Estimated Glomerular Filtration Rate and Urinary Albumin Excretion Are Independently Associated with Greater Arterial Stiffness: The Hoorn Study

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Mild renal insufficiency is a risk factor for cardiovascular disease (CVD). Both a decline in GFR and (micro)albuminuria are associated with greater cardiovascular mortality. In ESRD, arterial stiffness, an important cause of CVD, is known to be greater, but few data exist in individuals with mild renal insufficiency or microalbuminuria. This study investigated the association of impaired renal function expressed as lower GFR or greater urinary albumin excretion with arterial stiffness. In a population-based study in 806 individuals (402 men), mean age 68 yr (range 50 to 87), peripheral arterial stiffness (by compliance and distensibility of the carotid, brachial, and femoral arteries and by the carotid elastic modulus [E_{inc}]) and central arterial stiffness (by total systemic arterial compliance, carotid-femoral transit time, and aortic augmentation index) were measured ultrasonically. GFR was estimated (eGFR) by the Modification of Diet in Renal Disease (MDRD) formula. Urinary albumin excretion was expressed as urinary albumin/creatinine ratio (UACR). eGFR was 60.6 ± 11.1 ml/min per 1.73 m^2. Median UACR was 0.57 mg/mmol (range 0.1 to 26.6). After adjustment for age, mean arterial pressure (MAP), gender, and glucose tolerance status (GTS), each 5-ml/min per 1.73 m^2 lower eGFR was associated with a lower distensibility coefficient of the carotid (regression coefficient β $-0.20\ 10^{-3}$/kPa; 95% confidence interval [CI] -0.34 to $-0.07\ 10^{-3}$/kPa) and brachial artery ($-0.15\ 10^{-3}$/kPa; 95% CI -0.28 to $-0.03\ 10^{-3}$/kPa) and a greater carotid E_{inc} (0.02 kPa; 95% CI 0.0004 to 0.04 kPa). No statistically significant association was found of eGFR with other arterial stiffness indices. After adjustment for age, MAP, gender, and GTS, a greater UACR (per quartile) was associated with a greater E_{inc} (0.03 kPa; 95% CI 0.001 to 0.07 kPa) and a trend to a lower distensibility coefficient ($-0.24\ 10^{-3}$/kPa; 95% CI -0.49 to $0.02\ 10^{-3}$/kPa) of the carotid artery. After adjustment for age, MAP, gender, and GTS, a greater UACR (per quartile) was in addition associated with a shorter carotid-femoral transit time (-1.67 ms; 95% CI -3.24 to -0.10 ms). These associations were not substantially changed by mutual adjustment for eGFR and UACR. In individuals with mild renal insufficiency, both a lower eGFR and a greater albumin excretion, even below levels that are considered to reflect microalbuminuria, are independently associated with greater arterial stiffness. Moreover, these associations were mutually independent. These findings may explain, in part, why eGFR and microalbuminuria are associated with greater risk for CVD and suggest that amelioration of arterial stiffness could be a target of intervention.

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Chronic kidney disease (CKD) is defined as a lowering of the GFR and/or the presence of (micro)albuminuria (1). In severe CKD (ESRD), cardiovascular mortality is greatly increased (2). Mild renal insufficiency has also been associated with a greater cardiovascular mortality (3,4). In addition, (micro)albuminuria has been associated with an increase in cardiovascular disease (CVD) and mortality in a wide variety of populations (5–7). The underlying mechanisms are incompletely understood. Increased arterial stiffness is a widely known process in severe CKD (8–10) and has been associated with greater cardiovascular mortality (11,12).

We hypothesized that arterial stiffness may be increased in mild renal insufficiency (stages 2 to 3 CKD [1]) and in individuals with (micro)albuminuria and that this may be one of the mechanisms that link these conditions to CVD. To test this hypothesis, we investigated, in a population-based study of 806 individuals, the association between GFR (estimated by the Modification of Diet in Renal Disease [MDRD] formula [13]) and arterial stiffness. In addition, we investigated the association between urinary albumin excretion (UAE) and arterial stiffness and whether these associations were mutually independent.

Materials and Methods

Study Population

For this cross-sectional investigation, we used data from the 2000 Hoorn Study follow-up examination and the Hoorn Screening Study. Details have been described elsewhere (14,15). Briefly, the Hoorn Study

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is a cohort study of glucose tolerance and CVD in the general population. The Hoorn Screening Study is a population-based targeted type 2 diabetes screening study. The local ethics committee approved the studies, and written informed consent was obtained from all participants. Each participant underwent an oral glucose tolerance test, except those with previously diagnosed diabetes, and glucose tolerance status (GTS) was classified according to the 1999 World Health Organization criteria (16). The final study population consisted of 806 individuals (299 with normal glucose metabolism, 181 with impaired glucose metabolism, and 326 with type 2 diabetes).

Estimates of Renal Function

Renal function was estimated by the MDRD formula in ml/min per 1.73 m^2: $170 \times \text{creatinine}^{-0.999} \times \text{age}^{-0.176} \times \text{urea}^{-0.170} \times \text{albumin}^{0.318} \times 0.762$ if female (all participants where white). Because of missing laboratory values, estimated GFR (eGFR) could not be determined in 31 cases. Urinary albumin-creatinine ratio (UACR) in mg/mmol was determined in an overnight first-voided urine sample. Microalbuminuria was defined as a UACR between 2 and 30 mg/mmol. Urinary albumin was measured by rate nephelometry (Array Protein System; Beckman Coulter, Fullerton, CA) with an assay threshold of 2 mg/L. Urinary and serum creatinine was measured by a modified Jaffé test. Patients with macroalbuminuria (>30 mg/mmol; $n = 8$) were excluded from further analysis. To include patients ($n = 86$) with an albuminuria level below the assay threshold, a UACR was calculated with albumin concentration set at 1.9 mg/L divided by the urinary creatinine concentration. Formulas are given in traditional units. To convert to International System units, multiply creatinine in mg/dl by 88.4, urea in mg/dl by 0.357, and albumin in g/dl by 10.

