Albuminuria changes are associated with subsequent risk of end-stage renal disease and mortality

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Current guidelines for chronic kidney disease (CKD) recommend using albuminuria as well as estimated glomerular filtration rate (eGFR) to stage CKD. However, CKD progression is solely defined by change in eGFR with little regard to the risk implications of change in albuminuria. This is an observational study from the Stockholm CREAtinine Measurements (SCREAM) project, a health care utilization cohort from Stockholm, Sweden, with laboratory measures from 2006–2011 and follow-up through December 2012. Included were 31,732 individuals with two or more ambulatory urine albumin to creatinine ratio (ACR) tests. We assessed the association between change in ACR during a baseline period of 1, 2, or 3 years and end-stage renal disease (ESRD) or death. Using a 2-year baseline period, there were 378 ESRD events and 1712 deaths during a median of 3 years of follow-up. Compared to stable ACR, a 4-fold increase in ACR was associated with a 3.08-times (95% confidence interval 2.59 to 3.67) higher risk of ESRD while a 4-fold decrease in ACR was associated with a 0.34-times (0.26 to 0.45) lower risk of ESRD. Similar associations were found in people with and without diabetes mellitus, with and without hypertension, and also when adjusted for the change in eGFR during the same period. The association between change in ACR and mortality was weaker: ACR increase was associated with mortality, but the relationship was largely flat for ACR decline. Results were consistent for 1-, 2-, and 3-year ACR changes. Thus, changes in albuminuria are strongly and consistently associated with the risk of ESRD and death.

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Chronic kidney disease (CKD) is a significant global public health problem with poor prognosis and elevated health care costs.[1] Recent clinical guidelines on CKD incorporate albuminuria and the estimated glomerular filtration rate (eGFR) to define and stage CKD.[2–4] However, guidelines define CKD progression solely by eGFR changes and disagree with regard to the usefulness and/or frequency of albuminuria monitoring.[5–7] The progression of CKD is often slow, and there are few specific symptoms until the disease is very advanced. Changes in albuminuria may serve as early indicators of CKD progression and complications beyond eGFR, but the risk implications of these changes are not well documented, with existing studies predominantly limited to subjects with diabetic kidney disease.[8,9]

There is increased interest in the surrogate endpoints of CKD progression for the testing of new treatments in patients with CKD because the clinically meaningful event of end-stage renal disease (ESRD) requires large and lengthy trials to assess drug efficacy. A 30% decline in eGFR has been proposed as an acceptable surrogate of CKD progression in some circumstances.[10,11] Changes in albuminuria may also be considered a potential surrogate endpoint, with the advantage that they often occur earlier in the disease course than eGFR decline. Recent meta-analyses of randomized controlled trials (RCTs) attempted to validate the usefulness of short-term albuminuria changes to predict the incidence of ESRD.[12–14] Collectively, they concluded that placebo-adjusted treatment effects on albuminuria correlated well with the treatment effect on ESRD endpoints. However, they also acknowledged the limitation that the duration of these trials was relatively short (maximum 24-month intervention), and

that they included a selected population of mainly diabetic and hypertensive patients. Definitive conclusions have not been reached, and recent debate has highlighted the significant controversy.[15–18]

Observational studies in large representative health care usefulness cohorts can fill some of these knowledge gaps, with the possibility of modeling longer time frames for albuminuria change, testing its predictive accuracy in real-life heterogeneous populations, and contributing to provide clinical guidance as to how to interpret albuminuria changes at the bedside in the face of substantial biologic variability. Against this background, the objective of this study was to analyze the prognostic nature of albuminuria changes with regard to the subsequent risk of ESRD and mortality in a real-life health care setting.

RESULTS

Participant selection and baseline characteristics

There were 88,055 individuals aged 18 years or older who underwent urine albuminuria testing in Stockholm from 2006 to 2011, with 202,598 albumin-to-creatinine ratio (ACR) tests performed. Of those individuals, there were 39,864 who had ≥2 ACR tests. We then imposed the requirement that ≥2 ACR tests must have been performed in the outpatient setting, which excluded 1541 individuals. Of the 38,323 individuals with ≥2 outpatient ACR tests, 6533 individuals had urine ACR changes that did not fit the prespecified baseline periods; thus, our analyses were finally based on 31,732 individuals. Depending on the baseline period considered, different numbers of individuals were eligible (Supplementary Figure S1).

