ORIGINAL ARTICLE

Clinical Trial Study

Albuminuria as a marker of arterial stiffness in chronic kidney disease patients

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Abstract

AIM: To access the association between albuminuria levels and arterial stiffness in non-diabetic patients with hypertension and chronic kidney disease (CKD) stages 1-2, treated with renin angiotensin blockade agents plus other hypertensive drugs when needed.

METHODS: One hundred fifteen patients [median age 52 years (68% males)] were consequently enrolled in the study. For each patient, we recorded gender, age, body mass index (BMI), peripheral systolic blood pressure (pSBP), peripheral diastolic blood pressure, peripheral pulse pressure, central systolic blood pressure (cSBP), central diastolic blood pressure (cDBP), central pulse pressure (cPP), hematocrit, hemoglobin, hsCRP, total cholesterol triglycerides, high-density lipoprotein-C, low-density lipoprotein-C, calcium, phosphorus, parathormone, and albumin, as well as 24 h urine albumin excretion. According to 24-h urine albumin collection, patients were then classified as those with moderately increased albuminuria (formerly called macroalbuminuria) ($\leqslant$ 300 mg/d) and those with severely increased albuminuria (formerly called macroaluminuria (> 300 mg/d). We considered aortic stiffness (AS) indices [carotid femoral pulse wave velocity (PWVc-f) and augmentation index (AIx)] as primary outcomes of

the study. We explored potential correlations between severely increased albuminuria and AS indices using a multiple linear regression model.

RESULTS: Fifty-eight patients were included in the moderately increased albuminuria group and 57 in the severely increased albuminuria. Blood pressure measurements of the study population were 138 ± 14/82 ± 1.3 mmHg (systolic/diastolic). There were no significant differences in age, sex, and BP measurements between the two groups. Patients with severely increased albuminuria had higher PWV and AIx than patients with moderately increased albuminuria ($P < 0.02$, $P < 0.004$, respectively). In addition these patients exhibited higher BMI ($P < 0.03$), hsCRP ($P < 0.001$), and fibrinogen levels ($P < 0.02$) compared to patients with moderately increased albuminuria. In multivariate linear regression analysis, severely increased albuminuria ($\beta = 1.038$, $P < 0.010$) pSBP ($\beta = 0.028$, $P < 0.034$) and Ht ($\beta = 0.171$, $P = 0.001$) remained independent determinants of the increased PWVc-f. Similarly, severely increased albuminuria ($\beta = 4.385$, $P < 0.012$), cSBP ($\beta = 0.242$, $P < 0.001$), cPP ($\beta = 0.147$, $P < 0.01$) and Ht levels ($\beta = 0.591$, $P < 0.013$) remained independent determinants of increased AIx.

CONCLUSION: These findings demonstrate an independent association between AS indices and severely increased albuminuria in non-diabetic, hypertensive patients with CKD stages 1-2 treated with renin angiotensin aldosterone system blockers.

Key words: Arterial stiffness; Pulse wave velocity; Augmentation index; Albuminuria

Core tip: Albuminuria heightened cardiovascular disease risk. Pulse wave velocity and augmentation index are markers of aortic stiffness (AS). However, whether severely increased albuminuria is a factor of AS elevation and its progressive deterioration in non-diabetic hypertensive patients treated with renin angiotensin aldosterone blockade agents (RAAS) has not be studied. In this study we aimed to access the association between albuminuria levels and AS, in chronic kidney disease (CKD) stage 1-2 non-diabetic patients with hypertension. All patients were already treated with RAAS blockade agents. Our findings demonstrate an independent association between AS indices and severely increased albuminuria in non-diabetic, hypertensive patients with CKD stages 1-2 treated with RAAS blockers.

INTRODUCTION

The presence of albuminuria is associated with faster progression of renal failure and is also recognized as a marker of vascular dysfunction and heightened cardiovascular disease risk in hypertensive and chronic kidney disease (CKD) patients with or without diabetes[1,2].

