Association of Increasing GFR with Change in Albuminuria in the General Population

Toralf Melsom,† Vidar Stefansson,* Jørgen Schei,*† Marit Solbu,*† Trond Jenssen,*‡ Tom Wilsgaard,§ and Bjørn O. Eriksen*†

Abstract

Background and objectives Hyperfiltration at the single-nephron level has been proposed as an early stage of kidney dysfunction of different origins. Evidence supporting this hypothesis in humans is lacking, because there is no method of measuring single-nephron GFR in humans. However, increased whole-kidney GFR in the same individual implies an increased single–nephron GFR, because the number of nephrons does not increase with age. We hypothesized that an increase in GFR would be associated with an increased albumin-to-creatinine ratio in a cohort of the general population.

Design, setting, participants, & measurements We measured GFR by iohexol clearance at baseline in 2007–2009 and follow-up after 5.6 years in a representative sample of 1246 persons (aged 50–62 years) who were nondiabetic from the general population of Tromso, northern Norway. Participants were without cardiovascular disease, kidney disease, or diabetes at baseline. We investigated the association between change in GFR and change in albumin-to-creatinine ratio. Increased GFR was defined as a positive change in GFR (change in GFR>0 ml/min) from baseline to follow-up. An albumin-to-creatinine ratio >30 mg/g was classified as albuminuria.

Results Change in GFR was positively associated with a change in albumin-to-creatinine ratio in the entire cohort in the multiple linear regression. The albumin-to-creatinine ratio$_{\text{follow-up}}$-to-albumin-to-creatinine ratio$_{\text{baseline}}$ ratio increased by 8.0% (95% confidence interval, 1.4 to 15.0) per SD increase in change in GFR. When participants with increased GFR (n=343) were compared with those with a reduced GFR (n=903), the ratio increased by 16.3% (95% confidence interval, 1.1 to 33.7). The multivariable adjusted odds ratio for incident albuminuria (n=14) was 4.98 (95% confidence interval, 1.49 to 16.13) for those with an increased GFR (yes/no).

Conclusions Increasing GFR is associated with an increase in albumin-to-creatinine ratio and incident albuminuria in the general nondiabetic population. These findings support single-nephron hyperfiltration as a risk factor for albuminuria in the general population.

Clin J Am Soc Nephrol 11: 2186–2194, 2016. doi: 10.2215/CJN.04940516

*Metabolic and Renal Research Group and §Department of Community Medicine, UiT The Arctic University of Norway, Tromso, Norway; †Section of Nephrology, University Hospital of North Norway, Tromso, Norway; and ‡Section of Nephrology, Department of Organ Transplantation, Oslo University Hospital, Rikshospitalet, Oslo, Norway

Correspondence: Dr. Toralf Melsom, Section of Nephrology, University Hospital of North Norway, N-9038 Tromso, Norway. Email: tmels@online.no

Introduction

The global death rates from CKD increased by 37% from 1990 to 2013 (1). Reduced eGFRs below 60 ml/min per 1.73 m^2 and even small increments in urinary albumin excretion are independent risk factors for cardiovascular disease (CVD) and all-cause mortality (2). Recent cohort studies of the general population have found that elevated and increasing eGFRs also predict CVD and death (3,4). This apparent increased risk associated with a high or increasing eGFR has been explained by confounding because of muscle wasting and thus, lower serum creatinine levels in individuals with chronic illness. However, an abnormally high GFR or glomerular hyperfiltration may be a pathologic state in response to metabolic disturbances and a cause of albuminuria (5,6).

This hypothesis is on the basis of experimental studies in animals that show that hyperfiltration at the single-nephron level is a risk factor for albuminuria and subsequent glomerulosclerosis (5). Because single-nephron GFRs cannot be measured in humans, investigators have used elevated whole–kidney GFR as a proxy for single-nephron hyperfiltration. Whole-kidney GFR increases in a large proportion of patients with diabetes before albuminuria develops (7,8). Recently, we reported that having prediabetes predicted both an increased whole–kidney GFR and an increased albumin-to-creatinine ratio (ACR) at follow-up in a longitudinal study of the general population (9). Several other CKD risk factors, such as hypertension, obesity, and smoking, have been associated with elevated whole–kidney GFR in cross-sectional studies (10–15). However, whether hyperfiltration is a risk factor for albuminuria in the general population remains unclear. The primary reason for this uncertainty may be that assessing hyperfiltration defined as the elevated whole–kidney GFR in a cross-sectional design may not represent hyperfiltration at the single-nephron level, because there is a large variation in nephron number between individuals ranging from 200,000 to 1,800,000 (16). However, an increase in the whole-kidney GFR of the same individual implies an increased

single–nephron GFR as well as hyperfiltration in all or at least a large proportion of the nephrons, because the number of nephrons does not increase with age. Accordingly, we tested the hypothesis that an increase in GFR from baseline to follow-up would be associated with increases in the ACR and albuminuria in a cohort representative of the general population.

Because the eGFRs on the basis of serum creatinine and cystatin C are imprecise and biased in the normal GFR range (15,17–19), we measured GFR using iohexol clearance in the Renal Iohexol Clearance Survey in Tromsø 6 (RENIS-T6) Study at baseline and after a median of 5.6 years of follow-up (the Renal Iohexol Clearance Survey in Tromsø 6 Follow-Up [RENIS-FU] Study).

Materials and Methods

Study Participants

The RENIS-T6 Study was conducted from 2007 to 2009 as a substudy of the population–based sixth Tromsø Study in the municipality of Tromso, northern Norway (20). The RENIS-T6 Study included a representative sample of 1627 persons aged 50–62 years old from the general white population without self–reported kidney disease, CVD, or diabetes (Figure 1).

In the RENIS-FU Study, we invited all 1627 participants from the RENIS-T6 Study, with the exceptions of seven persons who had a possible adverse reaction to iohexol in the RENIS-T6 Study and 23 persons who had died during the follow-up period (Figure 1). In total, 1324 (83%) participants were examined with an updated GFR measurement between September of 2013 and January of 2015. In this study, we excluded participants who had diabetes (fasting glucose ≥7.0 mmol/L [126 mg/dl], hemoglobin A1c [HbA1c] ≥6.5%, or the use of antidiabetic medication; n=25) or albuminuria (ACR>30 mg/g) at baseline (n=17). Finally, we excluded 36 participants who had diabetes at follow-up (Figure 1).