Table 1 describes the baseline characteristics of 19,897 participants with data on 2-year ACR changes. Mean age was 59 years (range:18–96), 41% were women, 61% had diabetes mellitus, and 69% had a history of hypertension. Sixteen percent had a history of cardiovascular disease (CVD). The baseline average eGFR was 81 ± 30 ml/min per 1.73 m^2, and the baseline median ACR was 1.9 mg/mmol (interquartile range: 0.8–8.5) (16 mg/g; interquartile range: 7–5). When stratified by change in ACR, individuals with increases in ACR tended to be older, and had more comorbid conditions and a somewhat lower baseline eGFR than individuals with decreases in ACR. Similar patient characteristics were observed for the 1- and 3-year baseline periods (Supplementary Tables S1 and S2).

When stratified by the presence of diabetes mellitus, diabetic patients were older, more often men, and more often had a history of hypertension or CVD compared with nondiabetic patients. Baseline eGFR was slightly higher and median ACR slightly lower among diabetic patients compared with nondiabetic patients (Supplementary Table S3).

During a median follow up of 3.0 years, 378 (2%) individuals developed ESRD, and 1712 (9%) died (Table 2). Of the 1712 deaths, 672 were attributed to cardiovascular causes. Death and ESRD events were more common in patient groups with increases in ACR and more common in individuals with a higher baseline ACR. The same pattern was observed for the 1- and 3-year baseline periods (Supplementary Tables S4 and S5).

ESRD risk according to fold-change in the ACR

ACR fold-change followed a normal distribution for each baseline period, with increases in ACR being slightly more

Table 1 | Baseline characteristics of individuals eligible for 2-year albumin-to-creatinine ratio (ACR) changes, further stratified by prespecified ACR-fold changes

	Overall	4+ fold decrease	2-4 fold decrease	Stable	2-4 fold increase	4+ fold increase
No.	19,897	1977	2511	10,568	2817	2024
Age (yr), mean ± SD	59 ± 18	56 ± 20	59 ± 18	59 ± 18	60 ± 18	60 ± 19
Women, n (%)	8105 (41)	912 (46)	1044 (42)	4063 (38%)	1160 (41)	926 (46)
Diabetes mellitus, n (%)	12,090 (61v)	1015 (51)	1512 (60)	6511 (62)	1791 (64)	1261 (62)
Hypertension, n (%)	13,671 (69)	1363 (69)	1699 (68)	7146 (68)	1992 (71)	1471 (73)
Cardiovascular disease, n (%)	3191 (16)	307 (16)	375 (15)	1623 (15)	481 (17)	405 (20)
Total cholesterol (mmol/l), mean ± SD	4.9 ± 1.1	5.2 ± 1.3	5.0 ± 1.2	4.9 ± 1.1	4.9 ± 1.1	4.9 ± 1.1
eGFR (ml/min per 1.73 m^2), mean ± SD	81 ± 30	82 ± 35	82 ± 29	82 ± 28	80 ± 29	77 ± 35
ACR (mg/mmol), median (IQR)	1.9 (0.8–8.5)	11 (3–45)	3 (1–14)	2 (1–6)	1 (1–5)	1 (1–4)
ACR (mg/g), median (IQR)	16 (7–75)	97 (27–398)	27 (9–124)	13 (6–57)	9 (9–44)	9 (9–35)
No. of ACR tests, median (IQR)	3.0 (2.0–4.0)	3.0 (2.0–5.0)	3.0 (2.0–4.0)	3.0 (2.0–4.0)	3.0 (2.0–4.0)	3.0 (2.0–4.0)
ACR <30 mg/g, n (%)	12,171 (61)	495 (25)	1279 (51)	6949 (66)	1977 (70)	1471 (73)
ACR 30–299 mg/g, n (%)	5495 (28)	916 (46)	879 (35)	2571 (24)	667 (24)	462 (23)
ACR 300+ mg/g, n (%)	2231 (11)	566 (29)	353 (14)	1048 (10)	173 (6)	91 (4)
ACR fold-change, median (IQR)	1.0 (0.5–2.0)	0.14 (0.08–0.20)	0.38 (0.32–0.44)	1.01 (0.75–1.41)	2.63 (2.28–3.14)	6.95 (5.00–12.62)
Median ACR (IQR) across ACR categories						
ACR < 30 mg/g	8 (4–14)	16 (10–22)	12 (8–18)	8 (4–13)	7 (4–12)	7 (4–12)
ACR 30–299 mg/g	74 (45–132)	90 (51–147)	75 (43–141)	72 (45–128)	69 (43–119)	69 (42–122)
ACR 300+ mg/g	806 (482–1639)	880 (492–2092)	911 (518–1872)	839 (491–1627)	613 (412–1008)	558 (404–832)

ESRD, end-stage renal disease; IQR, interquartile range.