Association of uric acid in serum and urine with subclinical renal damage: Hanzhong Adolescent Hypertension Study

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Abstract

Background and objectives
The aim of the study was to examine the associations of uric acid (UA) in blood and urine with subclinical renal damage (SRD) and its progression in a Chinese cohort.

Methods
1) 2342 participants from our previously established cohort who were followed up in 2017 were included. Cross-sectional analysis was used to examine the relationships between serum and urinary UA and the risk of SRD. 2) A total of 266 participants were recruited from the same cohort in 2013, and followed up in 2017. Longitudinal analysis was used to determine the relationships of serum and urinary UA with progression of SRD, which was defined as urinary albumin-to-creatinine ratio (uACR) progression or estimated glomerular filtration rate (eGFR) decline.

Results
In cross-sectional analysis, higher levels of uACR were associated with higher levels of serum uric acid (SUA) and urinary uric acid/creatinine ratio (uUA/Cre). Lower eGFR was associated with higher levels of SUA and fractional excretion of uric acid (FEUA) but lower uUA/Cre levels in all subjects. In addition, the multivariate-adjusted odds ratios for SRD compared with non-SRD were 3.574 (2.255–5.664) for uUA/Cre. Increasing uUA/Cre levels were associated with higher risk of SRD. In longitudinal analysis, 4-year changes of uUA/Cre and SUA were significantly associated with eGFR decline.
Conclusions
This study suggested that urinary UA excretion was significantly associated with the risk of SRD in Chinese adults. Furthermore, 4-year changes of serum and urinary UA were associated with SRD progression. These findings suggest that UA, especially urinary UA, may be used as a simple, noninvasive marker for early detection of decreased renal function in otherwise healthy subjects.

Introduction
Chronic kidney disease (CKD) has become a major public health issue because of the global prevalence and the associated increase in the incidence of cardiovascular disease and premature death [1,2]. Studies have reported that the prevalence of CKD among adults is 13.0% in United States and 10.8% in China [3,4]. Subjects with early-stage CKD always have no symptoms, and the majority in the early stage of CKD remains undiagnosed even in developed countries [1]. In addition, CKD, from the earliest stages, is associated with a high risk of cardiovascular events [2]. Therefore, identifying the markers of early renal damage and risk factors associated with its progression are useful for establishing effective therapeutic strategies to prevent the onset and progression of end-stage renal disease and the accompanying cardiovascular complications.

Uric acid (UA) is the final oxidation product of purine catabolism in humans [5,6]. For decades, it has been hypothesized that the antioxidant properties of UA might be protective against oxidative stress, oxidative cell injury and ageing [7]. However, recent clinical and cohort studies suggest that hyperuricaemia is a risk factor for cardiovascular events and renal disease [8,9]. An elevated albuminuria and impaired glomerular filtration rate (GFR) are important indicators for grading the severity of renal damage and predicting long-term prognosis. Several studies have shown the relationships of serum uric acid (SUA) with albuminuria and decreased GFR, which has been observed in subjects with diabetes mellitus, hypertension and heart failure [8,10–12]. Recently, few studies have indicated that hyperuricaemia is associated with subclinical renal damage (SRD), defined as slightly increased albuminuria or decreased estimated GFR (eGFR), in hypertensive patients [13,14]. However, such an association is still unclear in the general population, especially for people who are non-hypertensive and non-diabetic.

Although multiple studies have shown that hyperuricaemia is common in CKD patients [8,15,16], the association between urinary UA excretion and target organ damage is rarely studied. UA homeostasis is under tight regulation, with the kidney assuming a pivotal role. Approximately two-thirds of UA in blood is easily filtered by glomeruli into the renal tubule [17]. Nearly 90% of filtered UA is reabsorbed by the S1 segment of the proximal convoluted tubule, and the remaining 10% of them is finally excreted into urine [17]. Previous studies showed that elevated urinary UA was a suspected risk factor for calcium oxalate kidney stones in subjects with calcium nephrolithiasis [18,19]. Recently, studies indicate that the urinary UA can be used as a simple, noninvasive parameter of the severity of disease and mortality. For instance, urinary uric acid/creatinine ratio (uUA/Cre) has found to be remarkably higher in hypoxic premature infants or in neonates with birth asphyxia, and this ratio was correlated significantly with the clinical severity of the disease [20–22]. However, the relationship between urinary UA and early renal damage has not been published previously. In addition, there is virtually no data on urinary UA in relation with the progression of SRD.
In the present study, we therefore conducted cross-sectional analysis based on our previously established cohort to investigate the relationships of UA in blood and urine with SRD. Furthermore, in the longitudinal analysis, we also aimed to determine the relationship between UA and the progression of SRD, which was defined as uACR progression or eGFR decline during 4-year follow-up.  

**Materials and methods**  

**Study cohort**  

The study population was derived from the Hanzhong Adolescent Hypertension Study, which was established in 1987. This ongoing prospective, population-based cohort study of 4623 adolescents who regularly undergo several follow-ups for investigating the development of cardiovascular risk factors originating from children and young adults (S1 Fig). Details of the study protocol have been published elsewhere [23,24].  

**This study was divided into two sections.**  

1. In order to explore the associations of UA in blood and urine with SRD, we used cross-sectional analysis of data from the large cohort that was followed up in 2017. The participant selection process is described in Fig 1. Participants were excluded if they had missing data on serum or urinary biochemistry (N = 17 and 388, respectively), blood pressure (N = 28),
height and weight (N = 1) and if they had a self-identified history of coronary heart disease, renal failure or stroke (N = 4), leaving 2342 subjects for our primary analyses. The outcome variable was the risk of SRD, and the potential exposure variables for clinical outcome were the increased levels of SUA and urinary UA excretions in the cross-sectional analysis.

2. To further examine the relationships of changes in serum and urinary UA with SRD progression, a 4-year longitudinal analysis was also conducted in this study. We used data from a small cohort of 338 subjects that was created based on the large cohort in 2005. The detailed study design and procedures have been published previously [25,26]. We followed up with this small cohort in 2013 and 2017. For the current analysis, we did not measure the serum and urinary levels of UA and creatinine in 2005, so the small cohort that was followed up in 2013 was considered the baseline for investigating the association of changes in serum and urinary UA with the progression of SRD (2013–2017). Participants who were lost to follow-up in 2017 (N = 70) and those with missing data on anthropometry and blood pressure (N = 2) were excluded. The remaining 266 subjects were included in the analysis. No significant difference was observed when these subjects were excluded from the cohort (S1 Table). The potential exposure variables were 4-year change in serum and urinary UA, and the outcome variables was the progression of SRD, which was defined as the uACR progression or eGFR decline.