The Regional Ethics Committee of Northern Norway approved the study, and all participants provided written informed consent.

Data

The RENIS-T6 Study and the RENIS-FU Study were conducted at the Clinical Research Unit at the University Hospital of Northern Norway with a standardized procedure, and the same staff members were responsible for all

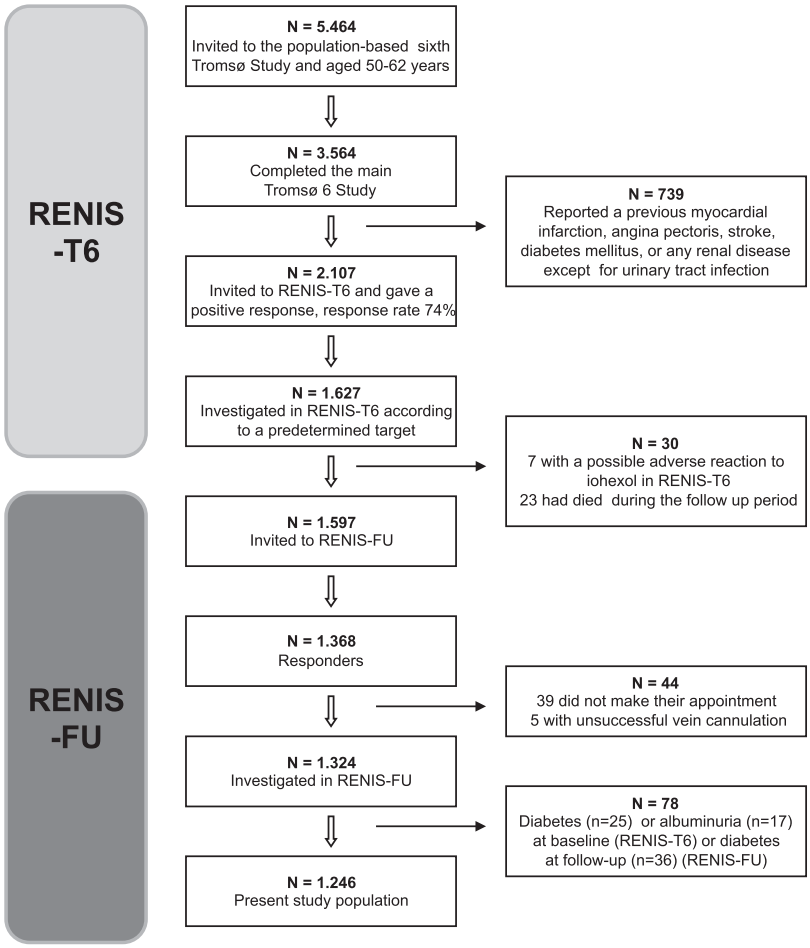

Figure 1. | **Inclusion of participants.** The Renal Iohexol Clearance Survey in Tromsø 6 (RENIS-T6) Study and the Renal Iohexol Clearance Survey in Tromsø 6 Follow-Up (RENIS-FU) Study.

measurements. The participants met with study staff between 8:00 a.m. and 10:00 a.m. after an overnight fast, including abstinence from tobacco. Participants with intercurrent disease (*e.g.*, respiratory or urinary infection) had their appointments rescheduled.

Both visits included a health questionnaire with questions on alcohol and tobacco use and all current medications. Regular alcohol use was categorized as consuming alcohol more than once a week (yes/no), and current smoking was categorized as daily tobacco use (yes/no).

Measurements

The GFR was measured using single–sample plasma clearance of iohexol as described in detail elsewhere (9,20). The participants were instructed to avoid large meals with meat and nonsteroidal anti–inflammatory drugs 2 days before the investigation. The serum iohexol (300 mg/ml; Omnipaque; Amersham Health, London, United Kingdom) concentration was measured using HPLC as described by Nilsson-Ehle (21). The analytic coefficients of variation during the study period were 3.0% in the RENIS-T6 Study and 3.1% in the RENIS-FU Study. The GFR was calculated as described by Jacobsson (22). In the RENIS-FU Study, we obtained a repeated GFR measurement after 2 weeks and within 2 months from a random sample of 86 participants. The mean coefficient of variation for the intraindividual variation in GFR was 4.2% (95% confidence interval, 3.4% to 4.9%) as recently reported (23).

Three samples of first void morning spot urine were collected on separate days at baseline and follow-up. Urinary albumin excretion and urinary creatinine were measured in unfrozen urine (24). The ACR in milligrams per millimole was calculated for each urine specimen, and the median ACR value was used in the analyses. Albuminuria was defined as an ACR>30 mg/g according to Kidney Disease Improving Global Outcomes 2012 (25).

Serum fasting lipids, fasting glucose, and HbA1c were analyzed as previously reported (26). Ambulatory BP recordings began after the baseline GFR measurement and continued for 24 hours (12).

Statistical Analyses

The study population characteristics are presented as the mean (SD) values, medians (interquartile ranges [IQRs]) in cases of skewed data, or numbers (percentages). Differences in characteristics between baseline and follow-up variables were tested with paired *t* tests for mean values, Wilcoxon signed rank tests for median values, and McNemar tests for paired dichotomous variables. The differences between participants in the follow-up investigation and persons lost to follow-up were tested with two–sample *t* tests, Wilcoxon rank sum tests, two-sample tests of proportions, or Fisher exact test as appropriate.

The 14 missing values in ambulatory BP were replaced by the office BP values.

