Cross Sectional Analysis of Chronic Kidney Disease Complications

By Glomerular Filtration Rate and Albuminuria

A thesis
submitted by

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In partial fulfillment of the requirements
for the degree of

Master of Science
In

Clinical and Translational Science

TUFTS UNIVERSITY
Sackler School of Graduate Biomedical Sciences
May, 2011

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Abstract:

Introduction: Albuminuria is strongly associated with future risk for cardiovascular and kidney outcomes, and has been proposed to be included in the classification of chronic kidney disease (CKD) along with glomerular filtration rate (GFR). However, it is not known whether albuminuria is associated with concurrent complications of CKD. We aimed to determine the association of albuminuria with the complications of CKD in participants screened for enrollment in the Modification of Diet in Renal Disease (MDRD) Study.

Methods: In a cross-sectional analysis of 1665 participants screened for the MDRD Study, the association of albumin-creatinine ratio (ACR) and GFR with anemia (hemoglobin < 12 g/dL for women, <13.5 g/dL for men), acidosis (bicarbonate < 22 mmol/L), hyperphosphatemia (phosphate > 4.6 mg/dL) and hypertension (based on review of medical records and anti-hypertensive medication use) was evaluated using logistic and log-binomial regression. Albuminuria was determined by converting proteinuria to ACR and GFR was measured using iothalamate clearance.

Results: Mean GFR (±SD) was 39 ml/min/1.73m^2 (± 21) and the median (inter-quartile range, IQR) ACR was 152 (631) mg/g). In multivariable models adjusted for age, sex, race, kidney disease etiology and GFR, higher levels of ACR levels (>300 mg/g) were not associated with any complication (odds ratio (95% CI) for anemia 0.96 (0.66-1.39), acidosis 1.18 (0.80-1.74), hyperphosphatemia 1.83 (0.83-4.02) and hypertension 1.40 (0.91-2.16)) when compared to ACR levels <29 mg/g. Lower levels of GFR, however

were associated with all complications (p-values < 0.0001 for all complications). GFR levels lower than 29 ml/min/1.73m^2 were associated with higher odds (95% CI) of anemia 12.8 (8.4-19.3), acidosis 8.9 (5.4-14.8), hyperphosphatemia 36.2 (11.4-114.9) and hypertension 2.7 (1.8-3.9) compared to GFR levels 60-89 ml/min/1.73m^2.

Conclusions: ACR alone does not appear to provide additional information regarding CKD complications. Albuminuria may be included along with GFR in the classification of CKD based on the prognostic outcomes, but would not affect clinical action plans for decisions regarding evaluation and treatment of complications.

Acknowledgements

I would like to acknowledge my mentors Drs. Lesley Stevens and Mark Sarnak for their immense support and guidance and without whom this thesis would not have been possible. I would also like to acknowledge Hocine Tighiouart for his support with the statistical analysis and helping me understand SAS better. I would like to acknowledge Drs. David Kent and Christopher Schmid from the Sackler faculty, my fellow MS students and my Nephrology colleagues Shani Shastri, Navdeep Tangri and Smita Padala for their valuable input and support not only with the thesis, but also during the two years in the MS program. Another important person I would like to acknowledge is Dr. Scott Gilbert, Program Director of Nephrology Fellowship at Tufts Medical Center, for having given me the opportunity to become a fellow at the Division and thereby enroll in the MS program. I would also like to recognize Dr. Paul Muntner, an epidemiologist at the University of Alabama who provided valuable input for the thesis, Okparavero, Aghogho, Research Associate at our Nephrology Division who helped me with his excellent skills in Microsoft word, excel and Endnote and Nina Bonnoyer, Clinical Research Education Coordinator, Tufts CTSI for her immense support throughout the Sackler school. Finally, my family who put up with my absence and encouraged me to pursue my dream, I owe everything to them.

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Introduction:

Chronic kidney disease (CKD) is a major health problem with an increasing incidence and prevalence, is associated with poor outcomes, and is preventable. The National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) guidelines for the evaluation, classification and stratification of risk of CKD defines CKD by glomerular filtration rate (GFR) < 60 ml/min per 1.73 m^2 or the presence of kidney damage (most commonly by the level of albuminuria) for three or more months, and classifies it by the level of GFR.[1] The guidelines included stage specific clinical action plan to guide clinicians' evaluation and management of patients with CKD. The staging system has been criticized as it does not provide sufficient information about prognosis, leading to unnecessary investigations, referrals, cost and patient anxiety. [2-4]

Studies have consistently demonstrated that albuminuria is an independent risk factor for mortality, cardiovascular outcomes and progression of CKD. [5-8] Based on such data, a recent Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference recommended revision of the CKD staging system, such that CKD is classified by both level of albuminuria and GFR.[9] Thus far, the study of albuminuria has focused its association with future events. It remains unknown however whether albuminuria is associated with concurrent complications of CKD. The latter is relevant in establishing a clinical action plan and guiding physicians in their decision making and management at a particular patient encounter.