Written informed consent was obtained from each subject, and the study protocol was approved by the Ethics Committee of the First Affiliated Hospital of Xi’an Jiaotong University (code: 2015–128). This study was performed in accordance with the Declaration of Helsinki (2008). (ClinicalTrials.gov. registration number: NCT02734472).

**Anthropometric measurements**

Participants completed standardized questionnaires that inquired about past medical history, current medications, alcohol and tobacco use, family history and physical activity. Body weight and height were measured. Body mass index (BMI) was calculated as weight (kg) divided by height (m²). Blood pressure (BP) was measured in the sitting position using a standard mercury sphygmomanometer as previously described [23,24,27,28]. Hypertension was defined as a systolic BP of ≥ 140 mm Hg, a diastolic BP ≥ 90 mm Hg or as the use of antihypertensive drugs according to subjects’ clinical data or self-report.

**Blood biochemical analyses**

Venous blood samples were obtained, immediately centrifuged, and then stored at –80 °C until analysis. Standardized measurements for lipid profile [triglycerides, total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL)], serum uric acid (SUA), serum creatinine, alanine aminotransferase (ALT), aspartate transaminase (AST) and fasting glucose were measured by an automatic biochemical analyser (model 7600; Hitachi, Ltd., Tokyo, Japan). Hyperuricemia was defined as SUA level of ≥ 420μmol/L in men or ≥ 360μmol/L in women. eGFR was calculated using the formula adapted from the Modification of Diet in Renal Disease equation on the basis of data from Chinese subjects with CKD [23,24,29].

**Urinary biochemical testing**

The first-void and mid-stream urine was collected, followed by venous blood sampling. Urinary levels of creatinine, albumin and UA were measured by an automatic biochemical
analyser (Hitachi, Ltd., Japan). Details of these assays were described previously [23,27,28]. The urinary albumin-to-creatinine ratio (uACR) was calculated by dividing urinary albumin in mg by urinary creatinine in mmol (mg/mmol). UA is transported in the proximal tubule by secretory and reabsorbing transporters, and its handling is a useful marker of proximal tubular function [30,31]. Fractional excretion of uric acid (FEUA) quantifies the percent of filtered UA that is excreted into urine. FEUA was calculated from the standard formula: (urinary uric acid) × (serum creatinine) / (urine creatinine) × (serum uric acid) × 100, expressed as percentage. The presence of subclinical renal damage (SRD) was defined as an uACR of ≥ 3.5 mg/mmol in women and 2.5 mg/mmol in men or an eGFR between 30 and 60 ml/min/1.73 m², as previously reported [14,24,32].

Statistical analysis

Data are expressed as the means ± standard deviations for normally distributed values, as geometric mean (interquartile range) for non-normally distributed values, and as percentages. The differences between the groups were calculated using the χ²-test, Student’s t-test and Mann–Whitney test as appropriate. Analysis of variance (ANOVA) was used to test the linearity across quintiles. We first performed linear and logistic regression analyses to test associations of SRD with UA in serum and urine (cross-sectional analyses). The dependent variables were the risk of SRD while the potential confounders were age, gender, hypertension, diabetes, BMI, total cholesterol and triglycerides. We next performed linear regression analyses to investigate relationships of changes in serum and urinary UA with SRD progression (longitudinal analyses). uACR progression or eGFR decline was used as dependent variable, and 4-year changes of serum and urinary UA were also used as covariates in the models. All variables were checked for multicollinearity before multivariate analysis, and the variables with multicollinearity were excluded. All statistical analyses were conducted using SPSS 16.0 (SPSS, Inc., Chicago, IL). Statistical significance is set as a 2-sided P value of < 0.05.

Results

Characteristics of participants in a cross-sectional study

Table 1 presents the characteristics of subjects according to the quartiles of uUA/Cre levels. Participants with higher UA excretions tended to have higher HDL, eGFR, FEUA and uACR levels but lower SUA, ALT, AST, LDL, serum creatinine, and a lower prevalence of hyperuricemia, smoking and alcohol use.

Associations of serum and urinary UA levels with uACR and eGFR

uACR levels were positively correlated with sex, the prevalence of hypertension and diabetes, total cholesterol, SUA (β = 0.093, P < 0.001), and uUA/Cre (β = 0.042, P = 0.041) but inversely correlated with age. In addition, eGFR was negatively related to age, total cholesterol, SUA (β = -0.300, P < 0.001) but positively related to uUA/Cre levels (β = 0.086, P < 0.001) in all subjects (Table 2). Furthermore, uUA/Cre [3.574 (2.255–5.664), P < 0.001] was significantly associated with the risk of SRD after adjusting for multiple confounders. However, SUA [1.000 (0.998–1.002), P = 0.676] and FEUA [1.009 (0.999–1.019), P = 0.080] were not associated with SRD (Table 3). We further assessed the effect of UA excretion on the risk of SRD when uUA/Cre was modelled in quartiles (Table 4). In an age- and sex-adjusted model, the ORs (95% CIs) of SRD across increasing quartiles of uUA/Cre were 1.00, 1.115 (0.767–1.622), 1.427 (0.996–2.045) and 2.303 (1.632–3.251) (P for trend < 0.001). In the multivariate model, further adjusting for
Table 1. Baseline characteristics according to uUA/Cre levels in all subjects (n = 2342).