Arterial stiffness (AS) assessment helps to predict cardiovascular events in patients with or without diabetes[3-5]. It is usually assessed with the aortic pulse wave velocity (PWV)[6,7] and peripheral pressure wave reflections, (AIx)[1,8]. These indices (PWV and AIx), as major determinants of the aortic pulse pressure, are early markers of atherosclerotic vascular changes and in CKD have been shown to be associated with renal micro vascular damage and kidney dysfunction[9]. On the other hand, AS was showed to be associated with incident albuminuria and the rate of decline in glomerular filtration rate (GFR)[10]. More recent information in patients with type 2 diabetes mellitus showed that levels of urinary albumin excretion, but not reduced estimated GFR, were associated with increased AS and atherosclerosis[11]. High normal albuminuria in the range (0-30 mg/g) is also associated with aortic stiffness[12] even in younger type 2 diabetic patients with shorter durations of disease[13], while in newly diagnosed patients with type 2 diabetes mellitus, moderately increased albuminuria was independently associated with AS and vascular inflammation[14].

However, limited data are available whether severely increased albuminuria is associated with AS in non-diabetic hypertensive patients already treated with renin angiotensin aldosterone blockade agents (RAAS)[15]. It has been suggested that endothelial dysfunction could be a possible mechanism involved in the remodeling of the arterial wall affecting AS and modifying glomerular permeability leading to increased albumin excretion[16,17]. In addition, AS could influence glomeruli function through an increased pulsatile stress, causing glomerular damage[18].

In this study we aimed to access the association between albuminuria levels and AS, in CKD stage 1-2 non-diabetic patients with hypertension. All patients were already treated with RAAS blockade agents plus other hypertensives when needed. RAAS blockers play an important role in the regulation of BP. These agents have demonstrated favorable effects beyond blood pressure control in situations, such as albuminuria, left ventricular hypertrophy and AS[16].

MATERIALS AND METHODS

We included 115 consecutive hypertensive patients with CKD stages 1-2 (Stage 1: kidney damage with normal or increased GFR, Stage 2: kidney damage with mild reduced GFR 60-89 mL/min). None of our patients had albuminuria > 1 g per 24 h. Albuminuria levels were stable for the past 6 mo. Patients with

Table 1 Demographic and aortic stiffness indices characteristics			
Patients characteristics	Study population	Patients with moderately increased albuminuria	Patients with severely increased albuminuria	P value
No	115	58	57	-
Age (yr)	52.6 ± 14.6	51.4 ± 14.4	54.2 ± 15.07	NS
Sex (M/F), (n)	76/39	39/19	37/20	NS
BMI (kg/m^2)	30.9 ± 19.3	28.6 ± 4.5	33.9 ± 28.2	< 0.03
Smoking, n (%)	5	3	2	NS
pSBP (mmHg)	138.0 ± 14.2	139 ± 12.7	138.0 ± 15.5	NS
pDBP (mmHg)	84.2 ± 9.7	84.9 ± 10.7	82.6 ± 9.8	NS
pPP (mmHg)	57.9 ± 15.9	56.7 ± 15.1	59.4 ± 16.9	NS
cSBP (mmHg)	130.3 ± 14.6	130 ± 13.3	130.2 ± 16.5	NS
cDBP(mmH)	84.2 ± 9.7	84.9 ± 10.7	84.3 ± 8.6	NS
cPP (mmHg)	48.1 ± 17.6	47.9 ± 17.9	48.4 ± 17.8	NS
AIx (%)	21.1 ± 10.6	18.4 ± 10.0	24.5 ± 10.0	< 0.004
PWVc-f (m/sec)	8.7 ± 2.0	8.3 ± 2.0	9.1 ± 1.9	< 0.02
ACEIs, n (%) (ramipril or quinapril)	100 (86)	56 (96)	44 (77)	NS
AT1 RB, n (%) (valsartan or olmesartan)	20 (17.4)	9 (15.5)	11 (19.2)	NS
CCBs, n (%)	11 (9.5)	6 (10.3)	5 (8.7)	NS
Statins, n (%)	7 (6.08)	3 (5.1)	4 (7.01)	NS

