is amplified in normotensive patients with autosomal-dominant polycystic kidney disease and normal renal function. *Am J Nephrol*. 2007;27(3): 240–246.
15. Myers GL, Miller WG, Coresh J, et al. Recommendations for improving serum creatinine measurement: a report from the Laboratory Working Group of the National Kidney Disease Education Program. *Clin Chem*. 2006;52(1):5–18.
16. Devereux RB, Reichek N. Echocardiographic determination of left ventricular mass in man. Anatomic validation of the method. *Circulation*. 1977;55(4):613–618.
17. Zoungas S, Asmar RP. Arterial stiffness and cardiovascular outcome. *Clin Exp Pharmacol Physiol*. 2007;34(7):647–651.
18. Maldonado J, Pereira T, Polonia J, et al. Arterial stiffness predicts cardiovascular outcome in a low-to-moderate cardiovascular risk population: the EDIVA (Estudo de DIstensibilidade VAscular) project. *J Hypertens*. 2011;29(4):669–675.
19. Tomiyama H, Yamashina A. Non-invasive vascular function tests: their pathophysiological background and clinical application. *Circ J*. 2010; 74(1):24–33.
20. Dernellis J, Panaretou M. Aortic stiffness is an independent predictor of progression to hypertension in nonhypertensive subjects. *Hypertension*. 2005;45(3):426–431.
21. Redheuil A, Yu WC, Wu CO, et al. Reduced ascending aortic strain and distensibility: earliest manifestations of vascular aging in humans. *Hypertension*. 2010;55(2):319–326.
22. Park S, Lakatta EG. Role of inflammation in the pathogenesis of arterial stiffness. *Yonsei Med J*. 2012;53(2):258–261.
23. Boos CJ, Lip GY. Elevated high-sensitive C-reactive protein, large arterial stiffness and atherosclerosis: a relationship between inflammation and hypertension? *J Hum Hypertens*. 2005;19(7): 511–513.
24. Zieman SJ, Melenovsky V, Kass DA. Mechanisms, pathophysiology, and therapy of arterial stiffness. *Arterioscler Thromb Vasc Biol*. 2005; 25(5):932–943.
25. Duprez DA, Somasundaram PE, Sigurdsson G, et al. Relationship between C-reactive protein and arterial stiffness in an asymptomatic population. *J Hum Hypertens*. 2005;19(7):515–519.
26. Ridker PM, Glynn RJ, Hennekens CH. C-reactive protein adds to the predictive value of total and HDL cholesterol in determining risk of first myocardial infarction. *Circulation*. 1998;97(20):2007–2011.
27. Ridker PM, Buring JE, Shih J, et al. Prospective study of C-reactive protein and the risk of future cardiovascular events among apparently healthy women. *Circulation*. 1998;98(8):731–733.
28. Kocyigit I, Kaya MG, Orscelik O, et al. Early arterial stiffness and inflammatory bio-markers in normotensive polycystic kidney disease patients. *Am J Nephrol*. 2012;36(1):11–18.
29. Akpek M, Kaya MG, Yarlioglues M, et al. Relationship between platelet indices and spontaneous echo contrast in patients with mitral stenosis. *Eur J Echocardiogr*. 2011;12(11):865–870.
30. Muller K, Aichele S, Herkommer M, et al. Impact of inflammatory markers on platelet inhibition and cardiovascular outcome including stent thrombosis in patients with symptomatic coronary artery disease. *Atherosclerosis*. 2010;213(1):256–262.
31. Akpek M, Kaya MG, Uyarel H, et al. The association of serum uric acid levels on coronary flow in patients with STEMI undergoing primary PCI. *Atherosclerosis*. 2011;219(1):334–341.
32. Kaya MG, Akpek M, Elcik D, et al. Relation of left atrial spontaneous echocardiographic contrast in patients with mitral stenosis to inflammatory markers. *Am J Cardiol*. 2012;109(6):851–855.
33. Mannaioni PF, Di Bello MG, Masini E. Platelets and inflammation: role of platelet-derived growth factor, adhesion molecules and histamine. *Inflamm Res*. 1997;46(1):4–18.
34. Yazici S, Yazici M, Erer B, et al. The platelet indices in patients with rheumatoid arthritis: mean platelet volume reflects disease activity. *Platelets*. 2010;21(2):122–125.
35. Beyazit Y, Sayilir A, Torun S, et al. Mean platelet volume as an indicator of disease severity in patients with acute pancreatitis. *Clin Res Hepatol Gastroenterol*. 2012;36(2):162–168.
36. Gasparyan AY, Ayvazyan L, Mikhailidis DP, et al. Mean platelet volume: a link between thrombosis and inflammation? *Curr Pharm Des*. 2011;17(1):47–58.
37. Li X, Magenheimer BS, Xia S, et al. A tumor necrosis factor-alpha-mediated pathway promoting autosomal dominant polycystic kidney disease. *Nat Med*. 2008;14(8):863–868.
38. Menon V, Rudym D, Chandra P, et al. Inflammation, oxidative stress, and insulin resistance in polycystic kidney disease. *Clin J Am Soc Nephrol*. 2011;6(1):7–13.

39. Heffernan KS, Kuvin JT, Sarnak MJ, et al. Peripheral augmentation index and vascular inflammation in autosomal dominant polycystic kidney disease. *Nephrol Dial Transplant*. 2011;26(8): 2515–2521.
40. Guiducci S, Distler O, Distler JH, et al. Mechanisms of vascular damage in SSc—implications for vascular treatment strategies. *Rheumatology (Oxford)*. 2008;47(suppl 5):v18–v20.
41. Morel O, Toti F, Hugel B, et al. Procoagulant microparticles: disrupting the vascular homeostasis equation? *Arterioscler Thromb Vasc Biol*. 2006;26(12):2594–2604.
42. Vaitkevicius PV, Fleg JL, Engel JH, et al. Effects of age and aerobic capacity on arterial stiffness in healthy adults. *Circulation*. 1993; 88(4 Pt 1):1456–1462.
43. Sutton-Tyrrell K, Mackey RH, Holubkov R, et al. Measurement variation of aortic pulse wave velocity in the elderly. *Am J Hypertens*. 2001;14(5 Pt 1):463–468.
44. Dastjerdi MS, Emami T, Najafian A, et al. Mean platelet volume measurement, EDTA or citrate? *Hematology*. 2006;11(5):317–319.
45. Macey M, Azam U, McCarthy D, et al. Evaluation of the anticoagulants EDTA and citrate, theophylline, adenosine, and dipyridamole (CTAD) for assessing platelet activation on the ADVIA 120 hematology system. *Clin Chem*. 2002;48(6 Pt 1):891–899.