| Characteristics                  | Quartiles of uUA/Cre |  |  |  | P for trend |
|----------------------------------|----------------------|----------------|----------------|----------------|----------------|
| No. of subjects                  | 587                  | 585            | 587            | 583            | –              |
| Age (years)                      | 43.0 (40.0–45.0)     | 43.0 (40.0–45.0) | 43.0 (40.0–45.0) | 43.0 (40.0–45.0) | 0.289 |
| Alcohol consumption (n, %)       | 192 (32.7)           | 197 (33.7)     | 163 (27.8)     | 176 (30.2)     | <0.001 |
| Current smoking (n, %)           | 306 (52.1)           | 276 (47.2)     | 250 (42.6)     | 176 (30.2)     | <0.001 |
| Diabetes mellitus (n, %)         | 21 (3.6)             | 25 (4.3)       | 35 (6.0)       | 16 (2.7)       | 0.832 |
| Hypertension (n, %)              | 129 (22)             | 117 (20)       | 123 (25.7)     | 110 (23.0)     | 0.012 |
| Hyperuricemia (n, %)             | 43 (7.3)             | 39 (6.7)       | 34 (5.8)       | 23 (3.9)       | 0.012 |
| BMI (kg/m²)                      | 24.1±3.2             | 24.1±3.1       | 24.0±3.1       | 24.0±3.1       | 0.368 |
| Heart rate (beats/min)           | 69.0 (63.5–75.5)     | 68.5 (63.5–75.0) | 69.3 (63.0–76.0) | 69.0 (63.0–76.0) | 0.833 |
| SBP (mmHg)                       | 121.3 (112.7–132.0)  | 121.3 (113.0–130.3) | 121.3 (112.0–130.3) | 121.3 (112.0–131.7) | 0.995 |
| DBP (mmHg)                       | 76.3 (69.7–84.3)     | 76.0 (70.0–84.0) | 75.3 (68.0–83.3) | 75.7 (68.3–83.0) | 0.870 |
| SUA (μmol/L)                     | 293.6 (242.8–353.7)  | 287.1 (230.0–340.1) | 275.2 (226.3–330.2) | 256.6 (211.5–313.2) | <0.001 |
| Fasting glucose (mmol/L)         | 4.52 (4.22–4.89)     | 4.58 (4.31–4.94) | 4.59 (4.29–4.93) | 4.58 (4.30–4.90) | 0.202 |
| ALT (U/L)                        | 20.0 (14.0–30.0)     | 19.0 (14.0–27.0) | 19.0 (13.0–27.0) | 17.0 (12.0–23.0) | <0.001 |
| Total cholesterol (mmol/L)       | 4.57 (4.10–5.14)     | 4.52 (4.03–5.01) | 4.47 (4.00–4.94) | 4.48 (4.07–4.99) | 0.171 |
| Triglycerides (mmol/L)           | 1.37 (0.97–2.01)     | 1.36 (0.99–1.96) | 1.32 (0.97–1.91) | 1.25 (0.90–1.81) | 0.125 |
| LDL (mmol/L)                     | 2.55 (2.15–2.99)     | 2.52 (2.14–2.92) | 2.44 (2.08–2.85) | 2.48 (2.14–2.88) | 0.008 |
| HDL (mmol/L)                     | 1.15 (0.99–1.32)     | 1.10 (0.98–1.31) | 1.15 (0.99–1.33) | 1.18 (1.01–1.38) | <0.001 |
| Serum creatinine (μmol/L)        | 80.4±14.7            | 77.9±13.3      | 76.2±13.7      | 72.6±14.2      | <0.001 |
| eGFR (mL/min/1.73m²)             | 94.0 (84.4–105.6)    | 96.5 (86.9–108.1) | 98.2 (87.6–111.0) | 100.7 (89.1–115.1) | <0.001 |
| uUA/Creatinine (μmol/L)          | 0.08 (0.06–0.09)     | 0.16 (0.13–0.18) | 0.25 (0.22–0.28) | 0.46 (0.38–0.62) | <0.001 |
| FEUA (mg/mmol)                   | 2.08 (1.43–2.63)     | 4.22 (3.48–5.06) | 6.74 (5.64–8.26) | 13.4 (10.4–18.8) | <0.001 |
| uACR (mg/mmol)                   | 0.73 (0.49–1.24)     | 0.88 (0.62–1.42) | 1.02 (0.72–1.70) | 1.42 (0.86–2.49) | <0.001 |

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; SUA, serum uric acid; ALT, alanine aminotransferase; AST, aspartate transaminase; LDL, low-density lipoprotein; HDL, high-density lipoprotein; uUA/Creatinine, urinary uric acid/creatinine ratio; FEUA, fraction excretion of uric acid; uACR, urinary albumin-to-creatinine ratio; Non-normally distributed variables are expressed as the median (interquartile range). All other values are expressed as mean ± SD or n, %.

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Table 2. Relationship between various characteristics and uACR and eGFR (n = 2342).

| Characteristics                  | uACR | eGFR |
|----------------------------------|------|------|
| Gender (Male)                    | 0.050 | 0.019 |
| Age (years)                      | -0.047 | 0.021 |
| Hypertension (%)                 | 0.106 | <0.001 |
| Diabetes mellitus (%)            | 0.050 | 0.016 |
| BMI (kg/m²)                      | 0.034 | 0.121 |
| Total cholesterol (mmol/L)       | 0.112 | <0.001 |
| Triglycerides (mmol/L)           | 0.024 | 0.278 |
| SUA (μmol/L)                     | 0.093 | <0.001 |
| uUA/Creatinine (μmol/L)          | 0.042 | 0.041 |
| FEUA (mg/mmol)                   | 0.012 | 0.549 |

uACR, urinary albumin-to-creatinine ratio; eGFR, estimated glomerular filtration rate; BMI, body mass index; SUA, serum uric acid; uUA/Creatinine, urinary uric acid/creatinine ratio; FEUA, fraction excretion of uric acid. The variables of smoking status, alcohol consumption, SBP, DBP, fasting glucose, serum creatinine, LDL, HDL and heart rate were excluded due to multicollinearity.

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hypertension, diabetes, BMI, total cholesterol and triglycerides, the ORs (95% CIs) were 1.00, 1.122 (0.756–1.664), 1.362 (0.928–1.998) and 2.480 (1.719–3.578), respectively; linear trend \( P < 0.001 \).

**Participant characteristics in the longitudinal study**

The characteristics of those who participated in both surveys are presented in Table 5. On average, subjects had higher uUA/Cre, FEUA, uACR, serum creatinine, heart rate, LDL and total cholesterol; lower eGFR, DBP, HDL and SUA levels; and a higher proportion of alcohol consumption after a 4-year follow-up.