The change in GFR (ΔGFR) from baseline to follow-up was calculated for each person ($\Delta GFR = GFR_{follow\text{-}up} - GFR_{baseline}$ in milliliters per minute; not indexed by body surface area). We defined an increased GFR within the

Table 1. Population characteristics at baseline and follow-up in the Renal Iohexol Clearance Survey in Tromsø 6 Follow-Up Study

Characteristics	Baseline	Follow-up	*P* Value
N (%)	1246	1246	
Men, *n* (%)	620 (49.8)	620 (49.8)	
Age, yr	57.9 (3.9)	63.5 (4.0)	
Height, cm	170.9 (8.6)	170.7 (8.7)	<0.001
Body weight, kg	79.1 (13.6)	78.9 (13.9)	0.33
Body mass index, kg/m^2	27.0 (3.7)	27.0 (3.9)	0.45
Current smoker, *n* (%)	225 (18.2)	162 (13.1)	0.01
Use of alcohol more than once a week, *n* (%)	358 (28.7)	420 (33.7)	<0.001
LDL cholesterol, mg/dl	141.3 (32.8)	138.6 (34.8)	0.01
HDL cholesterol, mg/dl	59.9 (17.8)	63.3 (18.2)	<0.001
Fasting glucose, mg/dl	95.4 (8.3)	98.0 (8.8)	<0.001
Hemoglobin A1c, %	5.51 (0.33)	5.59 (0.29)	<0.001
Fasting triglycerides, mg/dl	88.5 (61.9–123.9)	88.5 (71.0–115.0)	0.09
Urinary albumin-to-creatinine ratio, mg/g	1.85 (0.89–4.46)	2.96 (0.89–5.02)	<0.001
Conventional systolic BP, mmHg	128.7 (17.3)	130.4 (16.9)	<0.001
Conventional diastolic BP, mmHg	83.2 (9.7)	81.9 (9.2)	<0.001
Ambulatory systolic BP, mmHg	129.5 (13.0)		
Ambulatory diastolic BP, mmHg	82.0 (8.7)		
Antihypertensive medication, *n* (%)	206 (16.6)	373 (29.9)	<0.001
ACE inhibitor	21 (1.7)	40 (3.2)	<0.001
A2 blocker	96 (7.7)	183 (15)	<0.001
Measured GFR,[a] ml/min	103.4 (19.4)	98.1 (19.5)	<0.001
Measured GFR,[a] ml/min per 1.73 m^2	93.6 (14.1)	88.9 (14.2)	<0.001

Estimates are given as the means (SDs), medians (interquartile ranges), or numbers (percentages). Not including the Renal Iohexol Clearance Survey in Tromsø 6 Follow-Up Study participants with diabetes at baseline or follow-up or participants with albuminuria at baseline. ACE, angiotensin-converting enzyme.

[a]GFR was measured by plasma iohexol clearance.

same individual as ΔGFR>0 ml/min. In sensitivity analyses, we defined increased GFR as a ΔGFR greater than the 95th percentile for the intraindividual day to day variation in the GFR measurement. The ACR was log transformed (natural logarithm) because of its skewed distribution, and the change in albumin-to-creatinine ratio (ΔACR) was calculated as log $ACR_{follow\text{-}up}$ − log $ACR_{baseline}$.

We used multiple linear regression to assess the association between ΔGFR and ΔACR and multivariable logistic regression to estimate the odds ratios for incident albuminuria at follow-up. We adjusted for variables that have been associated with both GFR and risk of albuminuria. In model 1, we adjusted for sex and baseline age. Model 2 included the variables in model 1 as well as baseline daytime diastolic ambulatory BP, body mass index, fasting glucose, current smoking, regular use of alcohol, and use of an angiotensin–converting enzyme inhibitor (ACE-i) or angiotensin receptor blocker (ARB). Model 3 included the variables in model 2 and added baseline triglycerides, LDL cholesterol, HDL cholesterol, C-reactive protein, fasting insulin, regular physical exercise (yes/no), and changes in BP, fasting glucose, body weight, smoking habit, and use of antihypertensive medications from baseline to follow-up.

We repeated the logistic regression analyses using exact logistic regression (27). Possible nonlinear associations between ΔGFR and ΔACR were explored using multiple fractional polynomials (28).

Stata software, version 14 (StataCorp., College Station, TX) was used for statistical analysis. Statistical significance was set at $P<0.05$.

Results

Patient Characteristics

In total, 1246 participants who were nondiabetic and without albuminuria at baseline of the RENIS-T6 Study had a follow-up GFR measurement in the RENIS-FU Study after a median (IQR) observation time of 5.6 years (IQR, 5.2–6.0) (Figure 1).

All population characteristics changed from baseline to follow-up, except for body weight and fasting triglycerides (Table 1). The percentage of persons receiving antihypertensive medication increased from 16.6% to 29.9%.

The characteristics of the included participants compared with the 288 lost to follow-up are presented in Supplemental Table 1. The differences were small, except for the percentage of current smokers (18 versus 28; $P<0.01$).

Distribution of ΔACR and ΔGFR

The distributions of ΔACR and ΔGFR are shown in Figure 2. One hundred seventy-six (14.2%) participants had undetectable urinary albumin concentration at both baseline and follow-up, corresponding to the spike at zero in Figure 2. The mean (SD) annual ΔGFR was −0.94 (2.2) ml/min per year. In total, 343 (27.6%) participants (167 women and 176 men) had an increased GFR defined as ΔGFR>0 ml/min from baseline to follow-up.

The Association between ΔGFR and ΔACR

ΔGFR as a continuous variable in the entire study population and ΔGFR dichotomized as an increased GFR (yes/no) were both positively associated with ΔACR in the multiple linear regression (Table 2). There were no significant nonlinear associations between ΔGFR and ΔACR analyzed with multiple fractional polynomials and no statistically significant age or sex interactions. When analyzing ΔACR in relation to the annual rate of GFR change instead of the total change in the study period, the $ACR_{follow\text{-}up}$-to-$ACR_{baseline}$ ratio increased by 8.4% (95% confidence interval, 1.8 to 15.5) per SD change in annual GFR in the fully adjusted model (P=0.01). The