We evaluated whether albuminuria is associated with concurrent complications of CKD at participants screened for enrollment in the Modification of Diet in Renal Disease (MDRD) Study. We hypothesized that albuminuria would be associated with the prevalence of hypertension, anemia, hyperphosphatemia, or acidosis, and that these associations would persist despite adjustment for kidney disease etiology and level of GFR. We also evaluated if these associations would be modified by the level of GFR.

Methods:

Study Population:

The MDRD Study was a randomized, controlled trial of patients with reduced GFR, predominantly secondary to non-diabetic glomerular disease, tubulo-interstitial disease and polycystic kidney disease.[10] The goal of the study was to evaluate the effects of dietary protein restriction and strict blood pressure control on the progression of kidney disease. It was conducted between 1988 and 1993. Details of the screening and enrollment procedures have been published previously.[11-13] Briefly, entry criteria for the screening phase included age between 18 and 70 years, serum creatinine of 1.2 to 7.0 mg/dL in women, 1.4 to 7.0 mg/dL in men, or creatinine clearance less than 70 mL/min/1.73 m^2. Exclusion criteria included pregnancy, type 1 diabetes, insulin-dependent type 2 diabetes, glomerulonephritis due to autoimmune diseases such as systemic lupus erythematosus, obstructive uropathy, renal artery stenosis, proteinuria greater than 10 g/d, mean arterial pressure greater than 125 mm Hg, and prior kidney transplantation. A total of 2507 potential participants were screened, and 1795 met the criteria and were invited for participation into the baseline phase to determine eligibility

for the trial. Of the 1795 participants, 1665 had data on all the variables of interest for our analysis and are included in the current analysis. The investigational review board at Tufts Medical Center, Boston, MA, approved the study.

Exposure Variables:

Urine protein: 24 hour urine protein excretion was obtained in the MDRD Study. However, since guidelines, including the National Kidney Disease Education Program (NKDEP) currently recommend use of ACR to detect and evaluate CKD and it is currently the most commonly used measure of urine protein excretion in clinical practice and in research studies, we report most of our analyses using urine albumin to creatinine ratio (ACR).[14-16] 24 urine protein excretion was converted to ACR using the relationship observed in the Irbesartan in Diabetic Nephropathy Trial (IDNT) where ACR = 0.396*UPro 1.007*2.45(F)*Upro-0.07 (F).[17] We categorized ACR into clinically meaningful categories; <29 mg/g (normoalbuminuria), 30-299 mg/g (microalbuminuria) and >300 mg/g (microalbuminuria).[18-19]

GFR: GFR was measured using ^{125}I-iothalamate clearance. After injecting 35µCi of ^{125}I-iothalmate subcutaneously, urine and serum radioactivity were measured. Clearance was calculated using a time weighted mean of four serum activity measurements and a volume-weighted mean of four urine activity measurements. GFR measurements were corrected for body surface area to 1.73 m^2 using the height and weight of the patient[11]. Based on NKF guidelines GFR was categorized into 3 categories; GFR 60-89, 30-59 and < 29 ml/min/1.73 m^2.[20] Participants with CKD Stage 1 were excluded due to the small number of participants. Participants with CKD Stage 4 (GFR 15-29 ml/min/1.73 m^2) and

5 (GFR <15 ml/min/1.73 m^2) were combined into one category due to the small number of participants in Stage 5.

Kidney Disease Etiology: The type of kidney disease was initially classified into 23 categories based on history, biopsy and physician diagnosis but for this analysis it was collapsed into 3 broader categories as previously defined[21] ; glomerular disease, polycystic kidney disease (PKD) and others. Diabetes was defined based on review of medical records or patient history.[12]

Outcome variables:

The definitions were based on accepted cutoffs for patients with CKD (Appendix Table 1).[21-24] Anemia was defined as hemoglobin less than 12 g/dL for women or less than 13.5 g/dL for men; acidosis as serum bicarbonate level less than 22 mmol/L; hyperphosphatemia as phosphorus level more than 4.6 mg/dL; and hypertension was based on review of patient history (including the use of antihypertensive medications) or medical records.[21]

Statistical Analysis:

We summarized baseline clinical characteristics according to the ACR categories using proportions for categorical variables and means and standard deviations for normally distributed continuous variables or medians and the inter-quartile range for skewed variables. The trend across the ACR categories for the baseline characteristics were tested using Spearman rank correlation for continuous variables and Cochran Armitage trend test for categorical variables.

We first explored the optimal functional form for ACR using generalized additive models of log ACR for association of each outcome. Since we did not find any non-linear relationships between albuminuria and any of the complications we used the clinical categories of ACR described above in the primary analysis.

We used logistic regression to evaluate the association between ACR category and GFR stage to each of the complications of CKD, using ACR < 29 mg/g and GFR 60-89 ml/min/1.73m^2, as the reference groups, respectively. Models were initially unadjusted, but sequential models adjusted for age; age, sex, race and GFR (or ACR); and age, sex, race, diagnostic category of kidney disease and GFR (or ACR). P-values for trend were calculated by scoring each level of categorical variable and entering it into the logistic regression model as a linear variable. Model fit was tested using scatter plots, ROC curves and by residual diagnostics. We tested the interaction of ACR categories and GFR stages for modification of the effect of ACR on the complications by level of GFR.