Men had lower eGFR during the two follow-ups than women, and men had a higher rate of eGFR decline (−4.3±4.0 vs. 1.0±6.1 mL/min/1.73m²/y, \( P < 0.001 \)). However, uACR progression rate was not significantly different between men and women (Table 6).

**Changes in serum and urinary UA levels for SRD progression**

The relationships of 4-year changes in serum and urinary UA levels with SRD progression (2013–2017) are shown in Table 7. The 4-year changes in uUA/Cre (\( \beta = -0.114, P = 0.040 \)) and

| Table 3. Association between various characteristics and the presence of SRD (n = 2342). |
|---------------------------------------------------------------|
| Characteristics | Odds Ratios (confidence interval) | \( P \) value |
|-----------------|---------------------------------|--------------|
| Gender (Male)   | 1.199 (0.911–1.576)             | 0.195        |
| Age (years)     | 0.979 (0.942–1.017)             | 0.268        |
| Hypertension (%)| 3.506 (2.650–4.638)             | <0.001       |
| Diabetes mellitus (%) | 3.889 (2.415–6.263) | <0.001       |
| BMI (kg/m²)     | 1.087 (1.042–1.133)             | <0.001       |
| Total cholesterol (mmol/L) | 1.078 (0.920–1.265) | 0.353       |
| Triglycerides (mmol/L) | 1.136 (1.039–1.242) | 0.005       |
| SUA (μmol/L)    | 1.000 (0.998–1.002)             | 0.676        |
| FEUA            | 1.009 (0.999–1.019)             | 0.080        |
| uUA/Cre         | 3.574 (2.255–5.664)             | <0.001       |

Logistic regression analyses were used to test the risk of SRD, after adjustment for age, gender, hypertension, diabetes, BMI, total cholesterol and triglycerides. The variables of smoking status, alcohol consumption, SBP, DBP, fasting glucose, serum creatinine, LDL, HDL and heart rate were excluded because of multicollinearity. SRD, subclinical renal damage; BMI, body mass index; SUA, serum uric acid; FEUA, fraction excretion of uric acid; uUA/Cre, urinary uric acid/creatinine ratio.

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| Table 4. Association between each quartile of uUA/Cre and presence of SRD (n = 2342). |
|---------------------------------------------------------------|
| Quartile | Odds Ratios (95% confidence interval) |
|-----------|-------------------------------------|
| Quartile 1 | Non-SRD controls: 528 (26.0%) | SRD patients: 59 (18.7%) | 1.00 (reference) |
| Quartile 2 | 521 (25.1%) | 64 (20.3%) | 1.115 (0.767–1.622) |
| Quartile 3 | 508 (25.1%) | 79 (25.1%) | 1.427 (0.996–2.045) |
| Quartile 4 | 470 (23.2%) | 113 (35.9%) | 2.303 (1.632–3.251) |

\( P \) for trend: <0.001

*Logistic regression analyses were used to test the risk of SRD, after adjustment for age, gender, hypertension, diabetes, BMI, total cholesterol and triglycerides. The variables of smoking status, alcohol consumption, SBP, DBP, fasting glucose, serum creatinine, LDL, HDL and heart rate were excluded due to multicollinearity. SRD, subclinical renal damage; FEUA, fraction excretion of uric acid; uUA/Cre, urinary uric acid/creatinine ratio.

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Table 5. Characteristics of the study participants at baseline and follow-up (n = 266).

| Characteristics | Baseline in 2013 | Follow-up in 2017 | P value |
|-----------------|-----------------|------------------|---------|
| Gender (M/F)    | 152/114         | 152/114          | –       |
| Age (years)     | 37.0 (35.0–40.0)| 41.0 (39.0–44.0) | <0.001 |
| Current smoking (n, %) | 113 (42.5)   | 120 (45.1)       | 0.541   |
| Alcohol consumption (n, %) | 26 (9.8)      | 78 (29.3)        | <0.001 |
| Hypertension (n, %) | 84 (31.6)     | 65 (24.4)        | 0.067   |
| Diabetes mellitus (n, %) | 5 (1.9)       | 16 (6.0)         | 0.014   |
| BMI (kg/m²)     | 24.6±3.7        | 24.7±3.5         | 0.695   |
| Heart rate (beats/min) | 66.0(60.0–72.0)| 70.0(63.5–76.5)  | <0.001 |
| SBP (mmHg)      | 122.0(114.0–132.0) | 122.7(114.3–133.3)| 0.505 |
| DBP (mmHg)      | 81.0(74.0–90.0) | 77.2(70.3–85.8)  | <0.001 |
| Fasting glucose (mmol/L) | 4.49 (4.26–4.71)| 4.61 (4.29–4.93) | 0.002 |
| Total cholesterol (mmol/L) | 4.34±0.79      | 4.58±0.79        | 0.001  |
| Triglycerides (mmol/L) | 1.42(1.00–2.13) | 1.38(0.98–2.00)  | 0.452  |
| LDL (mmol/L)    | 2.36(2.00–2.74) | 2.51(2.11–2.90)  | 0.010  |
| HDL (mmol/L)    | 1.65±0.32       | 1.17±0.26        | <0.001 |
| SUA (μmol/L)    | 316±87.7        | 295±81.2         | 0.004  |
| uUA/Cr          | 0.08(0.04–0.15) | 2.30(1.92–2.84)  | <0.001 |
| FEUA            | 1.92(1.00–3.69) | 4.71(2.74–7.81)  | <0.001 |
| Serum creatinine (μmol/L) | 76.6±14.4   | 81.0±12.8       | <0.001 |
| eGFR (mL/min/1.73 m²) | 99.1(87.2–112.9)| 89.4(77.5–108.3)| <0.001 |
| uACR (mg/mmol)  | 0.33(0.25–0.43) | 1.05(0.65–2.02)  | <0.001 |

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL, low-density lipoprotein; HDL, high-density lipoprotein; SUA, serum uric acid; eGFR, estimated glomerular filtration rate; uACR, urinary albumin-to-creatinine ratio. uUA/Cr, urinary uric acid/creatinine ratio; FEUA, fraction excretion of uric acid. Non-normally distributed variables are expressed as the median (interquartile range). All other values are expressed as mean ± SD or n, %.

