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The association between the increase in pulse pressure and renal function in chronic kidney disease patients with dyslipidemia

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In recent years, an association between chronic kidney disease (CKD) and arteriosclerosis has been identified. Pulse pressure (PP) is used as an index of arteriosclerosis. However, there have been few studies of the relationship between PP and renal dysfunction in patients with CKD. Therefore, we examined the association of increased PP on renal function in patients with CKD and dyslipidemia. This study included 104 patients with CKD who were diagnosed with dyslipidemia and commenced on drug treatment. In the present study, patients with PP ≥65 mmHg were included in the High PP group, and patients with PP <65 mmHg were included in the Low PP group. We compared the High PP group with the Low PP group about background patient characteristics, laboratory data and antihypertensive medications and type. Mutiple logistic regression analysis identified estimated glomerular filtration rate (eGFR) as a significant predictor of PP ≥65 mmHg. In addition, values of BUN, Ccr, and eGFR baseline and 12 months later were compared. In the High PP group, compared with baseline, BUN increased significantly and Ccr and eGFR decreased significantly after 12 months later. We consider that PP may be an auxiliary indicator of generalized arterial sclerosis and renal function.

1. Introduction

The prevalence of chronic kidney disease (CKD) is increasing steadily. In Japan, the number of patients with CKD is approximately 13,300,000 or 13% of the adult population (Japan Nephrology Society, JCS 2012). Diseases such as diabetes mellitus, hypertension, and obesity and the habit of smoking are known to contribute to the progression of CKD and to increase the risk of cardiovascular disease (CVD) (Brenner et al. 1982). In recent years, an association between CKD and arteriosclerosis has been identified (Shoji et al. 2012). According to guidelines for the primary prevention of ischemic heart disease revised version (JCS 2012), as CKD progresses, the prevalence and extent of arteriosclerotic lesions of the coronary arteries increase. The findings of the Atherosclerosis Risk in Communities (ARIC) study (Muntner et al. 2005) showed that increased total cholesterol (TC) and triglyceride (TG) levels are risk factors for CVD in patients with CKD. Therefore, it is important to manage dyslipidemia to reduce the incidence and progression of CVD in patients with CKD.

Abnormally high systolic blood pressure (SBP) impairs endothelial function and can lead to arteriosclerosis and sclerosis of the aorta (Chamiot-Clerc et al. 2001). Pulse Pressure (PP), the difference between SBP and diastolic blood pressure (DBP), is also used as an index of arteriosclerosis (Safar et al. 2003). An increase in PP is associated with renal dysfunction in patients with hypertension (Gosse et al. 2009; Wang et al. 2012) and is a significant risk factor for cardiovascular disease (Gasowski et al. 2002). Although ankle brachial index (ABI) and pulse wave velocity (PWV) are useful indicators of arteriosclerosis and the risk of CVD, these assessments can only be conducted in medical facilities because special equipment is required. However, PP is easy to measure in the clinic and at home. In this context it is important to understand the association between PP and renal dysfunction. Previous studies have investigated the relationship between PP and renal dysfunction in patients with hypertension (Gosse et al. 2009; Wang et al. 2012). However, there have been few studies of the relationship between PP and renal dysfunction in Japanese patients with CKD. Therefore, we examined the association of increased PP on renal function in Japanese patients with CKD and dyslipidemia.

2. Investigations and results

2.1. Background patient characteristics

Table 1 shows the background patient characteristics for the High PP group (males 26; females 11) and Low PP group (males 36; females 31). Diabetes mellitus was significantly more likely to occur in the High PP group than that in the Low PP group, and SBP was significantly higher in the High PP group than that in the Low PP group. There were no significant differences between the two groups for age, sex, body weight (BW), body mass index (BMI), height, hypertension, smoking history, or DBP.

2.2. Comparison of laboratory data

Table 2 shows the laboratory data for the High PP and Low PP groups. Compared with the Low PP group, the High PP group had significantly lower values for hemoglobin (Hb), hematocrit (Hct), albumin (Alb), creatinine clearance (Ccr), and estimated glomerular filtration rate (eGFR) and significantly higher values for glycohemoglobin (HbA_{1c}), blood glucose (BG), blood urea nitrogen (BUN), and urinary protein/urinary creatinine (UP/Ucr). There were no significant differences between the two groups for red blood cells (RBCs), platelets (PLTs), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), TC, TG, serum potassium (K), aspartate aminotransferase (AST), alanine aminotransferase (ALT), or serum uric acid (SUA).