We performed several sensitivity analyses. First, since ACR was not directly measured, we repeated the analyses using proteinuria in place of ACR, categorizing proteinuria by <199 mg/24 h, 200-999 mg/24 h and >1000 mg/24 h.[20, 25] Second, we used ACR and GFR as continuous variables. Since ACR was not distributed normally, we log transformed ACR. We then repeated the primary analyses of ACR categories and GFR stages with the complications using log-binomial regression to obtain prevalence ratios since some of the complications such as hypertension and anemia are frequent outcomes.

Statistical analyses were performed using SAS (version 9.2). A two-tailed p-value of <0.05 was considered statistically significant.

Results:

Baseline Characteristics:

The baseline characteristics of the study population according to the ACR categories are listed in Table 1. The mean age (±SD) of the cohort was 51 ± 13 years. Sixty percent of patients were male, 80% were white, and 6% had diabetes. Thirty two percent of patients had glomerular disease, 22% had polycystic kidney disease and 46% had tubulointerstitial, hypertension or other causes of kidney diseases. The mean GFR (±SD) was 38 ± 19 ml/min/1.73m^2, median (IQR) for ACR and proteinuria were 161 mg/g (642) and 320 mg/24 h, respectively. Patients with higher ACR were younger, less likely to be white and male and had lower GFR (P-value <0.001 for all). A higher proportion of glomerular disease was noted in the higher ACR category.

Complications by Level of Albuminuria:

The overall prevalence of anemia, acidosis, hyperphosphatemia and hypertension was 43%, 31%, 16% and 81% respectively. Across the three ACR categories there was a monotonic increase in the prevalence of anemia, acidosis, hyperphosphatemia and hypertension with increasing levels of albuminuria (Table 2).

In age adjusted analyses, there was a significant association between higher ACR levels with higher prevalence of all complications (p-value for all comparisons < 0.0001) (Table 3). Compared to ACR levels less than 29 mg/g, ACR greater than 300 mg/g was associated with higher odds ratio (95% CI) for anemia 2.68 (2.00-3.61), acidosis 2.55 (1.83-3.56), hyperphosphatemia 9.93 (4.98-19.80) and hypertension 1.96 (1.36-2.84) .

However, after adjustment for age, sex, race and GFR, higher ACR levels were associated only with a higher prevalence of hyperphosphatemia (p-value for trend = 0.04), and with further adjustment for etiology of kidney disease, the association with hyperphosphatemia was no longer significant (p=0.07).

Complications by Level of GFR:

The prevalence of anemia, acidosis, hyperphosphatemia and hypertension increased with decreasing GFR (p -value <0.0001) (Table 4). In age adjusted models and multivariable models adjusted for age, race, sex, ACR and diagnostic categories, lower GFR levels were significantly associated with a higher prevalence of anemia, acidosis, hyperphosphatemia and hypertension (p-value<0.0001 for all) (Table 5). Similarly, GFR levels lower than 29 ml/min/1.73m^2, when compared to GFR levels 60-89 ml/min/1.73m^2 were associated with higher odds of anemia, acidosis, hyperphosphatemia and hypertension.

Interaction of GFR and ACR:

Figure 1 shows the prevalence of CKD complications stratified by ACR categories and GFR stages. For all complications, there was a strong association with GFR within each ACR category. In contrast, the association of ACR with complications differed within GFR strata. In patients with GFR less than 29 ml/min/1.73 m^2, a progressively higher prevalence of hyperphosphatemia was noted with increasing levels of albuminuria, although the interaction was not significant (p-value = 0.7). There was no significant interaction for any of the other complications (p-value = 0.2 for anemia, for

hyperphosphatemia, p-value = 0.3 for acidosis and p-value = 0.2 for hypertension).

*Sensitivity Analyses**:***

The results were similar to the primary analysis with ACR when proteinuria was used as the exposure variable (Appendix Table 2). For example, in age adjusted analysis higher levels of proteinuria was associated with anemia, acidosis, hyperphosphatemia and hypertension (p–value <0.0001 for all), while in multivariable models adjusted for age, sex, race and GFR proteinuria greater than 1000 mg/24 h was associated with a higher odds (95% CI) of hyperphosphatemia 1.72 (1.10-2.69) but not with the other complications. Proteinuria greater than 1000 mg/24 h, however continued to be associated with a higher odds of hyperphosphatemia even after adjustment by kidney disease etiology (p-value for trend =0.04). The results were similar to the primary analysis when repeated using albuminuria and GFR as continuous variables (Appendix Table 3, 4) or when risk ratios were estimated using log-binomial regression (Appendix Table 5).

Discussion:

In this study of participants with predominantly non-diabetic CKD, there was no significant association between ACR and any of the complications. Higher levels of proteinuria however were significantly associated with hyperphosphatemia. In contrast, we observed strong associations between all complications and lower levels of GFR, consistent with previous reports.[1, 26] These differing results have implications in the management of chronic kidney disease, when considering combining both albuminuria

and GFR in CKD staging.