BP Measurement

Brachial artery (BA) systolic (SBP) and diastolic BP (DBP) were assessed in the left upper arm at 5-min intervals with an oscillometric device (Colin Press-Mate BP-8800, Colin Medical Instruments, San Antonio, TX), as described previously (17). Brachial pulse pressure (PP) was calculated as systolic minus DBP and brachial mean arterial pressure (MAP) as $(2 \times \text{DBP} + \text{SBP})/3$. PP at the carotid (CCA) and femoral artery (FA) was calculated according to the calibration method described by Kelly and Fitchett (18), with use of distension waveforms as adapted from Van Bortel *et al.* (19). This method assumes a constant difference between MAP and DBP along the arterial tree. PP can be calculated at a target artery (PPtar) from the PP at a reference artery (PPref) and a calibration factor (K) at target and reference arteries (Ktar and Kref) by the formula $\text{PPtar} = \text{PPref} \times \text{Ktar}/\text{Kref}$, in which K is

Table 1. Baseline characteristics of the study population according to tertiles of eGFR[a]

Characteristic	eGFR (ml/min per 1.73 m^2) ($N = 767$)			*P* (Trend)
	≥64 ($n = 255$)	56 to 64 ($n = 256$)	<56 ($n = 256$)	
Age (yr)	67.7 ± 7.0	67.8 ± 7.1	70.0 ± 7.0	<0.001
Gender (M/F)	124/131	126/130	133/123	0.72
Serum creatinine (μmol/L)	84 ± 10	93 ± 9	108 ± 20	<0.001
eGFR (ml/min per 1.73 m^2)	73 ± 8	60 ± 2	49 ± 5	<0.001
Microalbuminuria (%)	14	14	19	0.16
UACR (mg/mmol)	1.5 ± 2.9	1.4 ± 2.8	1.7 ± 3.1	0.48
HbA_{1c} (%)	6.1 ± 0.8	6.0 ± 0.7	6.2 ± 0.8	0.08
Type 2 diabetes (%)	38	41	40	0.53
Impaired glucose metabolism (%)	23	19	28	0.07
Normal glucose metabolism (%)	39	40	32	0.08
BMI (kg/m^2)	26.0 ± 3.4	27.8 ± 4.1	29.2 ± 4.4	<0.001
Waist-to-hip ratio	0.92 ± 0.09	0.94 ± 0.10	0.94 ± 0.09	0.01
Brachial BP (mmHg)				
SBP	140 ± 20	143 ± 19	146 ± 20	0.01
DBP	77 ± 9	78 ± 9	78 ± 9	0.09
MAP	98 ± 12	100 ± 11	101 ± 11	0.01
PP	64 ± 15	66 ± 14	68 ± 16	0.01
Hypertension (%)	62	72	76	<0.001
Antihypertensive medication (%)	26	38	50	<0.001
Total serum cholesterol (mmol/L)	5.7 ± 1.0	5.7 ± 1.1	5.7 ± 1.0	0.81
Total serum LDL (mmol/L)	3.6 ± 0.9	3.6 ± 0.9	3.6 ± 0.9	0.72
Total serum HDL (mmol/L)	1.5 ± 0.4	1.4 ± 0.4	1.3 ± 0.4	<0.001
Total serum triglycerides (mmol/L)	1.4 ± 0.8	1.5 ± 0.7	1.7 ± 1.0	<0.001
Lipid-lowering medication (%)	17	14	19	0.59
Previous CVD (%)	47	45	51	0.51
Current smoking (%)	19	15	11	0.01

[a]Data are total numbers, means ± SD, or percentage. Microalbuminuria was defined as UACR between 2 and 30 mg/mmol. BMI, body mass index; CVD, cardiovascular disease; DBP, diastolic BP; HbA_{1c}, glycosylated hemoglobin; MAP, mean arterial pressure; PP, pulse pressure; SBP, systolic BP; UACR, urinary albumin-creatinine ratio.

Table 2. Baseline characteristics of the study population according to quartiles of UACR[a]

Characteristic	UACR (mg/mmol) (n = 794)				P (Trend)
	<0.4 (n = 202)	0.4 to 0.6 (n = 195)	0.6 to 1.1 (n = 199)	1.1 to 30 (n = 198)	
Age (yr)	66 ± 6	68 ± 7	69 ± 7	70 ± 8	<0.001
Gender (M/F)	108/94	82/113	95/104	109/89	0.52
Serum creatinine (μmol/L)	98 ± 14	93 ± 13	91 ± 13	97 ± 20	0.29
eGFR (ml/min per 1.73m^2)	58 ± 9	60 ± 10	64 ± 12	61 ± 11	0.04
Microalbuminuria (%)	0	0	0	60	
UACR (mg/mmol)	0.3 ± 0.1	0.5 ± 0.1	0.8 ± 0.2	4.5 ± 4.7	<0.001
HbA_{1c} (%)	5.9 ± 0.6	6.1 ± 0.7	6.1 ± 0.8	6.2 ± 0.8	<0.001
Type 2 diabetes (%)	31	39	42	51	0.004
Impaired glucose metabolism (%)	23	22	23	23	0.82
Normal glucose metabolism (%)	46	39	35	26	0.01
BMI (kg/m^2)	27.9 ± 4.3	27.6 ± 3.8	27.4 ± 4.1	28.0 ± 4.4	0.72
Waist-to-hip ratio	0.93 ± 0.11	0.92 ± 0.10	0.93 ± 0.09	0.95 ± 0.09	0.09
Brachial BP (mmHg)					
SBP	137 ± 18	141 ± 20	145 ± 21	150 ± 18	<0.001
DBP	76 ± 9	76 ± 9	78 ± 10	80 ± 9	<0.001
MAP	96 ± 10	98 ± 12	100 ± 12	103 ± 11	<0.001
PP	61 ± 14	65 ± 15	67 ± 16	70 ± 15	<0.001
Hypertension (%)	61	66	71	80	<0.001
Antihypertensive medication (%)	32	33	41	48	<0.001
Total serum cholesterol (mmol/L)	5.7 ± 1.0	5.9 ± 1.1	5.6 ± 1.1	5.6 ± 1.0	0.32
Serum LDL (mmol/L)	3.6 ± 0.9	3.8 ± 1.0	3.5 ± 0.9	3.5 ± 0.8	0.02
Serum HDL (mmol/L)	1.4 ± 0.4	1.4 ± 0.4	1.4 ± 0.4	1.4 ± 0.4	0.76
Serum triglycerides (mmol/L)	1.6 ± 0.9	1.6 ± 0.7	1.5 ± 0.9	1.6 ± 1.0	0.60
Lipid-lowering medication (%)	15	12	19	19	0.41
Previous CVD (%)	42	41	49	60	<0.001
Current smoking (%)	11	17	13	17	0.58

[a]Data are total numbers, mean ± SD, or percentage. Microalbuminuria was defined as UACR between 2 and 30 mg/mmol.

defined as (MAP − DBP)/PP, and (MAP − DBP) can be calculated from the area under the pressure curve divided by time (18,19).