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Table 6. Change of the uACR and eGFR over time.

|                      | Male subjects | Female subjects | P-value |
|----------------------|---------------|-----------------|---------|
| No. of subjects      | 152           | 114             | –       |
| uACR data (mg/mmol)  |               |                 |         |
| uACR 2013,           | 0.59 (0.40–0.98) | 0.85 (0.53–1.50) | 0.002 |
| uACR 2017            | 1.00 (0.62–1.87) | 1.23 (0.70–2.18) | 0.207 |
| uACR progression     | 0.38 (-1.24–0.96) | 0.33 (-1.64–1.10) | 0.533 |
| uACR progression rate, per year | 0.10 (-0.31–0.24) | 0.08 (-0.41–0.28) | 0.533 |
| eGFR data (mL/min/1.73 m²) |               |                 |         |
| eGFR 2013            | 99.3±17.4     | 105.1±22.9      | 0.019  |
| eGFR 2017            | 80.2 (73.2–89.8) | 108.7 (90.9–125.2) | <0.001 |
| eGFR decline         | -17.3±16.0    | 4.0±24.3        | <0.001 |
| eGFR decline rate, per year | -4.3±4.0   | 1.0±6.1         | <0.001 |

uACR, urinary albumin-to-creatinine ratio; eGFR, estimated glomerular filtration rate; Non-normally distributed variables are expressed as the median (interquartile range). All other values are expressed as mean ± SD.

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SUA ($\beta = 0.187, \ P = 0.001$) were significantly associated with eGFR decline. However, we did not find an association between changes in UA and uACR progression over a 4-year follow-up (Table 7).

**Sensitivity analysis**

Several sensitivity analyses were performed. Firstly, we removed subjects with hyperuricemia under treatment in the cross-sectional study ($n = 11$) and longitudinal trial ($n = 3$) to exclude the potential influence of urate-lowering drugs. As shown in S2–S5 Tables, all the results remained similar after adjustment for potential confounders. In addition, to further exclude the potential influence of antihypertensive or hypoglycemic medications, we performed all analyses by excluding individuals with diabetes, hypertension or hyperuricemia under treatment in the cross-sectional study ($n = 92$) and longitudinal trial ($n = 26$), and similar results were obtained (S6–S9 Tables).

**Discussion**

To the best of our knowledge, the present study is the first to evaluate the relationship between urinary UA excretion and the risk of SRD. Interestingly, we showed that a higher uUA/Cre category was significantly associated with an increased OR for the presence of SRD compared with the reference group. The observed positive association between uUA/Cre and SRD consistently occurred when uUA/Cre was considered a continuous variable. These data suggest that the urinary UA may act as a simple, noninvasive, cost-effective, single biochemical marker for assessing the severity of early renal damage.

UA homeostasis is determined by the dynamic balance between its production and excretion, and the latter mainly includes intestinal and renal pathway [33]. In “renal excretion” pathway, the renal proximal tubule is an important regulator and the primary site of urate reabsorption [30] and is responsible for almost all the renal urate transportation in the kidney [33]. Several studies indicate that urinary UA has the potential to act as a simple, noninvasive indicator for evaluating the disease development and mortality. Chen et al. [21] showed that the uUA/Cre was significantly increased in hypoxic premature infants compared with in hypoxic term ones. Bahubali et al. [22] reported that uUA/Cre was higher in neonates with birth asphyxia, and this ratio was closely associated with the severity of disease. Nariman et al. [20] found that uUA/Cre levels increased with the clinical severity of disease and was correlated with adverse outcome and longer duration of stay in neonatal intensive care unit (NICU). Subclinical renal damage (SRD), defined as slightly elevated albuminuria and decreased GFR, was

| Table 7. Associations of 4-year changes in serum and urinary UA with the progression of SRD. |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
| uACR progression               | eGFR decline    |
| $\beta$                        | $P$ value       | $\beta$         | $P$ value       |
| 4-year change                  |                 |                 |                 |
| SUA ($\mu$mol/L)               | -0.009          | 0.890           | 0.187           | 0.001           |
| uUA/Cre($\mu$mol/L)            | 0.016           | 0.796           | -0.114          | 0.040           |
| FEUA($\mu$mol/L)               | 0.005           | 0.941           | -0.103          | 0.065           |

Included in the multivariate regression models: age, gender, hypertension, diabetes, BMI, total cholesterol, triglycerides and eGFR at baseline. The variables of smoking status, alcohol consumption, SBP, DBP, fasting glucose, serum creatinine, LDL, HDL and heart rate were excluded due to multicollinearity. SRD, subclinical renal damage; UA, uric acid; eGFR, estimated glomerular filtration rate; uACR, urinary albumin-to-creatinine ratio; SUA, serum uric acid; FEUA, fraction excretion of uric acid; uUA/Cre, urinary uric acid/creatinine ratio.

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SUA ($\beta = 0.187, \ P = 0.001$) were significantly associated with eGFR decline. However, we did not find an association between changes in UA and uACR progression over a 4-year follow-up (Table 7).
significantly associated with the increased incidence of CKD and associated cardiovascular complications. Few studies support the possible role of SUA as a risk factor for SRD in hypertensive subjects. Viazzi et al. [13] showed that hypertensive patients with increased SUA levels showed early signs of renal damage. The authors further showed that for each SD increment in SUA, there was a 69% increased risk of developing microalbuminuria and a 39% increased risk of ultrasound-detectable abnormalities [13]. Muleet et al. suggested that the presence of SRD was significantly associated with SUA in patients with hypertension [14]. However, the association of urinary UA excretion with the risk of SRD has not been fully understood. In the present study, we firstly showed that uUA/Cre was significantly associated with the presence of SRD. In fact, UA per se can be detrimental to the kidneys, as shown in recent studies. Verzola et al. [34] demonstrated that UA internalized by urate transporter 1 (URAT1) could promote reactive oxygen species (ROS)-induced tubular cell apoptosis by upregulating Nox4 expression at tubular level. They further showed that UA could trigger oxidative and inflammatory response mediated by toll-like receptor 4 (TLR4). In addition, cotreatment with UA and angiotensin II (Ang II) exert an additive unfavorable cellular effect, which cannot be completely prevented by renin-angiotensin-aldosterone system (RAAS) inhibitors [35]. These studies suggest the complex interaction between damage-associated molecular patterns (DAMPs), such as UA and Ang II, innate immunity and the development of renal damage.