There are several possible mechanisms by which albuminuria could be associated with CKD complications, including the association of albuminuria with systemic inflammation contributing to the development of anemia and hypertension[27-28]; the association of albuminuria with an increased glomerular loss of erythropoietin and hormone binding protein such as transferrin contributing to the development of anemia[29]; and the association of albuminuria with proximal tubular damage contributing to the development of acidosis.[30] In this study of patients with progressive CKD and moderate proteinuria, we were unable to find any association. It is possible that the findings in this study are negative because most of the previously reported associations between albuminuria and CKD complications had been noted in patients with nephrotic syndrome where the urinary protein excretion is greater than 3000 mg/24 hours,[29] whereas few people with urinary protein excretion above this level were included in the MDRD Study. Thus, it is possible that associations between albuminuria and these complications may be more apparent in populations with more severe levels of albuminuria and we might not have been adequately powered to detect any associations. This could explain the trend towards hyperphosphatemia with higher levels of proteinuria we noted in our study. Second, positive associations may be more likely to be seen in populations where albuminuria is due to generalized endothelial disease and inflammation[27-28] , which may be the cause of complications in such populations, rather than albuminuria per se. In our study, albuminuria probably reflects the severity of kidney damage and not the generalized endothelial dysfunction. Finally, albuminuria might just be a surrogate in the pathway of

complications, as evidenced by the loss of significance when models were adjusted for GFR.

Results from a similar cross-sectional analysis of the complications of CKD by level of albuminuria and estimated GFR (eGFR) in the general population are consistent with one of the above hypotheses that the negative findings in our study are related to the specifics of the population.[48] In an analysis of National Health and Nutrition Examination Survey (NHANES) participants, there was a significant association between increasing ACR levels and anemia, acidosis, hypoalbuminemia, hyperparathyroidism and hypertension, although as in the current study, the magnitude of each was much weaker than its association to eGFR. The divergent findings between the two analyses may be secondary to the higher prevalence of albuminuria secondary to generalized endothelial damage in this general population samples, compared to the MDRD Study. All together, the different findings from these two studies suggest that the mechanisms underlying the development of CKD complications are complex and multifactorial.

Many studies have now consistently demonstrated that albuminuria is an independent predictor of mortality, cardiovascular outcomes and progression of CKD.[5, 7, 31-32] For example, in a long term follow-up of the NHANES III participants, the presence of albuminuria > 300 mg/g was more strongly associated with death than lower levels of eGFR.[6] Similarly, a Chronic Kidney Disease Prognosis Consortium established by the KDIGO compiled data from 21 cohorts with 105872 participants and published a meta-analysis analyzing the combined and independent associations of albuminuria and eGFR

with mortality and kidney outcomes. eGFR less than 60 mL/min/1.73 m^2 and ACR 10 mg/g or more were independent predictors of all-cause and cardiovascular mortality risk in the general population.[33] As such, albuminuria is of critical value in determining long term prognosis, and has therefore been proposed as an additional marker to GFR in CKD staging.

The findings in our study have significant implications when considering the issues surrounding the current CKD staging and proposals to include albuminuria along with GFR during re-classification of CKD severity as well as in the management of CKD complications at a given clinical encounter. In our study, albuminuria was not associated with any of the complications and it did not modify the effect of GFR on complications. These results suggest that albuminuria will not provide additional benefit in the evaluation and management of complications at a clinical encounter. When health care professionals encounter patients with CKD who have both a decreased GFR and elevated albuminuria they would have to assess the risks associated with GFR and albuminuria separately. For example, they could use the information on albuminuria for prognostic outcomes and initiate appropriate treatments for reduction in albuminuria such as treatment with renin angiotensin system blockers and target blood pressure of less than 130/80 in slowing the rate of progression of non-diabetic kidney disease.[34] Conversely, clinicians could use the level of GFR to guide screening and management of complications, adjustment of drug dosing, stratifying patients at risk of acute kidney injury when using contrast agents and planning for renal replacement therapy.[20, 35-36]

The strengths of this study include the study of a large number of patients from a well-established cohort, availability of measured GFR, detailed ascertainment of confounding variables, robust statistical methods and use of clinically relevant ACR cut-offs that allows for comparability with future studies from other cohorts and thus allow for generalizability of study results. The cross sectional study design is appropriate as the question being asked refers to point of care in the management of patients with CKD There are several limitations to our study. First, the cross-sectional nature of the study does not allow causality to be inferred. Second, ACR was not measured directly but rather derived from 24-h urine protein excretion using a relationship observed between ACR and 24-h protein excretion in the IDNT study, a study of diabetic nephropathy, where albumin is the predominant urinary protein. The MDRD Study, consisted of non-diabetic kidney disease and the total urine protein in this population likely contains in addition to albumin, non-albumin proteins such as beta-2 microglobulin, retinol binding protein and other low molecular weight proteins.[37] Thus the relationship observed in IDNT might not be accurate. However, analyses using proteinuria demonstrated similar results to ACR. Third, we were unable to analyze the association between albuminuria and other CKD complications such as secondary hyperparathyroidism, malnutrition and inflammation as we did not have all the variables in the study population. Finally, the results are generalizable only to younger patients with non-diabetic CKD. The results will need to be reproduced in other populations such as diabetic kidney disease and other kidney diseases not represented in the MDRD study.