Data are presented as mean value. M/F: Male/female; BMI: Body mass index; pSBP: Peripheral systolic blood pressure; pDBP: Peripheral Diastolic blood pressure; pPP: Peripheral pulse pressure; cSBP: Central systolic blood pressure; cDBP: Central diastolic blood pressure; cPP: Central pulse pressure; AIx: Augmentation index; AP: Augmentation pressure; PWVc-f: Pulse wave velocity carotid-femoral; ACEIs: Angiotensin converting enzyme inhibitors; AT1RB: Angiotensin type 1 receptor blockers; CCBs: Calcium channel blockers.

known glomerulopathy proven by biopsy were excluded. Most of our patients had hypertensive nephosclerosis with duration of hypertension for more than 10 years and none of them had diabetes mellitus. Furthermore we excluded patients with acute myocardial infarction, unstable angina, stroke, heart failure or transient ischemic attack within the past year. We recorded the demographic data of the patients including age, gender, body mass index (BMI), peripheral blood pressure measurements [(systolic, diastolic, pulse pressure (pSBP, pDBP, pPP) respectively] as well as central blood pressure measurements [(systolic, diastolic, pulse pressure (cSBP, cDBP, cPP) respectively].

All the patients were treated with RAAS agents (ACE inhibitors or angiotensin type 1 (AT1) receptor blockers) plus other antihypertensive drugs as needed. Our choice for the first agent was a RAAS blocker based on the favorable effects of these agents on albuminuria and AS reduction as well as for their anti-fibrotic and anti-inflammatory effects[17,18]. Furthermore, the reno- and cardio-protective effects beyond their hypotensive effects were also well established[19] and for our patients with moderately or severely albuminuria this treatment was already applied for at least 6 mo. Ramipril or quinapril were the ACE inhibitors used as well as valsartan or olmesartan were the AT1 receptor blockers, used in maximum doses. Ramipril and quinapril were prescribed at the doses of 20 mg OD and valsartan and olmesartan at the doses of 320 and 20 mg OD respectively. Six patients received valsartan 160 mg OD and 2 patients received quinapril 40 mg OD. A very small number of patients received amlodipine at a dose of 10 mg OD (Table 1).

Blood pressure measurements

The patient's representative peripheral BP levels at each visit, were the average of three consecutive BP measurements in a sitting position after 5 min rest, within 2 min intervals between them by an automated sphygmomanometer. Peripheral PP was defined as the difference between pSBP and pDBP.

Arterial stiffness measurements

For the assessment of the central aortic pressure were used the Sphygmocor system (Atcor, Sydney, Australia) and its software with an applanation tonometry (Millar tonometer, Millar Instruments, Houston, TX). The AIx was calculated as the increment in pressure from the first systolic shoulder to the peak pressure of the aortic pressure waveform expressed as a percentage[20]. Carotid-femoral pulse wave velocity (PWVc-f) was also calculated non-invasively by the aforementioned software of the Sphygmocor system (Atcor, Sydney, Australia) described elsewhere[20]. Primary outcomes of the study were considered arterial stiffness indices, AIx and PWVc-f.

Laboratory measurements

In all patients, blood samples were obtained after 12 h fasting. Serum samples were analyzed for haematocrit (Ht), haemoglobin (Hb), hsC-Reactive Protein (hsCRP), and serum lipids, such as total cholesterol (T-CHOL), triglycerides (TRG), and high-density lipoprotein-C (HDL-C). Low-density lipoprotein-C (LDL-C) was calculated using the Friedewald formula provided fasting TRG levels less than 400 mg/dL. In

patients with serum TRG values greater than 400 mg/dL, LDL-C concentrations were not determined. HsCRP was measured using a latex enhanced immunonephelometry assay on a Dade Behring BN Ⅱ nephelometer. We also measured serum levels of calcium, phosphorus, parathormone and albumin, as well as 24 h urine albumin excretion, using common commercial serological kits. Albuminuria was the mean value of 2 separate 24 h urinary collections. Patients were then classified as those with moderately increased albuminuria (formerly called macroalbuminuria) (≤ 300 mg/d) and those with severely increased albuminuria (formerly called macroaluminuria (> 300 mg/d). Smoking status was defined as current or past smoker *vs* non-smoker.