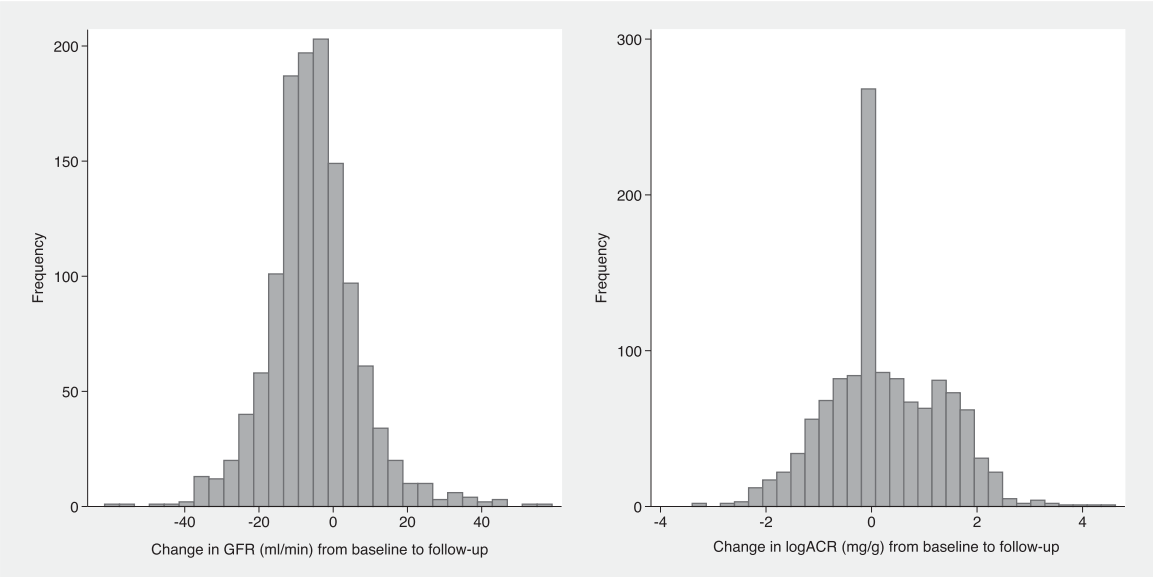

Figure 2. | **Distribution of change in GFR and ACR.** Frequency histogram of change in GFR (ΔGFR) and change in albumin-to-creatinine ratio (ΔACR) from baseline to follow-up. ΔGFR = $GFR_{follow\text{-}up}$ − $GFR_{baseline}$ in milliliters per minute. ΔACR = log $ACR_{follow\text{-}up}$ − log $ACR_{baseline}$.

Table 2. Association of change in albumin-to-creatinine ratio with change in GFR or increased GFR in separate linear regression analyses

Independent Variable	Model 1			Model 2			Model 3		
	ΔeGFR, %[a]	95% CI	*P* Value	ΔeGFR, %[a]	95% CI	*P* Value	ΔeGFR, %[a]	95% CI	*P* Value
ΔGFR, per SD higher	6.8	0.5 to 12.8	0.03	6.9	0.5 to 13.6	0.03	8.0	1.4 to 15.0	0.02
Increased GFR[b], yes/no	14.2	−0.2 to 30.6	0.05	14.6	0.1 to 31.3	0.05	16.3	1.1 to 33.7	0.03

Change in albumin-to-creatinine ratio: log albumin-to-creatinine ratio at follow-up − log albumin-to-creatinine ratio at baseline. Change in GFR (ΔGFR): measured GFR at follow-up − measured GFR at baseline (milliliters per minute). Model 1: adjusted for age and sex. Model 2: the same as model 1 and adjusted for baseline ambulatory daytime diastolic BP, body mass index, fasting glucose, current smoking, regular alcohol consumption, and use of angiotensin–converting enzyme inhibitor or angiotensin receptor blocker. Model 3: the same as model 2 and adjusted for baseline triglycerides, LDL cholesterol, HDL cholesterol, C-reactive protein, physical exercise, fasting insulin, and changes in diastolic BP, fasting glucose, body weight, smoking habits, and antihypertensive medication from baseline to follow-up. ΔeGFR, change in eGFR; 95% CI, 95% confidence interval.

[a]Represents the percentage change in albumin-to-creatinine ratio$_{\text{follow-up}}$-to-albumin-to-creatinine ratio$_{\text{baseline}}$ ratio.

[b]Increased GFR defined as ΔGFR>0 ml/min.

marginal association between ΔACR and annual ΔGFR in this model is shown in Figure 3.

Odds Ratios of Incident Albuminuria

Fourteen persons developed incident albuminuria at follow-up, eight of the 343 persons (2.3%) with an increased GFR (ΔGFR>0 ml/min) developed incident albuminuria at follow-up, and six of the 903 persons (0.7%) with a decreased GFR (ΔGFR≤0 ml/min) developed incident albuminuria at follow-up.

The odds ratios of incident albuminuria are presented in Table 3. Of the independent variables, only ΔGFR, increasing GFR (yes/no), and baseline fasting glucose were associated with new onset albuminuria. Similar results were obtained using exact logistic regression.

The results in Tables 2 and 3 were similar after adjusting for HbA1c instead of fasting glucose and after adjusting for ambulatory systolic instead of diastolic BP.

Sensitivity Analyses

In separate analyses, we excluded individuals with a measured GFR <60 ml/min per 1.73 m^2 (n=27) at baseline to investigate a subgroup without possible acute kidney disease or CKD. We also excluded participants ever on angiotensin blockers (at baseline or follow-up). The association between ΔGFR and albuminuria remained essentially unchanged. All analyses were repeated using a more conservative definition of increased GFR (defined as a >11 ml/min increase, which is above the 95th percentile of the day to day variation in the GFR measurement). Using this definition, the number of persons with an increased GFR was reduced from 343 (27.5%) to 91 (7.3%). The associations with ΔACR and incident albuminuria became stronger, although not significant for ΔACR (Supplemental Table 2). Finally, we obtained similar results when we included the 36 participants with diabetes at follow-up.

Discussion

Hyperfiltration followed by albuminuria has been proposed as a common pathway resulting in CKD (6); however, evidence supporting this hypothesis in persons without diabetes has been lacking. An obstacle to studies on hyperfiltration in humans has been the lack of consensus regarding how to measure hyperfiltration. Most investigators have defined hyperfiltration as an elevated whole–kidney GFR >120–150 ml/min per 1.73 m^2, often without adjusting for age (29). This definition may be poorly correlated with single-nephron hyperfiltration because of the interindividual variation in nephron endowment and because of the fact that the number of functional nephrons decreases with age as a result of age-related glomerulosclerosis (30,31).