In conclusion, ACR alone does not appear to be associated with the CKD complications

and no additional informational is obtained beyond what is already known with GFR. These findings in the management of CKD should be taken into account when considering including albuminuria level along with GFR in the classification of CKD, and for guiding physicians in the evaluation and care of patients at a clinical encounter. GFR and albuminuria represent different aspects of kidney disease and management decisions should be based on their individual association with complications and ability to predict adverse outcomes and should be assessed separately for their clinical utility.

Research Support:

This research is supported by a National Kidney Foundation/Amgen Research Fellowship grant.

Figure Legend:

3-D columns comparing the prevalence of CKD complications stratified by ACR and GFR. Abbreviation: ACR albumin-creatinine ratio, GFR glomerular filtration rate.

Table 1: Baseline characteristics overall and by Albumin-Creatinine Ratio (ACR) categories

Characteristics	Overall	ACR mg/g			
		<29	30-299	>300	p-trend
Total number of patients n (%)	1665	307 (18.4)	696 (41.8)	662 (39.8)	
Age (y)	51 (13)	56 (11)	50 (12)	49 (13)	<0.0001
Men (%)	60	84.0	46.8	64.2	0.0011
White (%)	80	86.6	82.8	74.8	<0.0001
Body mass index (kg/m2)	27 (5)	28 (4)	27 (5)	28 (5)	0.22
Diabetes (%)	6	3	4	9	<0.0001
Coronary Artery Disease n (%)	148 (8)	33 (10.7)	53 (7.6)	62 (9.4)	0.23
Serum albumin (g/dL)	4.0 (0.4)	4.2 (0.3)	4.1 (0.3)	3.8 (0.4)	<0.0001
Serum creatinine (mg/dL)	2.3 (1.2)	1.8 (0.7)	2.2 (1.0)	2.8 (1.3)	<0.0001
Potassium (mEq/L)	4.3 (0.6)	4.2 (0.5)	4.3 (0.6)	4.4 (0.6)	<0.0001
GFR (mL/min/1.73 m^2)	38 (19)	48 (17)	39 (19)	31 (17)	<0.0001
GFR 60-89 n (%)	223 (13.4)	69 (22.5)	104 (14.9)	50 (7.6)	<0.0001
GFR 30-59 n (%)	769 (46.2)	189 (61.6)	343 (49.3)	237 (35.8)	<0.0001
GFR <29 n (%)	673 (40.4)	49 (16)	249 (35.8)	375 (56.7)	<0.0001
Urine total protein mg/d[$]	320 (134)	40 (10)	210 (170)	2600 (2210)	<0.0001
Urine albumin-creatinine ratio mg/g[$]	161 (642)	17 (6)	106 (77)	1215 (993)	<0.0001
Kidney disease etiology n (%)					
PKD	368 (22.1)	75 (24.4)	239 (34.3)	54 (8.2)	<0.0001
GN (GN, Hereditary and DM)	539 (32.4)	26 (8.5)	150 (21.6)	363 (54.8)	<0.0001
Others	758 (45.5)	206 (67.1)	307 (44.1)	245 (37.0)	<0.0001
Hemoglobin (g/dL)	13.1 (1.9)	14 (1.6)	13 (1.8)	12.8 (2.16)	<0.0001
Bicarbonate (mEq/L)	23.3 (3.8)	24.4 (3.4)	23.4 (3.8)	22.5 (3.9)	<0.0001
Phosphorus (mg/dL)	3.8 (0.8)	3.4 (0.6)	3.8 (0.7)	4.0 (0.9)	<0.0001
Systolic blood pressure (mm Hg)	133 (18)	130 (18)	130 (18)	138 (19)	<0.0001
Diastolic blood pressure (mm Hg)	81 (11)	80 (10)	81 (11)	84 (11)	<0.0001

Means and SD unless mentioned, [$] Median (IQR).
Abbreviations: GFR Glomerular Filtration Rate, PKD Polycystic kidney disease, GN glomerulonephritis, DM diabetes

Table 2: Prevalence of complications across Albumin-Creatinine Ratio categories

	Overall	**ACR mg/g**			**p-trend**
		<29	**30-299**	**>300**	
Total number of patients n (%)	1665	307 (18.4)	696 (41.8)	662 (39.8)	
Anemia (%)	43	28.7	40.5	51.8	<0.0001
Acidosis (%)	31	18.6	29.7	38.2	<0.0001
Hyperphosphatemia (%)	16	2.9	12.9	24.3	<0.0001
Hypertension (%)	82	79.8	78.7	85.8	0.0045