2.3. Comparison of antihypertensive medication and type of medication

Table 3 shows the antihypertensive medication and type of medication for the High PP and Low PP groups. We selected angiotensin II receptor blockers (ARB), angiotensin converting enzyme inhibitors

Table 1: Comparison of patient background features between the high and low PP groups

Variables	High PP group (n = 37)	Low PP group (n = 67)	*p* value
Age (years)	69.3 ± 12.4	65.8 ± 9.9	0.1115
Sex (Male/Female) (%)	26 (70.3)/11 (29.7)	36 (53.7)/31 (46.3)	0.0988
Body weight (kg)	63.1 ± 14.0	62.4 ± 13.2	0.8168
BMI (kg/m^2)	24.5 ± 4.0	24.1 ± 5.9	0.4026
Height (cm)	159.6 ± 10.9	160.0 ± 9.7	0.8492
Diabetes Mellitus (%)	20 (54.1)	20 (29.9)	0.0151
Hypertension (%)	32 (86.5)	47 (70.2)	0.0620
Smoking history (%)	23 (63.9)	28 (44.4)	0.0626
SBP (mmHg)	149.3 ± 15.0	128.4 ± 14.4	<.0001
DBP (mmHg)	73.4 ± 13.1	77.3 ± 10.9	0.5044

mean ± standard deviation

Abbreviations: body mass index; BMI, systolic blood pressure; SBP, diastolic blood pressure; DBP, pulse pressure; PP

Table 2: Comparison of laboratory data between the high and low PP groups

Variables	High PP group (n = 37)	Low PP group (n = 67)	*p* value
RBC (–10^6/mm^3)	3.9 ± 1.3	4.0 ± 0.6	0.0110
Hb (g/dL)	11.7 ± 2.3	12.8 ± 2.0	0.0033
Hct (%)	33.8 ± 7.4	37.1 ± 6.7	0.0030
PLT (+10^3/mm^3)	227.2 ± 12.6	241.2 ± 86.3	0.7368
HbA1c (%)	6.6 ± 1.1	6.1 ± 0.8	0.0472
BG (mg/dL)	145.1 ± 65.0	112.7 ± 25.3	0.0209
Alb (g/dL)	3.3 ± 0.8	3.8 ± 0.7	0.0019
LDL-C (mg/dL)	146.9 ± 46.1	157.1 ± 74.0	0.7388
HDL-C (mg/dL)	46.8 ± 14.8	52.5 ± 12.8	0.0870
TC (mg/dL)	252.1 ± 58.3	252.7 ± 92.5	0.3185
TG (mg/dL)	229.2 ± 155.8	183.2 ± 84.7	0.4105
K (mEq/L)	4.3 ± 0.5	4.4 ± 0.5	0.5189
AST (IU/L)	22.5 ± 10.2	25.1 ± 15.9	0.3285
ALT (IU/L)	18.8 ± 9.3	20.8 ± 16.6	0.9753
BUN (mg/dL)	35.4 ± 15.7	25.5 ± 11.0	0.0004
C_{Cr} (mL/min)	35.2 ± 22.9	45.5 ± 19.9	0.0189
eGFR (mL/min)	27.9 ± 14.7	38.1 ± 15.3	0.0019
UP/Ucr (g/g·Cr)	3.9 ± 3.9	2.5 ± 3.3	0.0259
SUA (mg/dL)	7.4 ± 2.3	7.0 ± 1.4	0.5635

mean ± standard deviation

Abbreviations: red blood cells; RBC, hemoglobin; Hb, hematocrit; Hct, platelets; PLT, glycohemoglobin; HbAlc, blood glucose; BG, albumin; Alb, low-density lipoprotein cholesterol; LDL-C, high-density lipoprotein cholesterol; HDL-C, total cholesterol; TC, triglyceride; TG, serum potassium; K, aspartate aminotransferase; AST, alanine aminotransferase; ALT, blood urea nitrogen; BUN, creatinine clearance; Ccr, estimated glomerular filtration rate; eGFR, urinary protein/urinary creatinine; UP/Ucr, serum uric acid; SUA, pulse pressure; PP