Arterial Properties

Diameter, Distension, and Intima-Media Thickness. Details have been described elsewhere (17). Briefly, a single observer who was unaware of the participants' clinical or glucose tolerance status obtained properties of the right CCA, FA, and BA, with the use of an ultrasound scanner (350 Series, 7.5-MHz probe; Pie Medical, Maastricht, The Netherlands). The scanner was connected to a PC equipped with vessel wall movement detection software (Wall Track System; Pie Medical). Data were obtained from three consecutive measurements. Diastolic diameter was calculated as the difference between the anterior and posterior wall markers. The change of diameter as a function of time (distension) was estimated and presented on the computer screen (distension waveform). In addition, the carotid posterior wall thickness was calculated. The mean diameter, distension, and intima-media thickness (IMT) were used in analysis.

Peripheral Arterial Stiffness: Distensibility, Compliance, and Young's Elastic Modulus. We calculated CCA, BA, and FA distensibility and compliance coefficients as follows (20):

$$\text{Distensibility coefficient} = (2\Delta D \times D + \Delta D^2)/(\Delta P \times D^2) \text{ in } 10^{-3}/\text{kPa}$$

$$\text{Compliance coefficient} = \pi(2D \times \Delta D + \Delta D^2)/(4 \times \Delta P) \text{ in mm}^2/\text{kPa}$$

where ΔD is distension, D is diameter, and ΔP is PP.

The distensibility coefficient reflects the elastic properties, whereas the compliance coefficient reflects the buffering capacity. From IMT, diameter, and carotid distensibility, we calculated Young's elastic modulus (E_{inc}), an indicator of the intrinsic wall properties:

$$E_{inc} = \text{diameter}/(\text{IMT} \times \text{distensibility coefficient}) \text{ in kPa}$$

Central Arterial Stiffness: Carotid-Femoral Transit Time, Aortic Augmentation Index, and Total Systemic Arterial Compliance. Carotid-femoral transit time (CFTT), which is a measure of aortic (thoracic-abdominal) compliance, was measured as described elsewhere (17,21). Briefly, CFTT is the travel time of a pressure wave from the CCA to the FA, and it is an approximation of the pulse wave velocity (PWV) (22). We determined the CFTT by continuous measurement of the diameter (distension curves) of the right CCA and FA. We then determined the average time delay (mean of three recordings) from the electrocardiograph trigger to 10% of the ascending slope of the distension curve of both arteries and subtracted the carotid value from the femoral value to obtain the CFTT. We did not measure the carotid-femoral distance noninvasively because this might induce error in obese and older patients (tortuous aorta). Instead of measuring the carotid-femoral distance, we adjusted for height in statistical analysis. Reproducibility of the CFTT has been reported (23).

The aortic augmentation index (aAIX) represents the additional load to which the left ventricle is subjected as a result of the timing of wave reflection. In addition, the aAIX depends on the heart rate amplitude

Table 3. Arterial wall properties according to tertiles of eGFR[a]

Parameter	eGFR (ml/min per 1.73 m^2) (N = 767)			P (Trend)
	≥64 (n = 255)	56 to 64 (n = 256)	<56 (n = 256)	
CCA				
diameter (mm)	7.9 ± 1.1	7.9 ± 1.1	8.1 ± 1.0	0.01
distension (μm)	355 ± 112	350 ± 114	338 ± 102	0.10
PP (mmHg)	61 ± 15	62 ± 15	65 ± 19	0.005
IMT (mm)	0.85 ± 0.17	0.84 ± 0.16	0.89 ± 0.17	0.01
distensibility coefficient (10^{-3}/kPa)	12.4 ± 4.7	11.7 ± 4.2	10.7 ± 4.3	<0.001
compliance coefficient (mm^2/kPa)	0.58 ± 0.24	0.56 ± 0.24	0.54 ± 0.21	0.06
E_{inc} (kPa)	0.91 ± 0.47	0.97 ± 0.56	1.02 ± 0.47	0.02
BA				
diameter (mm)	4.5 ± 0.7	4.6 ± 0.8	4.8 ± 0.7	<0.001
distension (μm)	144 ± 66	136 ± 61	151 ± 71	0.42
PP (mmHg)	64 ± 15	65 ± 14	68 ± 16	0.01
distensibility coefficient (10^{-3}/kPa)	8.2 ± 4.6	7.1 ± 3.4	7.4 ± 3.8	0.04
compliance coefficient (mm^2/kPa)	0.13 ± 0.07	0.12 ± 0.07	0.13 ± 0.07	0.70
flow-mediated dilation (%)	3.62 ± 3.99	4.18 ± 4.17	3.66 ± 3.36	0.86
FA				
diameter (mm)	9.9 ± 1.7	10.0 ± 1.6	10.3 ± 1.7	0.004
distension (μm)	200 ± 74	205 ± 72	210 ± 77	0.19
PP (mmHg)	68 ± 17	71 ± 17	74 ± 19	0.001
distensibility coefficient (10^{-3}/kPa)	5.0 ± 2.5	4.6 ± 1.8	4.5 ± 2.1	0.03
compliance coefficient (mm^2/kPa)	0.37 ± 0.21	0.35 ± 0.16	0.37 ± 0.19	0.95
Central artery stiffness				
CFTT (ms)	53 ± 15	55 ± 15	55 ± 20	0.35
augmentation index (%)	33 ± 9	33 ± 9	32 ± 8	0.15
total systemic arterial compliance (SV/aortic PP; ml/mmHg)	1.03 ± 0.36	1.04 ± 0.32	1.01 ± 0.34	0.59