Table 3 Association of CKD complications by level of Albumin-Creatinine Ratio (ACR) adjusted for age, sex, race, GFR and kidney disease etiology

Complication	**Adjustment**	**ACR, mg/g**			**p-trend**
		<29 (n=307)	**30-299 (n=696)**	**> 300 (n=662)**	
Anemia	Age	1 (ref)	**1.70 (1.27-2.28)**	**2.68 (2.00-3.61)**	**<0.0001**
	MV	1 (ref)	1.16 (0.82-1.63)	1.04 (0.73-1.47)	0.86
	MV2	1 (ref)	1.08 (0.76-1.52)	0.96 (0.66-1.39)	0.63
Acidosis	Age	1 (ref)	**1.77 (1.27-2.48)**	**2.55 (1.83-3.56)**	**<0.0001**
	MV	1 (ref)	1.17 (0.81-1.68)	1.20 (0.83-1.74)	0.38
	MV2	1 (ref)	1.17 (0.81-1.69)	1.18 (0.80-1.74)	0.48
Hyperphosphatemia	Age	1 (ref)	**4.66 (2.31-9.41)**	**9.93 (4.98-19.80)**	**<0.0001**
	MV	1 (ref)	1.44 (0.66-3.16)	1.88 (0.87-4.04)	**0.04**
	MV2	1 (ref)	1.42 (0.65-3.10)	1.83 (0.83-4.02)	0.07
Hypertension	Age	1 (ref)	1.12 (0.79-1.57)	**1.96 (1.36-2.84)**	**<0.0001**
	MV	1 (ref)	1.02 (0.71-1.47)	1.34 (0.90-1.99)	0.10
	MV2	1 (ref)	0.97 (0.67-1.41)	1.40 (0.91-2.16)	0.077

MV: Adjusted for age, sex, race and GFR continuous
MV2: Adjusted for age, sex, race, diagnostic categories and GFR continuous

Table 4:Prevalence of complications across Glomerular Filtration Rate (GFR) stages:

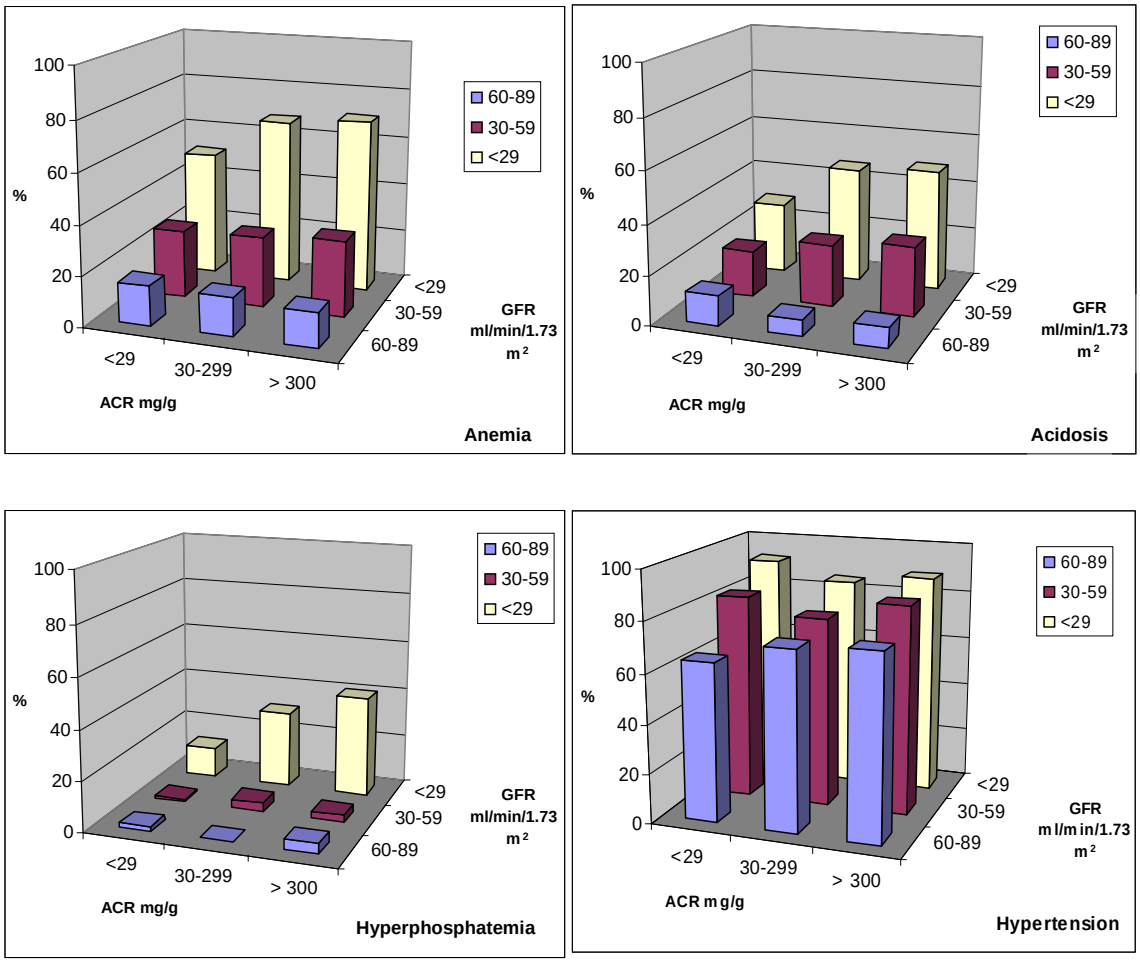
	Overall	**GFR ml/min/1.73m^2**			**p-trend**
		60-89 (n=223)	**30-59 (n=769)**	**<29 (n=673)**	
Total number of patients n (%)	1665	223 (13.4)	769 (46.2)	673 (40.4)	
Anemia (%)	43	15.3	29	67.8	<0.0001
Acidosis (%)	31	8.52	24.2	46.4	<0.0001
Hyperphosphatemia (%)	16	1.4	2.9	34.9	<0.0001
Hypertension (%)	82	69.9	80.2	87.4	<0.0001