Table 3: Comparison of the each antihypertensive medication and thei type between the high and low PP groups

Variables	High PP group (n = 37)	Low PP group (n = 67)	*p* value
ARB (+) (%)	32 (86.5)	47 (70.1)	0.062
Olmesartan (%)	6 (18.8)	2 (4.3)	0.3882
Candesartan (%)	1 (3.1)	4 (8.5)	
Telmisartan (%)	8 (25.0)	12 (25.5)	
Valsartan (%)	16 (50.0)	28 (59.6)	
Losartan (%)	1 (3.1)	1 (2.1)	
ACE-I (+) (%)	2 (5.7)	10 (14.9)	0.4359
Imidapril (%)	1 (50.0)	0 (0)	0.0046
Enalapril (%)	0 (0)	9 (90.0)	
Temocapril (%)	0 (0)	1 (10.0)	
Perindopril (%)	1 (50.0)	0 (0)	
CCB (+) (%)	26 (74.3)	41 (61.2)	0.1861
Azelnidipine (%)	3 (11.5)	4 (9.8)	0.7537
Amlodipine (%)	13 (50.0)	23 (56.1)	
Cilnidipine (%)	5 (19.2)	8 (19.5)	
Nicardipine (%)	0 (0)	1 (2.4)	
Nifedipine (%)	4 (15.4)	4 (9.8)	
Barnidipine (%)	0 (0)	1 (2.4)	
Benidipine (%)	1 (3.9)	0 (0)	

Abbreviations: Angiotensin II Receptor Blocker; ARB, Angiotensin Converting Enzyme Inhibitor; ACE-I, calcium channel blocker; CCB, pulse pressure; PP

(ACE-I), calcium channel blockers (CCB) in the antihypertensive medication. There were no significant differences between the two groups for ARB, ACE-I, and CCB. Additionaly, we investigated the type of medication. There were no significant differences between the two groups for olmesartan, candesartan, telmisartan, valsartan, and losartan in ARB, and azelnidipine, amlodipine, cilnidipine, nicardipine, nifedipine, barnidipine, and benidipine in CCB. However, between four agents (imidapril, enalapril, temocapril, and perindopril) in ACE-I were differences between the two groups.

2.4. Multiple logistic regression analysis

Multiple logistic regression analysis identified eGFR as a significant predictor of PP ≥65 mmHg (Table 4).

Table 4: Result of multiple logistic regression analysis for associated with high PP

Variables	Adjusted Odds ratio	95% CI	*p* value
Diabetes Mellitus	2.402	0.9685–6.1040	0.0587
eGFR (mL/min)	0.953	0.9228–0.9822	0.0014
Age (years)	0.975	1.0170–1.0260	0.2403
Sex	2.346	0.8872–6.5786	0.0862

(n=104)

Abbreviations: Confidence interval, CI; estimated glomerular filtration rate, eGFR, pulse pressure; PP

2.5. Comparison of renal function baseline and 12 months later

Values of BUN, Ccr, and eGFR baseline and 12 months later were compared (Table 5). In the High PP group, compared with Low PP group, BUN increased significantly and Ccr and eGFR decreased

Table 5: Comparison of renal function at baseline and 12 months between high and low PP groups

Variables	High PP group (n = 37)			Low PP group (n = 67)		
	baseline	12 months later	*p* value	baseline	12 months later	*p* value
BUN (mg/dL)	35.4 ± 15.7	43.5 ± 20.3	0.0077	25.5 ± 11.0	26.8 ± 15.1	0.8841
Ccr (mL/min)	35.2 ± 22.9	31.0 ± 23.7	0.0118	45.5 ± 19.9	43.5 ± 22.8	0.2801
eGFR (mL/min)	28.0 ± 14.7	23.6 ± 15.5	0.0004	38.1 ± 15.3	36.9 ± 17.2	0.1102

mean ± standard deviation

Abbreviations: blood urea nitrogen, BUN; creatinine clearance, Ccr; estimated glomerular filtration rate, eGFR, pulse pressure; PP

significantly after 12 months. In the Low PP group, there were no significant differences between baseline BUN, Ccr, and eGFR levels and levels 12 months later.