[a]Data means ± SD. Carotid-femoral transit time (CFTT) is shown unadjusted for height. BA, brachial artery; CCA, carotid artery; E_{inc}, Young's elastic modulus; FA, femoral artery; IMT, intima-media thickness SV/aortic PP, stroke volume/aortic pulse pressure.

and location of the reflection sites and is a less pure estimate of arterial stiffness (24). We used radial applanation tonometry performed with a Millar piezoresistive pressure transducer connected to an arterial wave form analysis device (Sphygmocor, Moreton-in-the-Marsh, UK) (25) to obtain the aAIX and aortic PP. The aAIX was calculated as augmented pressure divided by (tonometrically derived) central PP.

Total systemic arterial compliance (ml/mmHg) was determined according to the ratio of stroke volume to aortic PP (26). This method used the ratio of stroke volume to aortic PP (ml/mmHg) to determine total systemic arterial compliance, for which stroke volume was calculated as cardiac output divided by heart rate, and aortic PP was calculated by use of a calibration method (vide supra). This method multiplies the difficulty in accurately determining stroke volume and PP at the ascending aorta noninvasively (27), which means that these data should be interpreted with caution.

Reproducibility. Reproducibility of the aforementioned methods have been reported (17,25).

Statistical Analyses

All analyses were carried out with SPSS. Multiple linear regression analysis was used to investigate the associations between renal function estimates and arterial properties. All associations were first analyzed without adjustments and then with adjustments for potential confounders. Because the population was stratified according to age, gender, and GTS and arterial stiffness is affected by age, gender, GTS, and MAP (20,28), these variables were considered first in the adjusted models. We used brachial MAP for all adjustments because MAP is constant throughout the arterial tree (19). Diabetes is often accompanied with impaired renal function and arterial stiffness. Interaction terms were used to investigate whether the association between eGFR and UAE with arterial stiffness differed according to the presence of diabetes. Two sided $P < 0.05$ was considered statistically significant.

Results

Of the 806 participants, eGFR was missing in 31 cases and UACR in five cases. Seven patients were excluded because of macroalbuminuria (albuminuria >30 mg/mmol). The associations between eGFR and arterial stiffness were studied in the remaining 767 individuals, and the association between UACR and arterial stiffness was studied in 794 individuals. Qualitatively satisfactory examinations were obtained of 756 CCA, 689 BA, and 656 FA. The main reason for missing data was poor definition of the arterial wall attributable to obesity. Except for body mass index (BMI) the nonparticipants were comparable with the study population.

Table 4. CCA, BA, and FA stiffness indices according to eGFR: Adjusted analyses[a]

Model	CCA			BA			FA		
	β	95% CI	P	β	95% CI	P	β	95% CI	P
Distensibility coefficient									
age/GTS/gender	−0.26	−0.387 to −0.112	<0.001	−0.20	−0.317 to −0.042	0.01	−0.08	−0.149 to −0.011	0.03
2 + MAP	−0.20	−0.337 to −0.072	0.002	−0.15	−0.282 to −0.027	0.03	−0.07	−0.134 to 0.004	0.07
2 + MA	−0.22	−0.337 to −0.072	0.002	−0.15	−0.292 to −0.017	0.03	−0.07	−0.134 to 0.004	0.07
2 + BMI	−0.16	−0.287 to −0.032	0.02	−0.12	−0.262 to 0.012	0.10	−0.07	−0.134 to 0.009	0.10
Compliance coefficient									
age/GTS/gender	−0.01	−0.019 to −0.0002	0.04	−0.0007	−0.002 to 0.002	0.55	0.001	−0.008 to 0.011	0.68
2 + MAP	−0.005	−0.014 to 0.005	0.09	−0.0003	−0.002 to 0.001	0.77	0.005	−0.007 to 0.012	0.43
2 + MA	−0.005	−0.015 to 0.005	0.09	−0.0003	−0.002 to 0.001	0.74	0.005	−0.007 to 0.012	0.43
2 + BMI	−0.005	−0.015 to 0.005	0.06	−0.0005	−0.002 to 0.001	0.67	0.002	−0.007 to 0.012	0.48
E_{inc}									
age/GTS/gender	0.03	0.004 to 0.044	0.01						
2 + MAP	0.02	0.0004 to 0.039	0.04						
2 + MA	0.02	0.0004 to 0.039	0.02						
2 + BMI	0.02	−0.0005 to 0.035	0.13						

[a]Data are unstandardized regression coefficients β and their 95% confidence intervals (CI). Beta coefficients represent the change in stiffness per 5-ml/min per 1.73 m^2 decrease in eGFR. GTS, glucose tolerance status; MA microalbuminuria in quartiles.

Baseline Characteristics

Tables 1 and 2 show the characteristics of the study population according to tertiles of eGFR and according to quartiles of UACR, respectively. eGFR ranged from 24 to 114 ml/min per 1.73 m^2. Most individuals ($n = 755$) had mild to moderate CKD (stages 2 to 3). Three participants had severe (stage 4) CKD, and nine had stage 1 CKD (eGFR ≥90 ml/min per 1.73 m^2 with microalbuminuria). Median UACR was 0.57 mg/mmol (range 0.1 to 26.6 mg/mmol).

Arterial Properties According to eGFR

For the CCA, BA, and FA, a lower eGFR was associated with greater arterial diameter, PP, and carotid IMT, whereas associations with distension were NS. As a result, a lower eGFR was associated with lower distensibility coefficients and a greater carotid E_{inc}, whereas associations with the compliance coefficients were NS (Table 3). Lower eGFR was not associated with central arterial stiffness.