We found that an increase in GFR within the same individual was associated with increases in ACR and incident albuminuria in a representative sample of the general middle–aged, nondiabetic population. This finding has important implications, because it supports the hypothesis of hyperfiltration as a common early stage of CKD and because an elevated ACR is a risk factor for CVD and mortality in the general population (2). Although only 14 persons developed incident albuminuria

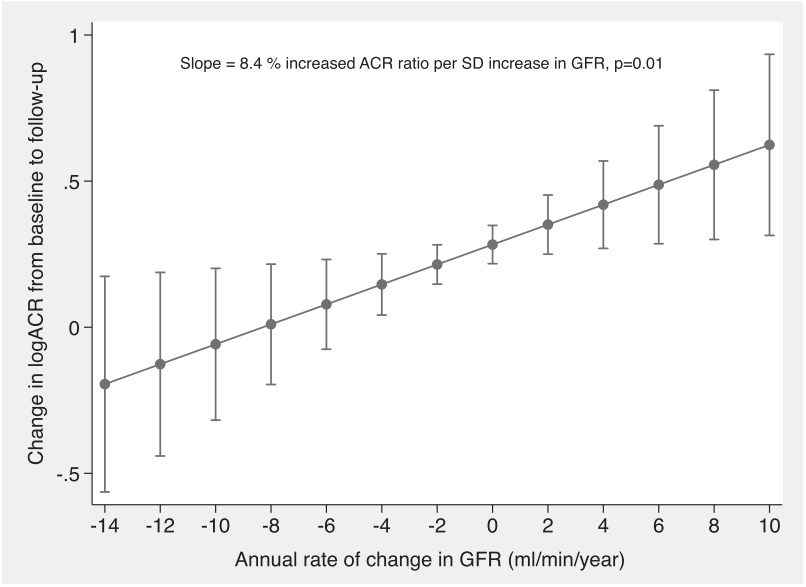

Figure 3. | **Association of annual change rate in GFR with change in albumin-to-creatinine ratio.** The marginal effect of annual GFR change on ΔACR (ΔACR = $\log ACR_{follow\text{-}up} - \log ACR_{baseline}$). Adjusted for sex, baseline age, ambulatory daytime diastolic BP, body mass index, fasting glucose, current smoking, regular alcohol consumption, triglycerides, LDL cholesterol, HDL cholesterol, use of angiotensin–converting enzyme inhibitors or angiotensin receptor blockers, C-reactive protein, fasting insulin, regular physical exercise (yes/no), and changes in BP, fasting glucose, body weight, smoking habit, and use of antihypertensive medication from baseline to follow-up. Vertical lines are 95% confidence intervals. ΔACR, change in albumin-to-creatinine ratio.

in this low-risk population, the association with an increased GFR was strong, with an odds ratio of 4.98 (95% confidence interval, 1.49 to 16.13) for those with an increased GFR in the fully adjusted model ($P<0.01$).

We are not aware of previous longitudinal studies on the risk of albuminuria associated with changes in GFR or hyperfiltration in the general population. However, a cross-sectional study of a general nondiabetic population reported an association between microalbuminuria and hyperfiltration defined as an elevated 24-hour urinary creatinine clearance (CrCl) (32). In a longitudinal study of 534 patients with hypertension, the risk of albuminuria increased across groups defined as persons with stable GFR (CrCl), incident hyperfiltration (CrCl>150 ml/min per 1.73 m^2), persistent hyperfiltration, and regression of hyperfiltration to normofiltration from baseline to follow-up (33). Although partially consistent with our findings, the studies are not comparable because of the different study populations and different methods of measurement of GFR.

Several studies on patients with types 1 and 2 diabetes have investigated the role of hyperfiltration in predicting albuminuria using different cutoff levels for hyperfiltration with or without adjustment for age and sex (8). The results have been inconsistent (8). Notably, the majority of the studies that measured GFR but not those that estimated GFR by creatinine or cystatin C observed an increased risk of developing albuminuria in persons with hyperfiltration (8,34). Recently, Ruggenenti *et al.* (35) reported that persistent hyperfiltration defined as a GFR>120 ml/min per 1.73 m^2 measured by plasma iohexol clearance at baseline and after 6 months but not hyperfiltration at baseline only predicted albuminuria after 4 years of follow-up in patients with type 2 diabetes.

Several other risk factors for CKD, such as obesity, prediabetes, metabolic syndrome, hypertension, and smoking, have been associated with hyperfiltration defined as having an elevated whole–kidney GFR (9,12–15,36–38). These conditions may cause albuminuria in part through mechanisms other than hyperfiltration, thus introducing a spurious association between hyperfiltration and albuminuria. However, our results remained similar after adjusting for these possible confounders, including the use of antihypertensive medication at baseline and follow-up.

Our findings should be interpreted with caution. Rather than being a causal factor, an increasing GFR could be a risk marker of an unmeasured pathologic process that leads to albuminuria, such as endothelial dysfunction or oxidative stress. In addition, hemodynamic effects without any long–term effects on ACR may have caused the observed association between ΔACR and ΔGFR. However, animal models have shown that single-nephron hyperfiltration and the coexisting glomerular hypertrophy induce shear stress and a loss of podocytes, which subsequently lead to albuminuria and glomerulosclerosis (39,40).

In humans, the number of functional glomeruli decreases with normal aging but is not closely correlated with the age-related decline in kidney volume, most likely because of the compensatory hyperfiltration and hypertrophy of the remaining nephrons (41). Indeed, we observed that the GFR increased along with an increasing ACR in a considerable proportion of healthy persons during the 5.6 years of follow-up. Moreover, not only an increased GFR but also increased glomerular volume have been associated with albuminuria in healthy adults, possibly caused by a loss of podocytes (42,43).

Table 3. Odds ratios for incident albuminuria analyzed with multiple logistic regression

Independent Variable	Model 1			Model 2			Model 3		
	OR	95% CI	*P* Value	OR	95% CI	*P* Value	OR	95% CI	*P* Value
Increasing GFR,[a] yes/no	3.55	1.21 to 10.35	0.02	4.22	1.41 to 12.67	<0.01	4.98	1.49 to 16.13	0.001
ΔGFR, per SD	1.79	1.21 to 2.67	0.004	1.94	1.23 to 2.79	0.003	2.13	1.38 to 3.32	0.001
Age, per yr	0.96	0.85 to 1.12	0.55	0.98	0.84 to 1.13	0.74	0.97	0.83 to 1.13	0.68
Men	0.87	0.28 to 2.57	0.81	0.51	0.15 to 1.79	0.29	0.41	0.10 to 1.61	0.20
Baseline ambulatory diastolic BP, per SD				1.28	0.72 to 2.27	0.38	1.10	0.57 to 1.95	0.85
Baseline BMI, per SD				1.27	0.75 to 2.16	0.91	1.47	0.80 to 2.70	0.20
Baseline fasting glucose, per SD				2.05	1.17 to 3.60	0.01	2.52	1.31 to 4.84	<0.01
Smoking at baseline, yes/no				2.81	0.81 to 9.72	0.10	2.49	0.52 to 11.89	0.25
Baseline regular alcohol use, yes/no				1.50	0.47 to 4.74	0.50	1.11	0.30 to 4.08	0.90
Baseline triglycerides, per SD							1.00	0.60 to 1.70	>0.99
Baseline LDL cholesterol, per SD							0.94	0.50 to 1.70	0.80
Baseline HDL cholesterol, per SD							0.94	0.36 to 1.90	0.90