All patients were received RAAS blockers (ACE inhibitors or AT1 receptor blockers and 5 patients (4.34%) were received double RAAS blockade agents (ACE inhibitor and AT1 receptor blocker). Our hospital Ethics Committee approved this study protocol. Informed consent was obtained from all patients.

Statistical analysis

We presented data separately for patients with moderately increased albuminuria and patients with severely increased albuminuria. Data were presented as absolute numbers and frequencies for binary and categorical variables, and as mean ± SD for continuous variables. Between the two groups, comparisons for binary variables were performed using χ^2 or Fisher's exact test. Comparisons for continuous variables were performed using Mann-Whitney U test. To investigate whether there was a potential relation between AS and patient characteristics, we first performed univariate linear regression analyses for each variable using the AS indices, *i.e.,* PWVc-f, and AIx as dependent variables.

We considered as independent covariates the following: albuminuria category (moderately *vs* severely increased albuminuria), age, sex, BMI, pSBP, pDBP, Ppp, cSBP, cDBP, cPP, anti-RAAS agents, Ht, Hb, T-CHOL, TRG, HDL-C, LDL-C, fibrinogen, and hsCRP.

Variables with a *P*-value < 0.1 from the univariate analysis were evaluated further in a multivariate regression analysis. For each variable beta (β) co-efficient with the corresponding confidence interval (CI) were calculated in the multivariate model. A two-sided P-value <0.05 was considered as statistically significant. The SPSS, version 16 (SPSS Inc.) statistical package was used for the statistical analysis. Statistically significant was considered a *P*-value < 0.05.

RESULTS

One-hundred fifteen hypertensive non diabetic patients were consequently enrolled in the study. The mean age of the patient's population was 52 years, and 68% of them were males. All enrolled patients exhibited estimated glomerular filtration rate (eGFR-MDRD)

> 60 mL/min per 1.73 m². Fifty-eight patients were included in the moderately increased albuminuria group and 57 in the severely increased albuminuria group. Demographic and AS indices characteristics are reported in Table 1.

Patients with severely increased albuminuria compared to patients with moderately increased albuminuria had higher BMI (*P* < 0.03), and higher PWV and AIx values (*P* < 0.02, *P* < 0.004, respectively) (Table 1). No differences were found in the parameters of peripheral and central BP measurements between the two groups (Table 1).

Biochemical characteristics of the study populations are reported in Table 2. Patients with severely increased albuminuria compared to patients with moderately increased albuminuria had significantly lower values of haematocrit (*P* < 0.01) and haemoglobin (*P* < 0.02), as well as increased levels of fibrinogen (*P* < 0.01), hsCRP (*P* < 0.001), and phosphorus levels (*P* < 0.01), and lower eGFR-MDRD values (*P* < 0.001) (Table 2).

Univariate linear regression analyses for the association of the absolute values of PWV with other parameters are shown in Table 3. In multivariate linear regression analysis, only severely increased albuminuria (β = 1.038, *P* < 0.010), pSBP (β = 0.028, *P* < 0.034) and Ht (β = 0.171, *P* = 0.001) remained independent determinants of increased PWVc-f (Table 4).

Univariate linear regression analyses for the association of the absolute values of AIx with other parameters are shown in Table 5. Similarly, severely increased albuminuria (β = 4.385, *P* < 0.012), cSBP (β = 0.242, *P* < 0.001), cPP (β = 0.147, *P* < 0.01) and Ht levels (β = 0.591, *P* < 0.013) remained independent determinants of increased AIx values (Table 6). No other variables correlated significantly to AS indices.

DISCUSSION

The findings of our study demonstrate an independent association between AS indices (PWV and AIx) and severely increased albuminuria in hypertensive non-diabetic patients with moderate kidney dysfunction, CKD stages 1-2, treated with RAAS blockers.