Table 5 Association of CKD complications by level of Glomerular Filtration Rate adjusted by age, race, sex, ACR and kidney Disease etiology

Complication	Adjustment	GFR ml/min/1.73m^2			p-trend
		60-89 (n=223)	**30-59 (n=769)**	**<29 (n=673)**	
Anemia	Age	1 (ref)	**2.32 (1.56-3.45)**	**11.88 (7.96-17.73)**	<0.0001
	MV	1 (ref)	**2.45 (1.64-3.68)**	**12.76 (8.43-19.32)**	<0.0001
	MV2	1 (ref)	**2.49 (1.66-3.74)**	**12.89 (8.50-19.55)**	<0.0001
Acidosis	Age	1 (ref)	**3.61 (2.19-5.96)**	**9.72 (5.92-15.96)**	<0.0001
	MV	1 (ref)	**3.28 (2.11-5.75)**	**8.95 (5.42-14.77)**	<0.0001
	MV2	1 (ref)	**3.49 (2.11-5.75)**	**8.94 (5.42-14.76)**	<0.0001
Hyperphosphatemia	Age	1 (ref)	2.30 (0.68-7.76)	**41.90 (13.25-132.56)**	<0.0001
	MV	1 (ref)	2.17 (0.64-7.34)	**36.18 (11.39-114.94)**	<0.0001
	MV2	1 (ref)	2.19 (0.65-7.39)	**36.18 (11.38-114.97)**	<0.0001
Hypertension	Age	1 (ref)	**1.63 (1.16-2.29)**	**2.88 (1.99-4.17)**	<0.0001
	MV	1 (ref)	**1.65 (1.16-2.33)**	**2.70 (1.84-3.98)**	<0.0001
	MV2	1 (ref)	**1.66 (1.17-2.36)**	**2.67 (1.81-3.94)**	<0.0001

MV: Adjusted for age, sex, race and ACR continuous
MV2: Adjusted for age, sex, race, diagnostic categories and ACR continuous

Figure 1: Prevalence of Chronic Kidney Disease complications stratified by level of Albumin-Creatinine Ratio (ACR) and Glomerular Filtration Rate (GFR)



Appendix 1:

Appendix Table 1: Complications to be studied and the variables defining them

Complication	Variable	Definition	NKF/KDIGO Guideline Source
Anemia	Hemoglobin	< 13.5g/dL in males < 12g/dL in females	Anemia 2006
Acidosis	Serum Bicarbonate	<22 mEq/L	Bone Metabolism and Disease 2003
Hypertension	Blood pressure	Based on review of patient history (including the use of antihypertensive medications)	-
Mineral bone disorders	Serum Phosphorus	>4.6 mg/dL	Bone Metabolism and Disease 2003 and 2009

Reference[20-22, 24]

Appendix Table 2: Age and multivariable adjusted odds ratio of CKD complications associated with level of proteinuria

Complication		**Proteinuria mg (24hour)**			
	Adjustment	**<199 (n=734)**	**200-999 (n=409)**	**1000 (n=522)**	**p-trend**
Anemia	Age	1 (ref)	**1.85 (1.45-2.37)**	**2.46 (1.79-3.38)**	**<0.0001**
	MV	1 (ref)	0.97 (0.73-1.29)	1.25 (0.87-1.79)	0.35
	MV2	1 (ref)	1.00 (0.74-1.35)	1.2 (0.81-1.77)	0.44
Acidosis	Age	1 (ref)	**1.69 (1.30-2.18)**	**1.78 (1.29-2.46)**	**<0.0001**
	MV	1 (ref)	1.13 (0.85-1.49)	1.07 (0.75-1.51)	0.55
	MV2	1 (ref)	1.11 (0.82-1.48)	1.04 (0.71-1.52)	0.71
Hyperphosphatemia	Age	1 (ref)	**2.43 (1.77-3.33)**	**3.43 (2.37-4.95)**	**<0.0001**
	MV	1 (ref)	1.20 (0.81-1.77)	**1.72 (1.10-2.69)**	**0.02**
	MV2	1 (ref)	1.22 (0.81-1.83)	**1.70 (1.03-2.79)**	**0.04**
Hypertension	Age	1 (ref)	**1.44 (1.04-2.01)**	**2.35 (1.433.85)**	**<0.0001**
	MV	1 (ref)	1.05 (0.74-1.48)	1.65 (0.99-2.75)	0.09
	MV2	1 (ref)	1.14 (0.79-1.63)	**1.75 (1.02 -3.00)**	0.052