3. Discussion

The results of the present study showed that PP ≥65 mmHg was associated with lower eGFR in CKD with dyslipidemia patients. Therefore, increased PP may have a role as a surrogate indicator to screen for subsequent renal function in patients with CKD. Previous research has shown that PP ≥65 mmHg increases the risk of CVD (Asmar et al. 2001). Therefore, it is important to be aware of the risk of both renal dysfunction and CVD in patients with PP ≥65 mmHg.

Both ABI and PWV have been used to screen for arteriosclerosis and renal dysfunction (Otsuka et al. 2011; Shiota and Watanabe 2007). However, these indicators can only be measured in a clinical setting and are not widely used. Maeda et al. (2008) reported that only 24.4% of patients with peripheral arterial disease underwent assessment using ABI. Of the patients in the present study, only 19.2% and 18.3% had undergone measurement of the ABI or PWV, respectively. On the other hand, PP is simply the difference between the SBP and DBP and can be measured at home if patients have a personal blood pressure measurement apparatus. PP shows a significant correlation with ABI and PWV (Otsuka et al. 2011; Shiota and Watanabe 2007) and is also an indicator of atherosclerosis (Safar et al. 2003). Therefore, PP is likely to become widely used as an alternative to ABI or PWV. Only a few previous studies have investigated and identified an association between PP and renal dysfunction in patients with hypertension, particularly in Japanese patients (Gosse et al. 2009; Wang et al. 2012). Therefore, in the present study, we examined differences in renal function between patients with PP ≥65 mmHg and patients with PP <65 mmHg.

eGFR was identified as a significant predictor of PP ≥65 mmHg on multiple logistic regression analysis. Nakagawa et al. (2008) evaluated the association between arteriosclerosis and eGFR. Furthermore, Tomiyama et al. (2010) reported that in a Japanese occupational cohort with normal renal function or early CKD, increased arterial stiffness was an independent risk factor for renal dysfunction. PP is also used as an index of arteriosclerosis (Safar et al. 2003). The results of these previous studies are consistent with the results of the present study.

In the High PP group, 12 months later from baseline, BUN was increased and CCr and eGFR were significantly decreased. However, in Low PP group, 12 months later from baseline, there were no significant differences for BUN, Ccr, and eGFR. Therefore, the subsequent decline in renal function was more pronounced in the group with PP ≥65 mmHg than that in the group with PP <65 mmHg. Furthermore, univariate analysis results showed that eGFR was significantly decreased in the abnormal group. The mechanisms underlying the decrease in eGFR associated with increased PP remain unclear. However, Ito et al. (2009) reported that when hypertension became persistent, the juxtamedullary afferent glomerular arterioles of the kidney were damaged. Arterioles that branched off the juxtamedullary afferent glomerular arterioles (strain vessels) were also damaged. As a result, albumin passed into the urine (Ito S et al. 2009). In the present study, a history of hypertension and SBP was significantly more common in the High PP group than that in the normal group, suggesting that the strain vessel theory is valid (Ito S et al. 2009). Therefore, it is necessary to examine the various factors contributing to arteriosclerosis in patients with renal dysfunction and to manage blood pressure to prevent an increase in PP. PP is primarily influenced by the SBP. Therefore, lifestyle changes such as a low salt diet and smoking cessation are essential.

There are a number of limitations to the present study that should be noted. First, this was a single-center cross-sectional study with a small sample size. Second, patients with diabetes mellitus were included. It is possible that some of the decrease in eGFR in these patients was the result of diabetic nephropathy. However, eGFR in the High PP group was significantly decreased by correcting with diabetes mellitus when analysing. Therefore, the inclusion of patients with diabetes mellitus is likely to have had minimal effect on the results. Third, blood pressure was measured at home. There is a circadian variation in blood pressure, blood pressure may be elevated in the clinical setting, and blood pressure also varies depending on the method of measurement (The Japanese society of Hypertension 2014). Because this study was retrospective we could not address these issues, and these factors may have affected the results of this study. In future studies, blood pressure should be measured using ambulatory blood pressure monitoring that is closely associated with the degree of hypertensive organ damage (Imai et al. 2013; Sokolow et al. 1966; Mancia et al. 1997).