After adjustment for age, MAP, gender, and GTS, a lower

Table 5. Associations of eGFR and arterial wall properties: Adjusted analyses[a]

Model	CCA			BA			FA		
	β	95% CI	P	β	95% CI	P	β	95% CI	P
Diameter									
age/GTS/gender	0.025	−0.004 to 0.054	0.14	0.04	0.020 to 0.059	<0.0001	0.085	0.026 to 0.143	0.004
2 + MAP	0.015	−0.014 to 0.044	0.32	0.04	0.020 to 0.059	0.001	0.085	0.026 to 0.143	0.005
2 + MA	0.025	−0.004 to 0.054	0.13	0.05	0.025 to 0.065	<0.001	0.080	0.021 to 0.138	0.009
2 + BMI	−0.005	−0.034 to 0.024	0.81	0.03	0.005 to 0.045	0.04	0.080	0.021 to 0.138	0.010
Distension									
age/GTS/gender	−4.281	−8.303 to −1.356	0.003	−0.57	−2.918 to 1.772	0.49	1.605	−0.880 to 4.084	0.21
2 + MAP	−4.705	−8.193 to −1.226	0.004	−0.66	−3.018 to 1.692	0.45	1.625	−0.870 to 4.114	0.20
2 + MA	−5.040	−8.656 to −1.433	0.003	−0.38	−2.757 to 1.991	0.41	1.480	−1.104 to 4.037	0.19
2 + BMI	−4.320	−8.152 to −0.498	0.009	−0.53	−3.085 to 1.969	0.51	1.230	−1.472 to 3.925	0.36
PP									
age/GTS/gender	0.445	−0.075 to 0.964	0.12	0.18	−0.271 to 0.630	0.48	0.710	0.111 to 1.308	0.02
2 + MAP	0.180	−0.262 to 0.621	0.47	−0.105	−0.458 to 0.247	0.46	0.470	−0.051 to 0.984	0.08
2 + MA	0.190	−0.267 to 0.636	0.47	−0.080	−0.473 to 0.272	0.45	0.450	−0.081 to 0.979	0.09
2 + BMI	0.230	−0.251 to 0.710	0.40	−0.165	−0.538 to 0.207	0.28	0.440	−0.110 to 0.989	0.11
IMT									
age/GTS/gender	0.005	−0.007 to 0.012	0.40						
2 + MAP	0.002	−0.007 to 0.011	0.49						
2 + MA	0.002	−0.008 to 0.011	0.5						
2 + BMI	0.002	−0.008 to 0.013	0.88						

[a]Data are expressed as unstandardized regression coefficients β and their 95% CI. β coefficients represent the change in stiffness per 5-ml/min per 1.73 m^2 decrease in eGFR. GTS indicates glucose tolerance status; MA, microalbuminuria in quartiles; MAP, mean arterial pressure; BMI, body mass index.

eGFR was inversely associated with CCA, BA, and FA distensibility ($P = 0.002$, $P = 0.03$, and $P = 0.07$, respectively) and carotid compliance ($P = 0.09$) and directly with carotid E_{inc} ($P = 0.04$). These associations were not affected by further adjustment for UACR. The association with carotid Young's elastic was NS after additional adjustment for BMI (Table 4).

Table 5 shows that the association between a lower eGFR and greater arterial stiffness of BA and FA was driven by associations with greater arterial diameter. The association with greater carotid E_{inc} was driven by a smaller distension of the CCA.

Arterial Properties According to UAE Expressed as UACR

For the CCA, BA, and FA, a greater UACR was associated with a greater CCA and BA and a smaller FA diameter, with less CCA and FA and more BA distension, with greater PP in all three arteries, and with greater carotid IMT. As a result, a greater UACR was associated with less CCA and FA distensibility and compliance and with a greater carotid E_{inc} (Table 6).

After adjustment for age, gender, GTS, and MAP, a greater UACR was associated with less CCA distensibility ($P = 0.07$) and with greater E_{inc} ($P = 0.04$; Table 7). Further adjustment for eGFR, the presence of hypertension, or previous CVD slightly strengthened the associations with CCA distensibility and E_{inc} (Table 7). Table 8 shows that the associations between UACR and CCA distensibility and E_{inc} were driven mainly by the association with CCA diameter.

With regard to central arterial stiffness indices, a greater UACR was associated with a lower CFTT and total systemic arterial compliance and an increase in the aAIX (Table 6). After adjustment for age, gender, GTS, and MAP, associations between UACR and measures of central arterial stiffness were not statistically significant except for the association between UACR and CFTT. Age and MAP seemed to be the strongest confounders. Further adjustments for eGFR, hypertension, and previous CVD slightly weakened the association between UACR and CFTT (Table 9).

Additional Analyses

The results did not change materially after additional adjustments for total cholesterol, triglycerides, HDL cholesterol, and LDL cholesterol; use of lipid-lowering or anti-hypertensive drugs; or current smoking. With regard to the eGFR analyses, results also did not change after adjustment for previous CVD, diagnosis of hypertension, or waist-to-hip ratio. With regard to the UACR analyses, results did not change after additional

Table 6. Arterial wall properties according to quartiles of the UACR[a]