Albuminuria is recognized as a marker of vascular dysfunction and heightened cardiovascular disease risk[1,2]. The presence of albuminuria is also an indicator of the underlying kidney disease with an increased probability of progressive kidney loss[18,21]. It is worth mentioning that the level of albuminuria and not the current level of GFR is the most relevant variable to predict CKD progression in those with a GFR of at least 30 mL/min[22].

In recent years, great emphasis has been placed on the role of AS in the development of cardiovascular diseases while this parameter has been used in the assessment of patients with hypertension and/or CKD, since AS measurement seems to have an additive value beyond traditional risk factors, including Framingham risk score[23]. Increased AS

Table 2 Biochemical characteristics of the study population

Patients characteristics	Study population	Patients with moderately increased albuminuria	Patients with severely increased albuminuria	P value
No	115	58	57	-
Ht (%)	42.3 ± 3.7	43.2 ± 3.7	41.4 ± 3.5	0.01
Hb (g/dL)	13.6 ± 1.3	14.1 ± 1.5	13.3 ± 1.5	0.02
Fe (μg/dL)	89 ± 35.5	90.2 ± 30	84.2 ± 38.5	NS
Ferritin (ng/L)	127.4 ± 90.1	127.8 ± 87.9	131.3 ± 96.5	NS
Fibrinogen (mg/dL)	336 ± 82.9	339 ± 86.5	394 ± 133.9	< 0.01
hsCRP (mg/dL)	0.19 ± 0.06	0.18 ± 0.05	0.23 ± 0.10	< 0.001
T-CHOL (mg/dL)	203 ± 37.5	208 ± 39.2	209 ± 46.8	NS
TRG (mg/dL)	126 ± 45.7	123 ± 46.3	145 ± 70.2	0.05
HDL-C (mg/dL)	53.4 ± 13.3	53 ± 12.9	54.2 ± 14.9	NS
LDL-C (mg/dL)	119 ± 32	120 ± 3.7	121 ± 3.6	NS
Ca^{2+} (mg/dL)	9.7 ± 0.4	9.7 ± 0.5	9.8 ± 0.4	NS
PO_4^{3-} (mg/dL)	3.42 ± 0.4	3.3 ± 0.4	3.5 ± 0.5	0.01
Ca^{2+} x PO_4^{3-}	33.7 ± 4.8	32.6 ± 4.5	33.9 ± 8.6	NS
PTH (pg/mL)	42.4 ± 15.4	39.8 ± 13.6	45.4 ± 29.9	NS
sAlb (gr/dL)	4.5 ± 0.2	4.5 ± 0.3	4.3 ± 0.5	0.03
eGFR-MDRD (mL/min per 1.73 m^2)	92 ± 0.5	91.5 ± 20.5	79.1 ± 15.3	< 0.001
CKD-EPI(mL/min per 1.73 m^2)	73.4 ± 1.25	73.1 ± 13.7	73.6 ± 11.2	NS

Data are presented as mean value. Ht: Haematocrit; Hb: Haemoglobin; Fe: Serum iron; Ferritin: Serum ferritin, hsCRP: High sensitive C-reactive protein; T-CHOL: Total cholesterol; TRG: Triglycerides; HDL-C: High density lipoprotein cholesterol; Ca^{2+}: Calcium; PO_4^{3-}: Phosphorus; PTH: Parathormone; sAlb: Serum albumin; eGFR-MDRD: Estimated-glomerular filtration rate-modification of diet in renal disease; RAAS-blocker: Renin angiotensin aldosterone system blocker; Alb: Albuminuria.