To our knowledge, this study is the first report concerning the association between urinary UA and the progression of SRD. We found that urinary UA change over 4 years was associated with eGFR decline in this Chinese population. Previous studies suggested that elevated SUA levels were significantly associated with GFR decline. For example, Akasaka et al. [36] attempted to examine the impact of SUA on the natural history of eGFR. They showed that elevation of SUA accelerated eGFR decline, and it was a result instead of a cause. De Cosmo et al. [37] found that SUA levels were significantly correlated with eGFR decline in a large cohort of type 2 diabetes (T2D) patients. Moreover, Wang et al. [11] conducted a prospective cohort study and found that elevated SUA was positively associated with incident eGFR decline. They further showed that for every 100 μmol/L increase in SUA, there was a 33% increased risk of incident eGFR decline [11]. Xu et al. [12] recently reported an association between increased SUA and greater GFR reduction during a 5-year follow-up in patients with T2D. In keeping with these observations, in our study, we found that SUA levels were negatively associated with eGFR in our cross-sectional study and that the change in SUA during a 4-year period was positively associated with eGFR decline. Our findings derived from cross-sectional and longitudinal cohort studies further confirmed the negative correlation between SUA and eGFR decline in the general population. Based on these previous findings, the present study further identified a significant association between urinary UA excretions and eGFR decline. Future studies investigating mechanisms underlying this phenomenon can be of interest.

Albuminuria not only an important prognostic indicator for renal damage, and but also a marker of endothelial dysfunction [38]. Increased albuminuria was associated with cardiovascular risk for kidney damage and vascular injury [39,40]. Previously, several studies found that SUA was positively associated with albuminuria and as a useful predictor for the development of albuminuria, including in subjects with hypertension [16] and diabetes mellitus [8]. Uric acid-lowering drugs have been found to decrease proteinuria in T2D patients [41]. In addition, Li et al. [42] recently reported that uACR was significantly correlated with 24-h urinary excretion of UA and its clearance rate, but not with FEUA, after adjusting for potential confounders in CKD patients. Consistent with this result, our study demonstrates that uACR levels were correlated with SUA and uUA/Cr, not with FEUA, in Chinese adults in the general population. Furthermore, Scheven et al. showed [10] that albuminuria was positively associated with tubular UA reabsorption. This relationship was demonstrated by Zou et al. from another...
perspective in that urinary UA excretion was significantly decreased in proteinuric patients than in healthy individuals [43]. Future large prospective trials are still needed to verify the relationship between urinary UA excretion and the progression of albuminuria.

Some limitations of our study deserve mention. Firstly, our results are obtained from northern Chinese individuals and consequently cannot be directly extrapolated to other ethnic groups. Secondly, we use spot urine specimens to determine urinary albumin excretion in present study. Nevertheless, 24-h urine is difficult to collect, and spot urine samples are more practical for use in large-scale studies. uACR has been verified to closely associate with estimates of microalbuminuria in 24-h urine and is effective in predicting kidney diseases [44,45]. Thirdly, all subjects in this study were youth and middle aged between 36 and 45 years during the follow-up at 2017, and thus the findings may not be generalizable to other age groups. Finally, some participants were lost during the follow-up. However, baseline characteristics in 2013 were similar between the participants and non-participants, and the study cohort seems to be representative of the original study population.

In summary, our study shows that urinary UA excretion is significantly associated with the risk of early renal damage in Chinese adults. However, we failed to find a significant relationship between serum UA and SRD. Our results also indicate that 4-year changes of UA in blood and urine are associated with eGFR decline in this Chinese population. These findings suggest that UA, especially urinary UA, may be used as a simple, noninvasive marker for early detection of decreased renal function in otherwise healthy subjects. Further clinical trials targeting hyperuricosuria can be of much interest.

**Supporting information**

S1 File. Minimal data set.
(XLS)

S1 Fig. The protocol of longitudinal follow-up of the cohort.
(TIF)

S1 Table. Comparison of baseline characteristic between those who did and did not participate in the longitudinal study.
(DOC)

S2 Table. Relationship between various characteristics and uACR and eGFR in subjects without urate-lowering treatment.
(DOC)

S3 Table. Association between various characteristics and the risk of SRD in subjects without urate-lowering treatment.
(DOC)

S4 Table. Association between each quartile of uUA/Cre and presence of SRD in subjects without urate-lowering treatment.
(DOC)

S5 Table. Associations of 4-year changes in serum and urinary UA with the progression of SRD in subjects without urate-lowering treatment.
(DOC)

S6 Table. Relationship between various characteristics and uACR and eGFR in subjects without medication use.
(DOC)
S7 Table. Association between various characteristics and the risk of SRD in subjects without medication use.

(SOC)

S8 Table. Association between each quartile of uUA/Cre and presence of SRD in subjects without medication use.

(SOC)

S9 Table. Associations of 4-year changes in serum and urinary UA with the progression of SRD in subjects without medication use.

(SOC)

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References

1. Schieppati A, Remuzzi G. Chronic renal diseases as a public health problem: epidemiology, social, and economic implications. Kidney Int Suppl. 2005; (98): S7–S10. https://doi.org/10.1111/j.1523-1755.2005.09801.x PMID: 16108976

2. Weiner DE, Tighiouart H, Amin MG, Stark PC, MacLeod B, Griffith JL, et al. Chronic kidney disease as a risk factor for cardiovascular disease and all-cause mortality: a pooled analysis of community-based studies. J Am Soc Nephrol. 2004; 15(5): 1307–15. https://doi.org/10.1097/01.asn.0000123691.46138.e2 PMID: 15100371

3. Zhang L, Wang F, Wang L, Wang W, Liu B, Liu J, et al. Prevalence of chronic kidney disease in China: a cross-sectional survey. Lancet. 2012; 379(9818): 815–22. https://doi.org/10.1016/S0140-6736(12)60033-6 PMID: 22386035

4. Coresh J, Selvin E, Stevens LA, Manzi J, Kusek JW, Eggers P, et al. Prevalence of chronic kidney disease in the United States. JAMA. 2007; 298(17): 2038–47. https://doi.org/10.1001/jama.298.17.2038 PMID: 17986697