Parameter	UACR (mg/mmol) ($n = 794$)				P (Trend)
	<0.4 ($n = 202$)	0.4 to 0.6 ($n = 195$)	0.6 to 1.1 ($n = 199$)	1.1 to 30 ($n = 198$)	
CCA					
diameter (mm)	7.7 ± 0.9	7.8 ± 1.0	8.1 ± 1.2	8.3 ± 1.2	<0.001
distension (μm)	354 ± 103	359 ± 116	332 ± 104	340 ± 115	0.06
PP (mmHg)	58 ± 14	63 ± 17	64 ± 18	67 ± 15	<0.001
IMT (mm)	0.83 ± 0.16	0.84 ± 0.16	0.87 ± 0.16	0.90 ± 0.18	<0.001
distensibility coefficient (10^{-3}/kPa)	13.1 ± 4.2	12.1 ± 4.4	10.8 ± 4.5	10.2 ± 4.1	<0.001
compliance coefficient (mm^2/kPa)	0.59 ± 0.23	0.56 ± 0.23	0.53 ± 0.22	0.53 ± 0.23	0.01
E_{inc} (kPa)	0.81 ± 0.31	0.90 ± 0.44	1.09 ± 0.62	1.10 ± 0.63	<0.001
BA					
diameter (mm)	4.6 ± 0.7	4.5 ± 0.7	4.7 ± 0.8	4.8 ± 0.7	0.01
distension (μm)	139 ± 66	136 ± 59	148 ± 71	150 ± 73	0.06
PP (mmHg)	61 ± 14	65 ± 15	67 ± 16	70 ± 15	<0.001
distensibility coefficient (10^{-3}/kPa)	8.0 ± 4.1	7.4 ± 3.8	7.5 ± 3.9	7.2 ± 4.2	0.06
compliance coefficient (mm^2/kPa)	0.13 ± 0.07	0.12 ± 0.06	0.13 ± 0.07	0.13 ± 0.08	0.99
flow-mediated dilation (%)	4.65 ± 4.36	3.46 ± 3.51	2.90 ± 3.85	3.08 ± 3.29	<0.01
FA					
diameter (mm)	10.3 ± 1.7	10.0 ± 1.5	9.9 ± 1.8	9.9 ± 1.7	0.03
distension (μm)	215 ± 73	209 ± 72	206 ± 77	190 ± 73	0.003
PP (mmHg)	66 ± 16	71 ± 18	71 ± 18	76 ± 17	<0.001
distensibility coefficient (10^{-3}/kPa)	5.1 ± 2.2	4.8 ± 2.0	4.8 ± 2.3	4.2 ± 2.1	<0.001
compliance coefficient (mm^2/kPa)	0.42 ± 0.21	0.38 ± 0.18	0.36 ± 0.19	0.31 ± 0.14	<0.001
Central artery stiffness					
CFTT (ms)	60 ± 15	55 ± 18	51 ± 15	50 ± 17	<0.001
augmentation index (%)	31 ± 9	33 ± 8	33 ± 8	34 ± 9	0.002
total systemic arterial compliance (SV/aortic PP; ml/mmHg)	1.13 ± 0.30	1.03 ± 0.33	1.00 ± 0.36	0.94 ± 0.33	<0.001

[a]Data are means ± SD. CFTT is shown unadjusted for height.

Table 7. Arterial stiffness indices according to quartiles of UACR: Adjusted analyses[a]

Model	CCA			BA			FA		
	β	95% CI	P	β	95% CI	P	β	95% CI	P
Distensibility coefficient									
gender/age/GTS	−0.533	−0.806 to −0.259	<0.001	−0.030	−0.302 to 0.243	0.83	−0.058	−0.199 to 0.084	0.43
2 + MAP	−0.235	−0.488 to 0.018	0.07	0.142	−0.128 to 0.412	0.30	0.053	−0.087 to 0.194	0.46
2 + eGFR	−0.317	−0.574 to −0.059	0.02	0.067	−0.209 to 0.344	0.63	0.018	−0.127 to 0.163	0.81
3 + RR	−0.296	−0.550 to −0.041	0.02	0.064	−0.211 to 0.338	0.65	0.022	−0.123 to 0.167	0.77
3 + CVD	−0.363	−0.627 to −0.099	0.01	0.052	−0.234 to 0.337	0.72	0.029	−0.121 to 0.178	0.71
Compliance coefficient									
gender/age/GTS	−0.009	−0.023 to 0.006	0.23	0.002	−0.003 to 0.006	0.47	−0.014	−0.026 to −0.002	0.02
2 + MAP	−0.004	−0.015 to 0.014	0.95	0.004	−0.001 to 0.009	0.08	−0.007	−0.019 to 0.005	0.25
2 + eGFR	−0.001	−0.016 to 0.014	0.88	0.004	−0.001 to 0.008	0.14	−0.007	−0.019 to 0.005	0.27
3 + RR	−0.001	−0.016 to 0.014	0.89	0.003	−0.001 to 0.008	0.16	−0.006	−0.019 to 0.006	0.30
3 + CVD	−0.003	−0.018 to 0.012	0.69	0.003	−0.002 to 0.008	0.18	−0.007	−0.020 to 0.006	0.28
E_{inc}									
gender/age/GTS	0.069	0.034 to 0.104	<0.001						
2 + MAP	0.034	0.001 to 0.067	0.04						
2 + eGFR	0.034	0.002 to 0.066	0.04						
3 + RR	0.033	0.001 to 0.065	0.04						
3 + CVD	0.040	0.007 to 0.073	0.02						

[a]Data are expressed as unstandardized regression coefficients β and their 95% CI. β coefficients represent the change in stiffness per quartile increase in UACR. RR, hypertension.

Table 8. Associations of UACR (in quartiles) and arterial wall properties: Adjusted analyses[a]