Incident albuminuria defined as albumin-to-creatinine ratio >30 mg/g. Model 1: adjusted for age and sex. Model 2: independent variables adjusted for each other and the use of angiotensin–converting enzyme inhibitor or angiotensin receptor blocker at baseline. Model 3: the same as model 2 and adjusted for baseline triglycerides, LDL cholesterol, HDL cholesterol, C-reactive protein, physical exercise, fasting insulin, and changes in diastolic BP, fasting glucose, body weight, smoking status, and use of antihypertensive medication from baseline to follow-up. OR, odds ratio; 95% CI, 95% confidence interval; ΔGFR, measured GFR at follow-up − measured GFR at baseline (milliliters per minute); BMI, body mass index.
[a]Increased GFR from baseline to follow-up (ΔGFR>0 ml/min). Adjusted for the variables below but separately from ΔGFR per SD.

Our results and these morphologic data indicate that an increased GFR in aging individuals represents hyperfiltration, which may be maladaptive over time. Individuals with a reduced nephron number because of reduced nephron endowment or nephron loss by glomerular injury may be more vulnerable to this process, because these individuals exhibit a higher single-nephron GFR, a higher glomerular volume, and a greater risk of kidney failure (44). There is also evidence indicating that treatment that causes an initial drop in GFR, such as ACE-is for hypertension, sodium-glucose cotransport inhibitors in diabetes, and bariatric surgery in obesity (45–47), mediates a long–term renoprotective effect (35,47–49).

Recent population studies have reported an independent association between a longitudinal increase in eGFR and risk of CVD and death (3,4). Whether this is a true association or caused by confounding from lower serum creatinine levels in persons with chronic illness is unknown. However, in a previous study from the RENIS-T6 Study cohort, we reported a cross–sectional independent association between a high GFR (by iohexol clearance) and carotid atherosclerosis and left ventricular hypertrophy (50). The association between increased GFR and incident albuminuria in this study suggests that hyperfiltration may be a marker of increased cardiovascular risk.

This study has limitations. Only middle–aged white individuals participated, which limits the generalizability to other groups. Although we used a longitudinal study design, the analyses were partly cross-sectional, and we cannot exclude reverse causality between changes in GFR and albuminuria. There were few cases of incident albuminuria in this study of relatively healthy individuals. An elevated ACR below this cutoff is a risk factor for CVD and mortality in both high– and low–risk groups, but its role in predicting CKD in the general nondiabetic population is unclear (2). We did not have information regarding possible confounders, like vitamin D levels, changes in protein intake, and the dosage of ACE-i or ARB. However, participants met in the morning after an overnight fast at baseline and follow-up, and we obtained similar results after excluding those ever on an ACE-i or ARB.

The major strength of this study is the GFR measurements. The RENIS-T6 Study is the only longitudinal study with repeated measurements of GFR in a representative sample of the general population. Moreover, the intra-individual variation in the GFR measurement was lower than in most previous studies (51). We investigated the role of increased GFR within the same individuals, which is likely to represent hyperfiltration at the single-nephron level. Urine was collected on 3 separate days at both baseline and follow-up, albumin and creatinine were assessed in unfrozen specimens, and we adjusted for several variables, such as ambulatory BP and changes in antihypertensive medication during follow-up.

An increase in GFR was associated with increasing albuminuria in the general nondiabetic population. These findings support the idea that single-nephron hyperfiltration is a common risk factor for albuminuria, a well known CVD and CKD risk factor. Whether hyperfiltration is a risk factor for subsequent GFR decline, CVD, and mortality should be investigated.

Acknowledgments

We thank the staff at the Clinical Research Unit, University Hospital of North Norway for their assistance in planning the study, performing the procedures, and collecting data according to the Good Clinical Practice standard.

We thank the Northern Norway Regional Health Authority for funding support. The Renal Iohexol Clearance Survey in Tromsø 6 Study and the Renal Iohexol Clearance Survey in Tromsø 6 Follow-Up (RENIS-FU) Study were funded by the Northern Norway Regional Health Authority. The RENIS-FU Study was also supported by a grant from Boehringer Ingelheim.

The results presented in this paper have not been published in whole or in part, except in poster abstract format at Kidney Week 2015, American Society of Nephrology, November 3–8, 2015.

The funding source had no role in the design and conduct of the study.

Disclosures

None.