5. Prasad SOS, Qing YX. Associations Between Hyperuricemia and Chronic Kidney Disease: A Review. Nephrourol Mon. 2015; 7(3): e27233. https://doi.org/10.5812/nemonthly.7(3)2015.27233 PMID: 26290849
6. Wang Y, Hu JW, Lv YB, Chu C, Wang KK, Zheng WL, et al. The Role of Uric Acid in Hypertension of Adolescents, Prehypertension and Salt Sensitivity of Blood Pressure. Med Sci Monit. 2017; 23790–5. https://doi.org/10.12659/MSM.899563 PMID: 28190873

7. Lippi G, Montagnana M, Franchini M, Favaloro EJ, Targher G. The paradoxical relationship between serum uric acid and cardiovascular disease. Clin Chim Acta. 2008; 392(1–2): 1–7. https://doi.org/10.1016/j.cca.2008.02.024 PMID: 18348869

8. Jalal DI, Rivard CJ, Johnson RJ, Maahs DM, McFann K, Rewers M, et al. Serum uric acid levels predict the development of albuminuria over 6 years in patients with type 1 diabetes: findings from the Coronary Artery Calcification in Type 1 Diabetes study. Nephrol Dial Transplant. 2010; 25(6): 1865–9. https://doi.org/10.1093/ndt/gfp740 PMID: 20064950

9. Feig DI, Kang DH, Johnson RJ. Uric acid and cardiovascular risk. N Engl J Med. 2008; 359(17): 1811–21. https://doi.org/10.1056/NEJMoa0800885 PMID: 18946066

10. Scheven L, Joosten MM, de Jong PE, Bakker SJ, Gansevoort RT. The association of albuminuria with tubular reabsorption of uric acid: results from a general population cohort. J Am Heart Assoc. 2014; 3(2): e000613. https://doi.org/10.1161/JAHA.113.000613 PMID: 24772520

11. Wang J, Yu Y, Li X, Li D, Xu C, Yuan J, et al. Serum uric acid levels and decreased estimated glomerular filtration rate in patients with type 2 diabetes: A cohort study and meta-analysis. Diabetes Metab Res Rev. 2018; 34(7): e3046. https://doi.org/10.1002/dmr.3046 PMID: 30003679

12. Xu Y, Liu X, Sun X, Wang Y. The impact of serum uric acid on the natural history of glomerular filtration rate: a retrospective study in the general population. PeerJ. 2016; 4 e1859. https://doi.org/10.7717/peerj.1859 PMID: 27069799

13. Viazzi F, Leoncini G, Ratto E, Falqui V, Parodi A, Conti N, et al. Mild hyperuricemia and subclinical renal damage in untreated primary hyperparathyroidism. Am J Hypertens. 2007; 20(12): 1276–82. https://doi.org/10.1016/j.amjhyper.2007.08.010 PMID: 18047917

14. Mule G, Calcaterria I, Costanzo M, Geraci G, Guarino L, Foraci AC, et al. Relationship Between Short-Term Blood Pressure Variability and Subclinical Renal Damage in Essential Hypertensive Patients. J Clin Hypertens (Greenwich). 2015; 17(6): 473–80. https://doi.org/10.1111/jch.12534 PMID: 25808042

15. Hayashino Y, Okamura S, Tsujii S, Ishii H. Association of serum uric acid levels with the risk of development or progression of albuminuria among Japanese patients with type 2 diabetes: a prospective cohort study [Diabetes Distress and Care Registry at Tenri (DDCRT 10)]. Acta Diabetol. 2016; 53(4): 599–607. https://doi.org/10.1007/s00592-015-0825-x PMID: 26935413

16. Forman JP, Scheven L, de Jong PE, Bakker SJ, Cushman GC, Gansevoort RT. Association between sodium intake and change in uric acid, urine albumin excretion, and the risk of developing hypertension. Circulation. 2012; 125(25): 3108–16. https://doi.org/10.1161/CIRCULATIONAHA.112.096115 PMID: 22711274

17. Lyytyni Y, Perkins BA, Cherney DZI. Uric acid as a biomarker and a therapeutic target in diabetes. Can J Diabetes. 2015; 39(3): 239–46. https://doi.org/10.1016/j.cjdi.2014.10.013 PMID: 25600084

18. Cole FL, Kavalach AG. Hypercalciuria and hyperuricosuria in patients with calcium nephrolithiasis. N Engl J Med. 1974; 291(25): 1344–50. https://doi.org/10.1056/NEJM197412192912510 PMID: 4610395

19. Mule G, Calcaterria I, Costanzo M, Geraci G, Guarino L, Foraci AC, et al. Relationship Between Short-Term Blood Pressure Variability and Subclinical Renal Damage in Essential Hypertensive Patients. J Clin Hypertens (Greenwich). 2015; 17(6): 473–80. https://doi.org/10.1111/jch.12534 PMID: 25808042

20. Nairman S, Mosayebi Z, Sagheb S, Rastad H, Hosseininode SS. Urinary Uric Acid/Creatinine Ratio as a Marker of Mortality and Unfavorable Outcome in NICU-Admitted Neonates. Iran J Pediatr. 2016; 26(4): e5739. https://doi.org/10.5812/ijp.5739 PMID: 27729961

21. Chen HJ, Yau KI, Tsai KS. Urinary uric acid/creatinine ratio as an additional marker of perinatal asphyxia. J Formos Med Assoc. 2000; 99(10): 771–4. PMID: 11061072

22. Gane Bahubali D, Bhat Vishnu B, Ramachandra R, Adhisivam B, Rojo J, Prasad P, et al. Biochemical marker as predictor of outcome in perinatal asphyxia. Current Pediatric Research. 2013; 17(2).