Model	CCA			BA			FA		
	β	95% CI	P	β	95% CI	P	β	95% CI	P
Diameter									
gender/age/GTS	0.134	0.067 to 0.199	<0.001	0.045	0.002 to 0.088	0.04	−0.085	−0.198 to 0.028	0.14
2 + MAP	0.093	0.027 to 0.156	0.004	0.033	−0.011 to 0.077	0.16	−0.097	−0.213 to 0.020	0.10
2 + eGFR	0.106	0.040 to 0.172	0.002	0.045	−0.004 to 0.090	0.05	−0.064	−0.182 to 0.055	0.29
3 + RR	0.101	0.036 to 0.166	0.002	0.043	−0.003 to 0.088	0.06	−0.064	−0.182 to 0.054	0.29
3 + CVD	0.111	0.044 to 0.178	0.001	0.049	0.003 to 0.095	0.04	−0.074	−0.194 to 0.047	0.23
PP									
gender/age/GTS	1.113	0.572 to 2.653	0.002	1.750	0.862 to 2.637	<0.001	1.444	0.278 to 2.609	0.02
2 + MAP	0.168	−0.745 to 1.060	0.71	0.355	−0.342 to 1.052	0.31	−0.331	−1.368 to 0.700	0.53
2 + eGFR	0.047	−0.873 to 0.967	0.92	0.259	−0.461 to 0.971	0.48	−0.251	−1.325 to 0.823	0.65
3 + RR	0.002	−0.916 to 0.921	0.99	0.230	−0.471 to 0.951	0.53	−0.254	−1.329 to 0.821	0.64
3 + CVD	0.108	−0.819 to 1.035	0.82	0.292	−0.426 to 1.020	0.43	−0.222	−1.299 to 0.855	0.69
Distension									
gender/age/GTS	−2.643	−9.707 to 4.421	0.46	4.488	−0.138 to 9.114	0.06	−1.252	−6.187 to 3.689	0.62
2 + MAP	−2.002	−9.174 to 5.170	0.58	4.438	−0.287 to 9.163	0.07	−1.848	−6.933 to 3.236	0.48
2 + eGFR	−4.138	−10.548 to 3.183	0.27	3.614	−1.191 to 8.419	0.14	−2.017	−7.238 to 3.204	0.45
3 + RR	−4.287	−11.670 to 3.095	0.26	3.289	−1.455 to 8.034	0.17	−2.007	−7.242 to 3.227	0.45
3 + CVD	−5.101	−12.600 to 2.398	0.18	3.345	−1.590 to 8.279	0.18	−1.883	−7.244 to 3.478	0.52
IMT									
gender/age/GTS	0.009	−0.002 to 0.020	0.11						
2 + MAP	0.006	−0.004 to 0.017	0.24						
2 + eGFR	0.008	−0.003 to 0.019	0.15						
3 + RR	0.008	−0.003 to 0.018	0.18						
3 + CVD	0.008	−0.003 to 0.019	0.17						

[a]Data are expressed as unstandardized regression coefficients β and their 95% CI. β coefficients represent the change in stiffness per quartile increase in UACR.

adjustment for BMI or waist-to-hip ratio (data not shown). Exclusion of individuals with stage 1 ($n = 9$) and stage 4 CKD ($n = 3$) did not materially change the results. Furthermore, endothelial dysfunction is known to be related to arterial stiffness and to mortality in renal insufficiency (29,30); therefore, analyses were also adjusted for flow-mediated endothelium-dependent vasodilation of the BA. Also these adjustments did not materially change the results. Interaction analyses showed

Table 9. Associations of UACR (in quartiles) and measures of central arterial stiffness: Adjusted analyses[a]

Model	β	95% CI	P
CFTT			
gender/age/GTS	−2.619	−4.205 to −1.034	0.001
2 + MAP	−1.669	−3.242 to −0.096	0.04
2 + eGFR	−1.550	−3.157 to 0.057	0.06
3 + RR	−1.502	−3.103 to 0.099	0.07
3 + CVD	−1.297	−2.939 to 0.340	0.12
aAIX			
gender/age/GTS	0.531	−0.065 to 1.127	0.08
2 + MAP	0.239	−0.345 to 0.823	0.42
2 + eGFR	0.242	−0.358 to 0.843	0.43
3 + RR	0.245	−0.356 to 0.846	0.42
3 + CVD	0.194	−0.413 to 0.801	0.53
SAC SV/PP			
gender/age/GTS	−0.032	−0.053 to −0.012	0.002
2 + MAP	−0.012	−0.031 to 0.007	0.22
2 + eGFR	−0.010	−0.030 to 0.010	0.34
3 + RR	−0.009	−0.029 to 0.010	0.35
3 + CVD	−0.011	−0.032 to 0.009	0.28

[a]Data are unstandardized regression coefficients β and their 95% CI. β coefficients represent the change in stiffness per quartile increase in UACR. aAIX, aortic augmentation index; SAC SV/PP, systemic arterial compliance estimated from stroke volume/pulse pressure; CFTT is adjusted for height.

that the association between eGFR and UAE with arterial stiffness was not substantially influenced by the presence of diabetes.

Discussion

This population-based study had four main findings. First, in mild renal insufficiency (stages 2 to 3 CKD), a lower eGFR as estimated by the MDRD formula was associated with greater arterial stiffness. Second, a greater UAE, even below levels that are considered to indicate microalbuminuria, was associated with greater arterial stiffness. Third, lower eGFR and greater UAE were mutually independently associated with a greater arterial stiffness, suggesting that the mechanisms that link these variables to risk for CVD are at least in part independent of each other. Fourth, in contrast to a greater UAE, eGFR was not related to greater central arterial stiffness.

Our results with respect to the association of eGFR with arterial stiffness are partially in line with previous studies. Konings *et al.* (31) showed, in a small study, that the distensibility coefficient of the CCA was lower in patients with stages 2 to 4 CKD compared with control subjects. In contrast to our study, Mourad *et al.* (32) showed, in a population with mild renal insufficiency, a negative association between creatinine clearance and carotid-femoral PWV. Wang *et al.* (33) recently showed a greater aortic PWV in patients with stages 1 to 5 CKD. We, in agreement with a recently published study by Briet *et al.* (34), did not find an association of CFTT, an approximation of the PWV, with eGFR. Also in agreement with that study was our finding of an independent, negative relationship between eGFR and carotid E_{inc}.

In general, with declining renal function, the distensibility of the arteries decreased, whereas the compliance coefficient remained largely unchanged. To a large extent, this phenomenon was explained by a greater arterial diameter in individuals with lower eGFR, which, for the BA and FA, was independent of MAP. It is not clear why there was no relation between eGFR and CCA diameter. In fact, Briet *et al.* (34) recently found an inverse relation between GFR and CCA internal diameter. The discrepancy with our results may be related to selective mortality in the Hoorn Study, because we previously showed that both a greater CCA diameter (35) and a lower eGFR (3,29) are related to increased mortality. A greater CCA diameter is thought to reflect so-called outward remodeling (36) and may be a defense mechanism to prevent loss of buffering capacity in case of a decrease in distensibility. The causes of a decrease in distensibility in mild renal insufficiency remain largely unclear. In animal models, renal insufficiency is associated with an accumulation of collagen instead of elastin in the aortic wall (37), and collagen represents the more rigid component of the arterial wall (10). Changes in water and salt balance (38), leading to renin-angiotensin-aldosterone system activation, may stimulate the collagen accumulation (39). Also other factors such as the accumulation of advanced glycosylation end products; the accumulation of asymmetric dimethylarginine, an endogenous inhibitor of nitric oxide synthesis; and oxidative stress may negatively influence the distensibility of the arterial wall (40,41).

