Urinary albumin excretion, even within the normal range, predicts an increase in left ventricular mass over the following 5 years

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There is increasing evidence that urinary albumin excretion, even when below the accepted threshold values for normal excretion, may have significant impact on future cardiovascular risks. To further define this, a total of 1086 patients, aged 45 years and older from the population-based, longitudinal 'Study of Health in Pomerania' were evaluated. Patients had echocardiographic analysis at baseline and 5-year follow-up, and were grouped into quartiles according to their baseline urinary albumin-to-creatinine ratio. At baseline, left ventricular mass in the first three quartiles was similar; however, the fourth quartile was significantly elevated and further increased over the 5-year follow-up. In the first quartile, the albumin-to-creatinine ratio and left ventricular mass did not significantly change over 5 years. In the second and third quartiles, the left ventricular mass progressively increased and was significantly correlated with the albumin-to-creatinine ratio. In multivariable analysis, this association was independent of other common cardiovascular risk factors and applicable to both genders. Our study found that the urinary albumin-to-creatinine ratio, even below the current threshold for definition of microalbuminuria, is significantly associated with increased left ventricular mass.

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The development of left ventricular hypertrophy (LVH) is significantly associated with the occurrence of adverse cardiovascular events, such as myocardial infarction, heart failure, stroke, and also cardiovascular mortality.[1–4] Recently, various risk factors for LVH apart from arterial hypertension were identified on the basis of population-based studies and investigational trials: among others age, gender, renal function, hematocrit, and thyroid hormone status were significantly associated with left ventricular mass (LVM) in several investigations.[5–8] However, when considering principles of preventive medicine, it seems to be of outstanding relevance to identify parameters, associated with further increase of LVM over time in a longitudinal study design, as these variables may become a valuable basis on which preventive measures or intensified treatment could be initiated.[9]

Micro- and macroalbuminuria have long been recognized as important prognostic factors both in individuals with and without diabetes mellitus.[10–12] There is increasing evidence that urinary albumin excretion below currently accepted threshold values for the definition of microalbuminuria ($\geqslant$2.5 mg urinary albumin/mmol creatinine for men and $\geqslant$3.5 mg/mmol for women[13]) has also significant prognostic impact with respect to several cardiovascular risk factors.[10,14,15] In the Heart Outcomes Prevention Evaluation Study (HOPE), for example, rates of cardiovascular events and mortality increased steadily with every quartile of the urinary albumin-to-creatinine ratio (ACR).[10] Interestingly, in the first three quartiles, ACR values were far below the definition of microalbuminuria; nonetheless, the prognostic impact of ACR within these quartiles was striking. Furthermore, most of the studies, investigating the impact of urinary albumin excretion, demonstrated associations independent of common cardiovascular risk factors, which highlights albuminuria as a potential useful parameter in preventive cardiovascular medicine.[10,12,14,16]

As microalbuminuria is regarded as a sensitive indicator of a generalized vascular process with different consequences in various organs, we sought to investigate whether urinary albumin excretion is associated with the development of

LVM over time. We used data from subjects aged 45 years and older of the population-based 'Study of Health in Pomerania' (SHIP) that provides a comprehensive set of echocardiographic investigations at baseline and at follow-up after 5 years in combination with sociodemographic, medical and laboratory parameters.[17]

RESULTS

Association of clinical characteristics, cardiovascular risk factors and drug therapy at baseline and at 5-year follow-up with urinary ACR

Age was significantly higher in ACR quartile IV, but similar in the first three quartiles (Tables 1 and 2). Women tended to have slightly higher urinary ACR than men (median: 0.90 mg/mmol; female 0.99 mg/mmol; male: 0.80 mg/mmol), which is reflected by the lower percentage of males in the two quartiles with higher ACR. Quartile IV (ACR > 1.804 mg/mmol) differed significantly from quartile I with respect to several cardiovascular risk factors at baseline: apart from being older, subjects in this quartile were characterized by a higher prevalence of hypertension and diabetes mellitus. Accordingly, blood pressure (BP) values, frequency of antihypertensive medication, and body mass index (BMI) and glycated hemoglobin levels were also significantly higher. No significant differences were found between quartile I and II, whereas quartile III showed slightly higher BP values compared with quartile I and II. It is interesting that renal function at baseline was similar in the four quartiles; only after five years estimated glomerular filtration rate was significantly lower in quartile IV. Non-parametric correlation analysis (Spearman) revealed a significant positive correlation between urinary ACR and systolic ($r = 0.220$, $P < 0.001$), diastolic BP ($r = 0.104$, $P < 0.001$), pulse pressure ($r = 0.239$, $P < 0.001$), glycated hemoglobin ($r = 0.105$, $P < 0.001$) and BMI ($r = 0.129$, $P < 0.001$) at baseline, but not with estimates of renal function and cholesterol levels. Antihypertensive treatment was similar in frequency in quartile I and II, but higher in quartile IV.