23. Wang Y, Hu JW, Qu PF, Wang KK, Yan Y, Chu C, et al. Association between urinary sodium excretion and uric acid, and its interaction on the risk of prehypertension among Chinese young adults. Sci Rep. 2018; 8(1): 7749. https://doi.org/10.1038/s41598-018-26148-3 PMID: 29773847

24. Zheng W, Mu J, Chu C, Hu J, Yan Y, Ma Q, et al. Association of Blood Pressure Trajectories in Early Life with Subclinical Renal Damage in Middle Age. J Am Soc Nephrol. 2018; 29(12): 2835–46. https://doi.org/10.16161/ASN.2018030263 PMID: 30420422

25. Wang Y, Lv YB, Chu C, Wang M, Xie BQ, Wang L, et al. Plasma Renalase is Not Associated with Blood Pressure and Brachial-Ankle Pulse Wave Velocity in Chinese Adults With Normal Renal...
26. Wang Y, Yuan Y, Gao WH, Yan Y, Wang KK, Qu PF, et al. Predictors for progressions of brachial-ankle pulse wave velocity and carotid intima-media thickness over a 12-year follow-up: Hanzhong Adolescent Hypertension Study. J Hypertens. 2019; 37(6): 1167–75. https://doi.org/10.1097/HJH.0000000000002020 PMID: 31026243

27. Wang Y, Wang D, Chu C, Mu JJ, Wang M, Liu FQ, et al. Effect of Salt Intake and Potassium Supplementation on Urinary Renalase and Serum Dopamine Levels in Chinese Adults. Cardiology. 2015; 130(4): 242–8. https://doi.org/10.1159/000371794 PMID: 25824645

28. Wang Y, Chu C, Wang KK, Hu JW, Yan Y, Lv YB, et al. Effect of Salt Intake on Plasma and Urinary Uric Acid Levels in Chinese Adults: An Interventional Trial. Sci Rep. 2018; 8(1): 1434. https://doi.org/10.1038/s41598-018-20048-2 PMID: 29362390

29. Ma YC, Zuo L, Chen JH, Luo Q, Yu XQ, Li Y, et al. Modified glomerular filtration rate estimation equation for Chinese patients with chronic kidney disease. J Am Soc Nephrol. 2006; 17(10): 2937–44. https://doi.org/10.1681/ASN.2006040368 PMID: 16988059

30. Maesaka JK, Fishbane S. Regulation of renal urate excretion: a critical review. Am J Kidney Dis. 1998; 32(6): 917–33. https://doi.org/10.1053/ajkd.1998.0070 PMID: 9856507

31. Lipkowitz MS. Regulation of uric acid excretion by the kidney. Curr Rheumatol Rep. 2012; 14(2): 179–88. https://doi.org/10.1007/s11926-012-0240-z PMID: 22359229

32. Leoncini G, Viazzi F, Conti N, Baratto E, Tomolillo C, Bezante GP, et al. Renal and cardiac abnormalities in primary hypertension. J Hypertens. 2009; 27(5): 1064–73. https://doi.org/10.1097/HJH.0b013e328321d13 PMID: 19357534

33. Bobulescu IA, Moe OW. Renal transport of uric acid: evolving concepts and uncertainties. Adv Chronic Kidney Dis. 2012; 19(6): 358–71. https://doi.org/10.1053/j.ackd.2012.07.009 PMID: 23089275

34. Verzola D, Ratto E, Villaggio B, Parodi EL, Pontremoli R, Garibotto G, et al. Uric acid promotes apoptosis in human proximal tubule cells by oxidative stress and the activation of NADPH oxidase NOX 4. PLoS One. 2014; 9(12): e115210. https://doi.org/10.1371/journal.pone.0115210 PMID: 25514209

35. Milanesi S, Verzola D, Cappadona F, Bonino B, Murugavel A, Pontremoli R, et al. Uric acid and angiotensin II additively promote inflammation and oxidative stress in human proximal tubule cells by activation of toll-like receptor 4. J Cell Physiol. 2019; 234(7): 10868–76. https://doi.org/10.1002/jcp.27929 PMID: 30536556

36. Akasaka H, Yoshida H, Takizawa H, Hanawa N, Tobisawa T, Tanaka M, et al. The impact of elevation of serum uric acid level on the natural history of glomerular filtration rate (GFR) and its sex difference. Nephrol Dial Transplant. 2014; 29(10): 1932–9. https://doi.org/10.1093/ndt/gfu197 PMID: 24891435

37. De Cosmo S, Viazzi F, Pacilli A, Giorda C, Ceriello A, Gentile S, et al. Serum Uric Acid and Risk of CKD in Type 2 Diabetes. Clin J Am Soc Nephrol. 2015; 10(11): 1921–9. https://doi.org/10.2215/CJN.03140315 PMID: 26342044

38. Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Bohm M, et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens. 2013; 31(7): 1281–357. https://doi.org/10.1097/HJH.0b013e328374a766 cc PMID: 23817082

39. Ozylimaz A, de Jong PE, SJL B, Visser ST, Thio C, Gansevoort RT. Screening for elevated albuminuria and subsequently hypertension identifies subjects in which treatment may be warranted to prevent renal function decline. Nephrol Dial Transplant. 2017; 32(suppl_2): ii200–200i208. https://doi.org/10.1093/ndt/gfw414 PMID: 28031343

40. Cerasola G, Cottone S, Mule G. The progressive pathway of microalbuminuria: from early marker of renal damage to strong cardiovascular risk predictor. J Hypertens. 2010; 28(12): 2357–69. https://doi.org/10.1097/HJH.0b013e32833ec377 PMID: 20842046

41. Momeni A, Shahidi S, Seirafi S, Taheri S, Khei S. Effect of allopurinol in decreasing proteinuria in type 2 diabetic patients. Iran J Kidney Dis. 2010; 4(2): 128–32. PMID: 20404423

42. Li F, Guo H, Zou J, Chen W, Lu Y, Zhang X, et al. Urinary excretion of uric acid is negatively associated with albuminuria in patients with chronic kidney disease: a cross-sectional study. BMC Nephrol. 2018; 19(1): 95. https://doi.org/10.1186/s12882-018-0892-7 PMID: 29699501

43. Zou H, Xiang M, Ye X, Xiong Y, Xie B, Shao J. Reduction of urinary uric acid excretion in patients with proteinuria. J Chromatogr B Analyt Technol Biomed Life Sci. 2015; 10069–64. https://doi.org/10.1016/j.jchromb.2015.10.027 PMID: 26523664
nephropathy. Diabetes Care. 1997; 20(4): 516–9. https://doi.org/10.2337/diacare.20.4.516 PMID: 9096972

45. Nathan DM, Rosenbaum C, Protasowicki VD Single-void urine samples can be used to estimate quantitative microalbuminuria. Diabetes Care. 1987; 10(4): 414–8. https://doi.org/10.2337/diacare.10.4.414 PMID: 3622198