Table 3 Univariate linear regression analysis of the parameters associated with the absolute values of pulse wave velocity

Covariates	β	*t*	β (95%CI)	P value
Alb	0.841	2.271	0.107-1.574	< 0.025
Age	0.026	2.047	0.001-0.051	< 0.043
BMI	0.009	0.880	0.011-0.028	0.381
pSBP	0.032	2.511	0.007-0.058	< 0.013
pDBP	0.005	0.285	-0.032-0.042	< 0.776
pPP	0.029	2.277	0.004-0.053	< 0.025
cSBP	0.031	2.298	0.004-0.508	< 0.024
cDBP	-0.004	-0.173	-0.045-0.038	0.963
cPP	0.014	1.257	0.008-0.037	0.212
Ht	0.103	2.077	0.005-0.202	0.040
Hb	0.227	1.812	0.020-0.476	0.070
T-CHOL	0.021	0.456	-0.011-0.007	0.649
TRG	0.002	0.752	0.009-0.004	0.454
HDL-C	-0.006	-0.417	-0.033-0.022	0.677
LDL-C	0.023	0.445	0.013-0.477	0.674
Fbrinogen	0.0001	0.524	-0.004-0.002	0.602
hsCRP	-0.011	0.046	-0.442-0.422	0.964
RAAS-blocker	0.081	-0.103	-1.650-1.487	0.918

Alb: Albumin; BMI: Body mass index; pSBP: Peripheral systolic blood pressure; pDBP: Peripheral diastolic blood pressure; pPP: Peripheral pulse pressure; cSBP: Central systolic blood pressure; cDBP: Central diastolic blood pressure; cPP: Central pulse pressure; Ht: Haematocrit; Hb: Haemoglobin; T-CHOL: Total cholesterol; TRG: Triglycerides; HDL-C: High density lipoprotein cholesterol; RAAS-blocker: Renin angiotensin aldosterone system blocker; LDL-C: Low density lipoprotein cholesterol; hsCRP: HsC-reactive protein.

provides prognostic information above traditional CV risk factors, such as BP itself, gender, age, smoking diabetes, and cholesterol[24,25]. It is an independent predictor of fatal stroke in patients with essential hypertension[3,4,26] and a powerful predictor of mortality in both diabetes mellitus and glucose-tolerance-tested multi-ethnic population samples[27]. In addition, PWVc-f is independently associated with a faster decline of kidney function in patients with type 2 diabetes mellitus[10]. The relationship between AS and events is continuous,

Table 4 Multivariate linear regression analysis of the parameters associated with the absolute values of pulse wave velocity

Covariates	β	*t*	β (95%CI)	*P* value
UAlb	1.038	2.638	0.257-1.820	< 0.010
pSBP	0.028	2.149	0.002-0.053	< 0.034
Ht	0.171	3.319	0.069-0.273	< 0.001

pSBP: Peripheral systolic blood pressure; Ht: Haematocrit.

Table 5 Univariate linear regression analysis of the parameters associated with absolute values of AIx

Covariates	β	*t*	β (95%CI)	*P* value
UAlb	6.201	2.977	2.065-10.337	< 0.004
Age	0.236	3.427	0.099-0.373	< 0.0001
BMI	0.036	0.667	0.070-0.142	0.507
pSBP	0.291	4.427	0.161-0.422	< 0.0001
pDBP	0.001	0.002	-0.216-0.216	< 0.002
pPP	0.278	4.536	0.156-0.400	< 0.0001
cSBP	0.349	5.518	0.223-0.474	< 0.0001
cDBP	-0.045	-0.401	0.265-0.176	0.689
cPP	0.265	4.912	0.558-0.372	< 0.0001
Ht	-0.848	0.002	-1.382-0.314	< 0.002
Hb	-0.599	-0.826	-2.040-0.841	0.411
T-CHOL	0.050	1.836	-0.041-0.042	0.069
TRG	0.021	1.164	0.015-0.057	0.247
HDL-C	0.104	1.318	-0.534-0.035	0.262
LDL-C	0.047	1.265	-0.045-0.052	0.243
Fbrinogen	0.007	0.749	-0.122-0.273	0.456
hsCRP	0.015	0.732	-1.738-3.768	0.466
RAAS-blocker	1.043	0.139	13.881-15.966	0.890

Alb: Albumin; BMI: Body mass index; pSBP: Peripheral systolic blood pressure; pDBP: Peripheral diastolic blood pressure; pPP: Peripheral pulse pressure; cSBP: Central systolic blood pressure; cDBP: Central diastolic blood pressure; cPP: Central pulse pressure; Ht: Haematocrit; Hb: Haemoglobin; T-CHOL: Total cholesterol; TRG: Triglycerides; HDL-C: High density lipoprotein cholesterol; RAAS-blocker: Renin angiotensin aldosterone system blocker; LDL-C: Low density lipoprotein cholesterol; hsCRP: HsC-reactive protein.