We showed that greater UAE, even in a low-grade albuminuric range, was associated with a greater diameter and E_{inc} of the CCA and a lower CFTT. In patients with type 1 diabetes, several authors have shown an association between microalbuminuria and greater CCA stiffness (42,43). Recently, Yokohama *et al.* (44) found in patients with type 2 diabetes that albuminuria was independently associated with carotid IMT. This was in line with the finding of Keech *et al.* (45), who showed in patients with type 2 diabetes that a greater UAE in the low-albuminuric range was independently associated with greater carotid IMT. However, in agreement with Kramer *et al.* (46), we did not find an association, either in the group as a whole or in the individuals with diabetes ($n = 318$) separately (data not shown). Our finding of an association between arterial stiffness and albumin excretion below the current microalbuminuria level is in agreement with studies that showed that the association between UAE and CVD starts at levels below microalbuminuria (7,47). Endothelial dysfunction and low-grade inflammation may be important mechanisms that link UAE with arterial stiffness and CVD (29,30), but it remains to be shown whether the association of UAE and arterial stiffness actually explains that between UAE and CVD.

The third major finding of our study was the mutual independence of the associations of eGFR and albuminuria with arterial stiffness. This suggests that both a decline in GFR and albuminuria, although they might share determinants such as

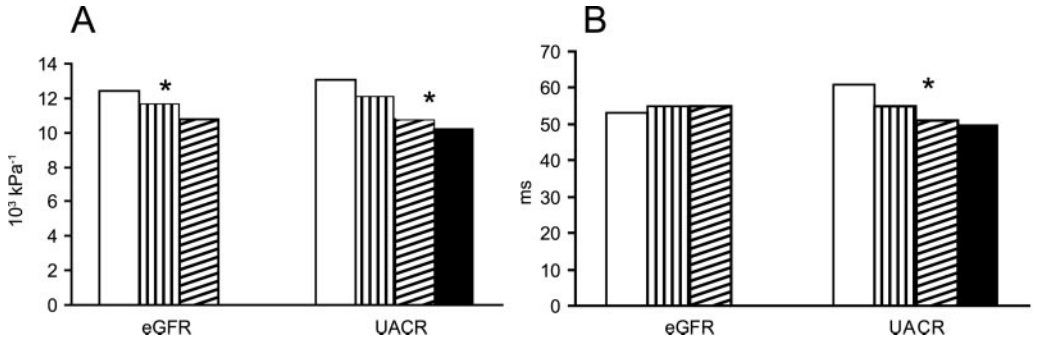

Figure 1. Means of distensibility coefficient of carotid artery (10^3/kPa; A) and carotid-femoral transit time (ms; B) according to estimated GFR (eGFR; in tertiles) and urinary albumin creatinine ratio (UACR; in quartiles). *$P < 0.05$ for trend.

hypertension and diabetes, could be independently associated with CVD in patients with CKD. Indeed, we recently showed that the association of eGFR with cardiovascular mortality is mostly independent of UAE (29).

A final finding of our study was that eGFR and UAE differed in their association with central arterial stiffness. Whereas both a lower eGFR and greater albuminuria were associated with a decrease in peripheral arterial stiffness, only greater albuminuria was associated with a lower CFTT (Figure 1). As stated in the foregoing, in individuals with mild to moderate renal insufficiency, conflicting results exist regarding the relation of eGFR with carotid-femoral PWV (32–34). In agreement with our results, in patients with type 2 diabetes (48) and in hypertensive patients (49), microalbuminuria has been associated with a greater carotid-femoral PWV. Again, one of the links between UAE and central arterial stiffness could be endothelial dysfunction and low-grade inflammation (50). However, also after adjustment for BA endothelial flow-mediated dilation, the associations between UAE and PWV remained largely unchanged. It is not clear why this relation is not seen between eGFR and central arterial stiffness.

The potential clinical impact of our findings can be appreciated from the following comparisons. The aortic PWV is an independent predictor of cardiovascular morbidity and mortality, and all-cause mortality (27). The change in CFTT (%), an approximation of the PWV, per quartile of UACR was approximately 3%, which was associated with an increase of CVD risk of 18% in the Rotterdam Study (51) and an increase of all-cause mortality risk of 3% (52). Although only aortic and carotid stiffness have shown to be of predictive value for CVD in CKD populations (27), data on FA stiffness are also of potential clinical importance. At least in patients with type 2 diabetes, FA stiffness is a predictor of peripheral vascular disease (53,54). To the best of our knowledge, no data exist on the relation between FA stiffness and peripheral vascular disease in patients with CKD.

This study had several limitations. First, the study population was relatively old. This might have caused underestimation of the relation between eGFR or UAE and arterial stiffness. A "healthy survivor effect" may also have weakened the associations of eGFR or UAE with IMT. Second, our data were cross-sectional and do not provide insight into the mechanisms that are responsible for the observed associations. Third, we studied a white population, and it remains to be established whether the results can be generalized to other ethnicities.

Conclusion

In this population-based study, we showed that stages 2 to 3 CKD was associated with peripheral but not central arterial stiffness. We also showed that UAE, even below levels that conventionally are considered to define microalbuminuria, was associated with greater CCA stiffness and a decrease in CFTT. This finding questions the current arbitrary cutoff point for microalbuminuria. Furthermore, our findings suggest that in patients with CKD, both GFR and albuminuria should be interpreted as independent risk factors for CVD.

Our data underscore the importance of adequate treatment of patients with mild renal impairment with or without albuminuria. At present, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers may have the best data on preventing a decline in renal function (55) and diminishing albuminuria (56). Most recently, in a hypertensive population, the combination of a calcium antagonist and an angiotensin-converting enzyme inhibitor resulted in a greater lowering of central aortic pressure and a better cardiovascular outcome compared with a strategy that consisted of a β blocker plus a diuretic (57). Most important, however, is a greater awareness of the importance of mild renal impairment and albuminuria for cardiovascular risk.

Disclosures

None.

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