References

1. Naghavi M, Wang H; GBD 2013 Mortality and Causes of Death Collaborators: Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: A systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 385: 117–171, 2015
2. Matsushita K, van der Velde M, Astor BC, Woodward M, Levey AS, de Jong PE, Coresh J, Gansevoort RT; Chronic Kidney Disease Prognosis Consortium: Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: A collaborative meta-analysis. *Lancet* 375: 2073–2081, 2010
3. Turin TC, Coresh J, Tonelli M, Stevens PE, de Jong PE, Farmer CK, Matsushita K, Hemmelgarn BR: Change in the estimated glomerular filtration rate over time and risk of all-cause mortality. *Kidney Int* 83: 684–691, 2013
4. Coresh J, Turin TC, Matsushita K, Sang Y, Ballew SH, Appel LJ, Arima H, Chadban SJ, Cirillo M, Djurdjev O, Green JA, Heine GH, Inker LA, Irie F, Ishani A, Ix JH, Kovesdy CP, Marks A, Ohkubo T, Shalev V, Shankar A, Wen CP, de Jong PE, Iseki K, Stengel B, Gansevoort RT, Levey AS; CKD Prognosis Consortium: Decline in estimated glomerular filtration rate and subsequent risk of end-stage renal disease and mortality. *JAMA* 311: 2518–2531, 2014
5. Brenner BM, Lawler EV, Mackenzie HS: The hyperfiltration theory: A paradigm shift in nephrology. *Kidney Int* 49: 1774–1777, 1996
6. Ruggenenti P, Remuzzi G: Time to abandon microalbuminuria? *Kidney Int* 70: 1214–1222, 2006
7. Nelson RG, Bennett PH, Beck GJ, Tan M, Knowler WC, Mitch WE, Hirschman GH, Myers BD; Diabetic Renal Disease Study Group: Development and progression of renal disease in Pima Indians with non-insulin-dependent diabetes mellitus. *N Engl J Med* 335: 1636–1642, 1996
8. Jerums G, Premaratne E, Panagiotopoulos S, MacIsaac RJ: The clinical significance of hyperfiltration in diabetes. *Diabetologia* 53: 2093–2104, 2010
9. Melsom T, Schei J, Stefansson VT, Solbu MD, Jenssen TG, Mathisen UD, Wilsgaard T, Eriksen BO: Prediabetes and risk of glomerular hyperfiltration and albuminuria in the general non-diabetic population: A prospective cohort study. *Am J Kidney Dis* 67: 841–850, 2016
10. Melsom T, Mathisen UD, Ingebretsen OC, Jenssen TG, Njølstad I, Solbu MD, Toft I, Eriksen BO: Impaired fasting glucose is associated with renal hyperfiltration in the general population. *Diabetes Care* 34: 1546–1551, 2011
11. Okada R, Yasuda Y, Tsushita K, Wakai K, Hamajima N, Matsuo S: Glomerular hyperfiltration in prediabetes and prehypertension. *Nephrol Dial Transplant* 27: 1821–1825, 2012
12. Mathisen UD, Melsom T, Ingebretsen OC, Jenssen TG, Njølstad I, Solbu MD, Toft I, Eriksen BO: Ambulatory blood pressure is associated with measured glomerular filtration rate in the general middle-aged population. *J Hypertens* 30: 497–504, 2012
13. Wuerzner G, Pruijm M, Maillard M, Bovet P, Renaud C, Burnier M, Bochud M: Marked association between obesity and glomerular hyperfiltration: A cross-sectional study in an African population. *Am J Kidney Dis* 56: 303–312, 2010
14. Pinto-Sietsma SJ, Mulder J, Janssen WM, Hillege HL, de Zeeuw D, de Jong PE: Smoking is related to albuminuria and abnormal renal function in nondiabetic persons. *Ann Intern Med* 133: 585–591, 2000
15. Mathisen UD, Melsom T, Ingebretsen OC, Jenssen T, Njølstad I, Solbu MD, Toft I, Eriksen BO: Estimated GFR associates with cardiovascular risk factors independently of measured GFR. *J Am Soc Nephrol* 22: 927–937, 2011
16. Hoy WE, Douglas-Denton RN, Hughson MD, Cass A, Johnson K, Bertram JF: A stereological study of glomerular number and volume: Preliminary findings in a multiracial study of kidneys at autopsy. *Kidney Int Suppl* 83: S31–S37, 2003
17. Inker LA, Schmid CH, Tighiouart H, Eckfeldt JH, Feldman HI, Greene T, Kusek JW, Manzi J, Van Lente F, Zhang YL, Coresh J, Levey AS; CKD-EPI Investigators: Estimating glomerular filtration rate from serum creatinine and cystatin C. *N Engl J Med* 367: 20–29, 2012
18. Rule AD, Bailey KR, Lieske JC, Peyser PA, Turner ST: Estimating the glomerular filtration rate from serum creatinine is better than from cystatin C for evaluating risk factors associated with chronic kidney disease. *Kidney Int* 83: 1169–1176, 2013
19. Melsom T, Fuskevåg OM, Mathisen UD, Strand H, Schei J, Jenssen T, Solbu M, Eriksen BO: Estimated GFR is biased by non-traditional cardiovascular risk factors. *Am J Nephrol* 41: 7–15, 2015
20. Eriksen BO, Mathisen UD, Melsom T, Ingebretsen OC, Jenssen TG, Njølstad I, Solbu MD, Toft I: Cystatin C is not a better estimator of GFR than plasma creatinine in the general population. *Kidney Int* 78: 1305–1311, 2010
21. Nilsson-Ehle P: Iohexol clearance for the determination of glomerular filtration rate: 15 years' experience in clinical practice. *EJIFCC* 13: 1–5, 2002
22. Jacobsson L: A method for the calculation of renal clearance based on a single plasma sample. *Clin Physiol* 3: 297–305, 1983
23. Eriksen BO, Stefansson VT, Jenssen TG, Mathisen UD, Schei J, Solbu MD, Wilsgaard T, Melsom T: Elevated blood pressure is not associated with accelerated glomerular filtration rate decline in the general non-diabetic middle-aged population. *Kidney Int* 90: 404–410, 2016
24. Solbu MD, Kronborg J, Eriksen BO, Jenssen TG, Toft I: Cardiovascular risk-factors predict progression of urinary albumin-excretion in a general, non-diabetic population: A gender-specific follow-up study. *Atherosclerosis* 201: 398–406, 2008
25. Levey AS, de Jong PE, Coresh J, El Nahas M, Astor BC, Matsushita K, Gansevoort RT, Kasiske BL, Eckardt KU: The definition, classification, and prognosis of chronic kidney disease: A KDIGO Controversies Conference report. *Kidney Int* 80: 17–28, 2011
26. Melsom T, Mathisen UD, Eilertsen BAW, Ingebretsen OC, Jenssen T, Njølstad I, Solbu MD, Toft I, Eriksen BO: Physical exercise, fasting glucose, and renal hyperfiltration in the general population: The Renal Iohexol Clearance Survey in Tromsø 6 (RENIS-T6). *Clin J Am Soc Nephrol* 7: 1801–1810, 2012
27. Hirji KF, Mehta CR, Patel NR: Computing distributions for exact logistic regression. *J Am Stat Assoc* 82: 1110–1117, 1987
28. Royston P, Ambler G, Sauerbrei W: The use of fractional polynomials to model continuous risk variables in epidemiology. *Int J Epidemiol* 28: 964–974, 1999
29. Cachat F, Combescure C, Cauderay M, Girardin E, Chehade H: A systematic review of glomerular hyperfiltration assessment and definition in the medical literature. *Clin J Am Soc Nephrol* 10: 382–389, 2015
30. Kremers WK, Denic A, Lieske JC, Alexander MP, Kaushik V, Elsherbiny HE, Chakkera HA, Poggio ED, Rule AD: Distinguishing age-related from disease-related glomerulosclerosis on kidney biopsy: The Aging Kidney Anatomy study. *Nephrol Dial Transplant* 30: 2034–2039, 2015
31. Kasiske BL: Relationship between vascular disease and age-associated changes in the human kidney. *Kidney Int* 31: 1153–1159, 1987