In conclusion, this study demonstrates an association between PP ≥65 mmHg and lower eGFR in patients with CKD and dyslipidemia. In addition, renal function in patients with PP ≥65 mmHg deteriorated further declined during the one year. Therefore, PP may be an auxiliary indicator of generalized arterial sclerosis and renal function.

4. Experimental

4.1. Study design

The following items were recorded for the High PP group and the Low PP group: background characteristics, including age, sex, BW, BMI, height, complications (e.g., diabetes mellitus, hypertension), smoking history, SBP, and DBP; and laboratory data, including the levels of RBCs, Hb, Hct, PLTs, HbA_{1c}, BG, Alb, LDL-C, HDL-C, TC, TG, K, AST, ALT, BUN, Ccr, eGFR, UP/Ucr, and SUA; and antihypertensive medications and type, including ARB [olmesartan, candesartan, valsartan, and losartan], ACE-I [imidapril, enalapril, temocapril, and perindopril], CCB [azelnidipine, amlodipine, cilnidipine, nicardipine, nifedipine, barnidipine, and benidipine]. Furthermore, we used eGFR of unadjusted body surface area. We collected these information from medical records retrospectively. We used the value before starting the drug (high potency statins [atorvastatin, rosuvastatin, and pitavastatin]) treatment of dyslipidemia about each data. We defined these data as baseline. In addition, measures of renal function (BUN, Ccr, and eGFR) of baseline and 12 months later were compared between the two groups. As recommended by the Yokosuka Kyousai Hospital, the study patients measured their blood pressure twice a day at home using an arm-cuff blood pressure monitor and recorded the values in a notebook. The average of the two values for each day was used for the analysis. Additionaly, we defined CKD stage in accordance with Clinical Practice Guidebook for Diagnosis and Treatment of Chronic Kidney Disease 2012 and defined diabetes mellitus, hypertension, and dyslipidemia in accordance with the International Statistical Classification of Diseases and Related Health Problems (ICD-10) code.

4.2. Patients

This study included 104 patients with CKD who visited the Nephrology Medicine Department of Yokosuka Kyousai Hospital between September 2006 and October 2011 and were diagnosed with dyslipidemia and commenced on drug treatment. The average normal PP is 50 mmHg, and the risk of CVD is increased when PP is ≥65 mmHg (Asmar et al. 2001). Therefore, in the present study, patients with PP ≥65 mmHg were included in the High PP group, and patients with PP <65 mmHg were included in the Low PP group.

4.3. Statistical analysis

Results are presented as mean±standard deviation (SD). The normality test was used to compare the data volume between the two groups. Student's *t*-test was used to compare normally distributed data, and the Mann–Whitney *U*-test was used to compare non-normally distributed data. The χ^2 test or Fisher's exact test was used to compare categorical data. Next, to investigate the relationship between background features, laboratory data, and antihypertensive medications and type, we adjusted for confounders and performed multiple logistic regression analysis in the presence or absence of PP ≥65 mmHg as the dependent variable. The factors diabetes mellitus and eGFR were selected as independent variables based on the results of univariate analysis. We incorporated age and sex configuration factors into regression equation compulsorily because there is a report the association between pulse pressure and age, sex. Spearman's rank-correlation coefficient was used to confirm that there was no multicollinearity between factors, and multiple logistic regression analysis was performed. In addition, the normality test was used to compare the data volume between the two groups baseline and 12 months later. Paired t-tests were used for normally distributed data, and the Wilcoxon signed-rank test was used for non-normally distributed data. The significance level was set at 5% ($p < 0.05$). All statistical analysis was performed using JMP® (Version 10; SAS Institute Inc., Cary, NC, USA).

4.4. Ethics regulation

This retrospective study using medical records was conducted with the approval of the Yokosuka Kyousai Hospital ethics committee (Approval number: 15-15). In addition, this study was conducted with the approval of the School of Pharmacy, Nihon Univer-

sity Ethics Committee (Approval number: 15-008). We complied with the Declaration of Helsinki and the Ethical Guidelines for Clinical Research.

Conflict of interest: The authors report no conflicts of interests in this work.

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