Table 6 Multivariate linear regression analysis of the parameters associated with the absolute values of AI

Covariates	β	*t*	β (95%CI)	*P* value
UAlb	4.385	2.557	1.023-8.146	< 0.012
cSBP	0.242	3.563	0.107-0.376	< 0.0001
cPP	0.147	2.623	0.036-0.259	< 0.0001
Ht	0.591	2.536	1.055-0.128	< 0.013

cSBP: Central systolic blood pressure; cPP: Central pulse pressure; Ht: Haematocrit.

however, a threshold of > 12 m/s has been suggested as a significant marker of vascular alterations and aortic dysfunction in middle-aged hypertensive patients[28]. A more recent expert consensus statement adjusted this threshold value to 10 m/s[29]. In fact in our study patients had mean PWV values < 10 m/s (Table 1).

Several cross-sectional studies demonstrated a relationship between AS and moderately increased albuminuria in the general population, in individuals with hypertension[30] and/or type 2 diabetes mellitus[5,14]. Additionally, epidemiologic evidence showed an independent association between AS, moderately increased albuminuria and other indices of subclinical target organ damage in non-hypertensive, non-diabetic individuals[28].

In our study we expanded this relationship in hypertensive patients with stage 1-2 CKD without diabetes already treated with RAAS blockers. Our results are in accordance with the results from the Framingham cross-sectional analyses in patients with moderate CKD that showed that PWVc-f was associated with both urinary albumin-to-creatinine ratio and moderately

increased albuminuria ($P < 0.0001$)[31]. In the study by Munakata *et al*[32] each 400 cm/s increase in brachial-ankle PWV, increased the incidence of new-onset moderately increased albuminuria about 2.4 times at 2-year follow-up, suggesting that higher brachial-ankle PWV could be an independent risk factor for the future development of moderately increased albuminuria in patients with hypertension[32]. A study by Kim *et al*[15] showed that AS is independently associated with moderately increased albuminuria, irrespectively of various covariates, in non-hypertensive, non-diabetic individuals. In our study we showed that these results are expanded to the patients with severely increased albuminuria.

The mechanisms linking AS and albuminuria are not fully established. However, it has been suggested that endothelial dysfunction could be a possible mechanism involved in the remodeling of the arterial wall causing structural and functional changes in the target vessels, resulting in the increase of the AS. On the other hand, endothelial dysfunction modifies glomerular permeability and as a consequence leads to increased albumin excretion[33,34]. Alternatively, an increased pulsatile stress mediated by an increased AS causes a pressure load on the glomeruli and could lead to their damage[35].

In our study the optimal BP control in our patients is believed to play a substantial role and contributed to a lower AS indices as well as lower levels of albuminuria. Furthermore all patients in our study were treated with a RAAS blocker.

In patients with arterial hypertension and albuminuria blockage of the RAAS is the treatment of choice[18]. These agents offer a cardio-renal protection which may be mediated, at least in part, by their beyond blood pressure control drug-specific effects. In the past, we showed that these agents improve AS and decrease significantly moderately increased albuminuria[36]. In the present study we showed that patients with severely increased albuminuria had a higher Alx which remained an independent determinant of increased AS. No significant differences in central aortic pressures between the groups were observed. It is known that Alx and central aortic pressures reflect different arterial wall properties compared to PWV. The latest, reflect changes in pressure wave reflections from the large arteries at the distal sites. In contrast, Alx reflect functional properties from the small arteries. In the Framingham study Alx was not associated with urinary albumin excretion[31]. In contrast, in our study, the association of Alx with severely increased albuminuria remains significant in multivariate analysis despite the administration of RAAS blockade agents.