32. Pinto-Sietsma SJ, Janssen WM, Hillege HL, Navis G, De Zeeuw D, De Jong PE: Urinary albumin excretion is associated with renal functional abnormalities in a nondiabetic population. *J Am Soc Nephrol* 11: 1882–1888, 2000
33. Palatini P, Mos L, Ballerini P, Mazzer A, Saladini F, Bortolazzi A, Cozzio S, Casiglia E; HARVEST Investigators: Relationship between GFR and albuminuria in stage 1 hypertension. *Clin J Am Soc Nephrol* 8: 59–66, 2013
34. Thomas MC, Moran JL, Harjutsalo V, Thorn L, Wadén J, Saraheimo M, Tolonen N, Leiviskä J, Jula A, Forsblom C, Groop PH; FinnDiane Study Group: Hyperfiltration in type 1 diabetes: Does it exist and does it matter for nephropathy? *Diabetologia* 55: 1505–1513, 2012
35. Ruggenenti P, Porrini EL, Gaspari F, Motterlini N, Cannata A, Carrara F, Cella C, Ferrari S, Stucchi N, Parvanova A, Iliev I, Dodesini AR, Trevisan R, Bossi A, Zaletel J, Remuzzi G; GFR Study Investigators: Glomerular hyperfiltration and renal disease progression in type 2 diabetes. *Diabetes Care* 35: 2061–2068, 2012
36. Ribstein J, du Cailar G, Mimran A: Combined renal effects of overweight and hypertension. *Hypertension* 26: 610–615, 1995
37. Tomaszewski M, Charchar FJ, Maric C, McClure J, Crawford L, Grzeszczak W, Sattar N, Zukowska-Szczechowska E, Dominiczak AF: Glomerular hyperfiltration: A new marker of metabolic risk. *Kidney Int* 71: 816–821, 2007
38. Palatini P, Dorigatti F, Saladini F, Benetti E, Mos L, Mazzer A, Zanata G, Garavelli G, Casiglia E: Factors associated with glomerular hyperfiltration in the early stage of hypertension. *Am J Hypertens* 25: 1011–1016, 2012
39. Srivastava T, Celsi GE, Sharma M, Dai H, McCarthy ET, Ruiz M, Cudmore PA, Alon US, Sharma R, Savin VA: Fluid flow shear stress over podocytes is increased in the solitary kidney. *Nephrol Dial Transplant* 29: 65–72, 2014
40. Kriz W, Lemley KV: A potential role for mechanical forces in the detachment of podocytes and the progression of CKD. *J Am Soc Nephrol* 26: 258–269, 2015
41. Glassock RJ, Rule AD: The implications of anatomical and functional changes of the aging kidney: With an emphasis on the glomeruli. *Kidney Int* 82: 270–277, 2012
42. Elsherbiny HE, Alexander MP, Kremers WK, Park WD, Poggio ED, Prieto M, Lieske JC, Rule AD: Nephron hypertrophy and glomerulosclerosis and their association with kidney function and risk factors among living kidney donors. *Clin J Am Soc Nephrol* 9: 1892–1902, 2014
43. Hodgin JB, Bitzer M, Wickman L, Afshinnia F, Wang SQ, O'Connor C, Yang Y, Meadowbrooke C, Chowdhury M, Kikuchi M, Wiggins JE, Wiggins RC: Glomerular aging and focal global glomerulosclerosis: A podometric perspective. *J Am Soc Nephrol* 26: 3162–3178, 2015
44. Luyckx VA, Bertram JF, Brenner BM, Fall C, Hoy WE, Ozanne SE, Vikse BE: Effect of fetal and child health on kidney development and long-term risk of hypertension and kidney disease. *Lancet* 382: 273–283, 2013
45. Chagnac A, Weinstein T, Herman M, Hirsh J, Gafter U, Ori Y: The effects of weight loss on renal function in patients with severe obesity. *J Am Soc Nephrol* 14: 1480–1486, 2003
46. Cherney DZ, Perkins BA, Soleymanlou N, Maione M, Lai V, Lee A, Fagan NM, Woerle HJ, Johansen OE, Broedl UC, von Eynatten M: Renal hemodynamic effect of sodium-glucose cotransporter 2 inhibition in patients with type 1 diabetes mellitus. *Circulation* 129: 587–597, 2014
47. Holtkamp FA, de Zeeuw D, Thomas MC, Cooper ME, de Graeff PA, Hillege HJ, Parving HH, Brenner BM, Shahinfar S, Lambers Heerspink HJ: An acute fall in estimated glomerular filtration rate during treatment with losartan predicts a slower decrease in long-term renal function. *Kidney Int* 80: 282–287, 2011
48. Górriz JL, Nieto J, Navarro-González JF, Molina P, Martínez-Castelao A, Pallardó LM: Nephroprotection by hypoglycemic agents: Do we have supporting data? *J Clin Med* 4: 1866–1889, 2015
49. Bolignano D, Zoccali C: Effects of weight loss on renal function in obese CKD patients: A systematic review. *Nephrol Dial Transplant* 28[Suppl 4]: iv82–iv98, 2013
50. Eriksen BO, Løchen ML, Arntzen KA, Bertelsen G, Eilertsen BA, von Hanno T, Herder M, Jenssen TG, Mathisen UD, Melsom T, Njølstad I, Solbu MD, Toft I, Mathiesen EB: Subclinical cardiovascular disease is associated with a high glomerular filtration rate in the nondiabetic general population. *Kidney Int* 86: 146–153, 2014
51. Stevens LA, Levey AS: Measured GFR as a confirmatory test for estimated GFR. *J Am Soc Nephrol* 20: 2305–2313, 2009

Received: May 5, 2016 **Accepted:** August 2, 2016

Published online ahead of print. Publication date available at www.cjasn.org.

This article contains supplemental material online at http://cjasn.asnjournals.org/lookup/suppl/doi:10.2215/CJN.04940516/-/DCSupplemental.