Echocardiographic variables at baseline and after 5 years in relation to the urinary ACR

At baseline, parameters of LVM assessed by echocardiography were very similar in the three lowest quartiles of urinary ACR (Figure 1). However, individuals in the highest ACR quartiles (> 1.804 mg/mmol) were characterized by significantly higher LVM and LVM indices at baseline (Table 3). For the entire population, LVM increased from 187.6 ± 1.7 g at baseline to 197.6 ± 1.8 g over 5 years (females ($n = 590$): 164.2 ± 1.8 to 174.7 ± 2.1 g; males ($n = 496$): 215.5 ± 2.5 g at baseline to 224.9 ± 2.6 g after 5 years) with a mean intra-individual

Table 1 | Clinical characteristics, laboratory parameters and drug therapy at baseline in relation to urinary albumin-to-creatinine ratio at baseline

	Urinary albumin-to-creatinine ratio (mg/mmol) at baseline (quartiles)				Statistics (ANOVA or χ^2 test between quartiles)	Entire population
Baseline	I 0–0.532 (n=272)	II >0.532–0.902 (n=271)	III >0.902–1.804 (n=272)	IV >1.804 (n=271)	P-value	(n=1086)
Age (years)	57.8 ± 0.5$^{(IV)}$	58.0 ± 0.5	59.7 ± 0.5	62.3 ± 0.6$^{(I, II, III)}$	0.001	59.4 ± 0.3
Sex (%, male)	49.6	50.2	40.4	42.4	0.044	45.7
Arterial hypertension (%)	53.3	56.8	66.2	81.2	0.001	64.4
Diabetes mellitus (%)	7.0	5.2	11.4	15.9	0.001	9.9
Cigarette smoker (%)	22.4	17.4	21.3	17.4	n.s.	19.6
Previous MI (%)	3.7	4.8	3.3	4.8	n.s.	4.2
Systolic BP (mm Hg)	137.6 ± 1.2$^{(III, IV)}$	138.4 ± 1.1$^{(IV)}$	142.4 ± 1.2$^{(I, IV)}$	151.0 ± 1.4$^{(I, II, III)}$	0.001	142.4 ± 0.6
Diastolic BP (mm Hg)	84.8 ± 0.7$^{(IV)}$	85.0 ± 0.6$^{(IV)}$	86.0 ± 0.7$^{(IV)}$	88.5 ± 0.7$^{(I, II, III)}$	0.001	86.1 ± 0.3
Pulse pressure (mm Hg)	52.8 ± 0.9$^{(III, IV)}$	53.4 ± 0.8$^{(IV)}$	56.4 ± 0.9$^{(I, IV)}$	62.5 ± 1.0$^{(I, II, III)}$	0.001	56.3 ± 0.5
LDL cholesterol (mmol/l)	3.88 ± 0.07	3.92 ± 0.07	3.74 ± 0.06	3.87 ± 0.08	n.s.	3.85 ± 0.04
HB A1c (%)	5.51 ± 0.05$^{(IV)}$	5.53 ± 0.05$^{(IV)}$	5.61 ± 0.06$^{(IV)}$	5.91 ± 0.08$^{(I, II, III)}$	0.001	5.64 ± 0.03
BMI (kg/m^2)	27.3 ± 0.3$^{(IV)}$	27.7 ± 0.2	28.1 ± 0.3	28.6 ± 0.3$^{(I)}$	0.004	27.9 ± 0.1
CCl (ml/min per 1.73 m^2)	78.3 ± 0.9	80.1 ± 0.9	78.9 ± 1.0	76.3 ± 1.1	n.s.	78.4 ± 0.5
$eGFR_{MDRD}$ (ml/min per 1.73m^2)	74.5 ± 0.8	76.1 ± 0.8	74.8 ± 0.7	73.5 ± 0.8	n.s.	74.7 ± 0.4
Antihypertensive drugs (%)	32.7	32.1	40.1	55.7	0.001	40.1
Diuretics (%)	9.6	5.5	11.4	16.2	0.001	10.7
β-Blocker (%)	18.0	18.5	19.1	23.6	n.s.	19.8
Calcium antagonist (%)	9.9	9.2	13.6	26.2	0.001	14.7
ACE-inhibitor (%)	13.6	11.1	16.9	28.4	0.001	17.4
Angiotensin-II-antagonist (%)	0.4	3.3	2.9	3.0	n.s.	2.4

Abbreviations: ACE, angiotensin converting enzyme; ANOVA, analysis of variance; BMI, body mass index; BP, blood pressure; CCl, estimated creatinine clearance (Cockcroft Gault); $eGFR_{MDRD}$ estimated glomerular filtration rate (MDRD-formula); HB A1c, glycated hemoglobin; LDL, low density lipoprotein; MI, myocardial infarction; n.s., not significant.

Mean ± s.e.m. for continuous variables, % for frequency data. Statistics: P-value for χ^2 test (numerical data) or one-way-ANOVA (continuous data) with Tukey's *post hoc* test for comparisons between quartiles (groups with significant differences according to Tukey's *post hoc* testing in superscript roman).