In patients with severely increased albuminuria lower Ht levels were found, which were independently associated with PWV and Alx. In this group of patients, despite the near normal degree of Ht levels along with increased inflammatory indices, such as fibrinogen and hsCRP, Ht might be related to the kidney dysfunction as suggested by Hiramoto *et al*[37]. Of note, in hypertensive patients, increased levels of inflammatory biomarkers, such hs-CRP, are associated with AS indices (*i.e.,* PWV and Alx)[38]. Furthermore, these markers are also increased with the deterioration of renal function[38]. Thus, our results, emphasize the possibility of a common pathophysiologic mechanism affecting renal dysfunction, anemia and AS deterioration: inflammation and endothelial dysfunction may play a prominent role in the interrelation of these entities[37,39].

The cross sectional design, which does not allow to establish cause-effect relationships as well as the small number of patients involved are potential limitations of our study. Subsequently, further prospective studies are required to verify whether albuminuria is a contributing factor and/or a consequence of the increased AS independently of the RAAS blockade and BP control.

Our findings suggest an independent association between AS and severely increased albuminuria in non-diabetic, hypertensive patients, already treated with RAAS agents, who exhibited early renal dysfunction.

COMMENTS

Background
Albuminuria is associated with higher cardiovascular risk. Pulse wave velocity (PWV) and augmentation index (Alx) are early markers of vascular changes and aortic stiffness (AS) in patients with chronic kidney disease (CKD).

Research frontiers
The current research hotspot is the association between albuminuria levels and arterial stiffness. Patients participated in the study were non-diabetic with hypertension and CKD stages 1-2. All patients were treated with renin angiotensin blockade agents plus other hypertensive drugs for a rational period of time. Limited data are available whether severely increased albuminuria is associated with AS in non-diabetic hypertensive patients already treated with renin angiotensin aldosterone blockade agents.

Innovations and breakthroughs
Previous studies showed that in patients with type 2 diabetes mellitus the levels of urinary albumin excretion, but not reduced estimated glomerular filtration rate, were associated with increased AS and atherosclerosis. Even high normal albuminuria in the range (0-30 mg/g) is also associated with aortic stiffness even in type 2 diabetic patients. Limited data are available whether severely increased albuminuria is associated with AS in non-diabetic hypertensive patients already treated with renin angiotensin aldosterone blockade agents. This association even in treated patients with agents that could reduce albuminuria or could reduce arterial stiffness still exists.

Applications
The study results suggest an independent association between AS indices and severely increased albuminuria in non-diabetic, hypertensive patients with CKD stages 1-2 treated with renin angiotensin aldosterone system (RAAS) blockers. Despite the treatment of these patients with RAAS blockers still an association between arterial stiffness and severe increased albuminuria exist.

Terminology
Albuminuria is associated with faster progression of renal failure and is also recognized as a marker of vascular dysfunction and heightened cardiovascular disease risk. Arterial stiffness assessment helps to predict cardiovascular events in patients with or without diabetes. It is usually assessed with the aortic PWV and peripheral pressure wave reflections. These indices (PWV and Alx), as major determinants of the aortic pulse pressure, are early markers of atherosclerotic vascular changes and in CKD have been shown to be associated with renal micro vascular damage and kidney dysfunction.

Peer-review
This is a cross sectional study in which the authors demonstrate an independent association between AS indices and severely increased albuminuria in non-diabetic, hypertensive patients with CKD stages 1-2 treated with RAAS blockers. The study is interesting because all the patients were treated with

RAAS agents [ACE inhibitors or angiotensin type 1 (AT1) receptor blockers] plus other antihypertensive drugs as needed. The choice for the first agent was a RAAS blocker based on the favorable effects of these agents on albuminuria and AS reduction as well as for their anti-fibrotic and anti-inflammatory effects and this treatment was already applied for at least 6 mo. The results suggest an independent association between AS indices (PWV and AIx) and severely increased albuminuria in hypertensive non-diabetic patients with moderate kidney dysfunction, CKD stages 1-2, even though these patients were treated with RAAS agents (ACE inhibitors or AT1 receptor blockers) for this period of time and the BP levels were well controlled.

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