MV: Adjusted for age, sex, race and GFR continuous

MV2: Adjusted for age, sex, race, diagnostic categories and GFR continuous

Appendix Table 3: Association of complications associated with ACR as continuous variable

Complication	Adjustment	Odds Ratio*	p-value
Anemia	None	**1.28 (1.21-1.36)**	**<0.0001**
	Age	**1.28 (1.21-1.36)**	**<0.0001**
	MV	1.01 (0.94-1.08)	0.74
Acidosis	None	**1.25 (1.17-1.33)**	**<0.0001**
	Age	**1.23 (1.16-1.31)**	**<0.0001**
	MV	1.04 (0.95-1.13)	0.35
Hyperphosphatemia	None	**1.56 (1.42-1.70)**	**<0.0001**
	Age	**1.54 (1.41-1.69)**	**<0.0001**
	MV	**1.18 (1.04-1.35)**	**0.0001**
Hypertension	None	**1.13 (1.05-1.21)**	**0.0001**
	Age	**1.20 (1.11-1.30)**	**<0.0001**
	MV	**1.10 (1.01-1.21)**	0.04

MV adjusted for age, sex, race and GFR continuous. *Odds ratio per unit increase in logACR

Appendix Table 4: Association of complications associated with GFR as continuous variable

Complication	Adjustment	Odds Ratio	p-value
Anemia	None	**0.94 (0.93-0.94)**	**<0.0001**
	Age	**0.94 (0.93-0.94)**	**<0.0001**
	MV	**0.93 (0.93-0.95)**	**<0.0001**
Acidosis	None	**0.95 (0.95-0.96)**	**<0.0001**
	Age	**0.95 (0.94-0.96)**	**<0.0001**
	MV	**0.95 (0.95-0.96)**	**<0.0001**
Hyperphosphatemia	None	**0.86 (0.84-0.88)**	**<0.0001**
	Age	**0.86 (0.84-0.88)**	**<0.0001**
	MV	**0.86 (0.85-0.88)**	**<0.0001**
Hypertension	None	**0.98 (0.97-0.99)**	**<0.0001**
	Age	**0.98 (0.97-0.99)**	**<0.0001**
	MV	**0.98 (0.97-0.99)**	**<0.0001**

MV adjusted for age, sex, race and ACR continuous. *Odds ratio per unit increase in GFR

Appendix Table 5: Adjusted risk ratio of CKD complications associated with level of albuminuria.

Complication		**ACR, mg/g**			
	Adjustment	**<29 (n=307)**	**30-299 (n=696)**	**> 300 (n=662)**	**p-trend**
Anemia	Age	1 (ref)	**1.42 (1.16-1.73)**	**1.81 (1.49-2.20)**	**<0.0001**
	MV	1 (ref)	1.07 (0.88-1.29)	1.01 (0.84-1.23)	0.76
	MV2	1 (ref)	1.04 (0.86-1.26)	0.98 (0.81-1.20)	0.99
Acidosis	Age	1 (ref)	**1.55 (1.19-2.02)**	**1.97 (1.52-2.55)**	**<0.0001**
	MV	1 (ref)	1.12 (0.86-1.46)	1.14 (0.88-1.48)	0.46
	MV2	1 (ref)	1.13 (0.86-1.47)	1.13 (0.86-1.48)	0.55
Hyperphosphatemia	Age	1 (ref)	**7.81 (4.03-15.13)**	**4.21 (2.15-8.26)**	**<0.0001**
	MV	1 (ref)	1.49 (0.79-2.79)	1.72 (0.92-3.21)	**0.02**
	MV2	1 (ref)	1.47 (0.78-2.76)	1.69 (0.91-3.17)	0.04
Hypertension	Age	1 (ref)	1.02 (0.95-1.09)	**1.12 (1.05-1.19)**	**<0.0001**
	MV	1 (ref)	0.99 (0.93-1.06)	1.03 (0.97-1.10)	**0.05**
	MV2	1 (ref)	0.98 (0.92-1.05)	1.04 (0.97-1.12)	0.06

MV adjusted for age, sex and GFR continuous
MV2 adjusted for age, sex, race, diagnostic categories and GFR continuous

Appendix II

Additional Background Information:

Chronic Kidney Disease:

The National Kidney foundation-Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) guidelines for the evaluation, classification and stratification of risk of Chronic Kidney Disease (CKD) defines CKD by glomerular filtration rate (GFR) < 60 ml/min per 1.73 m^2 or kidney damage for three or more months and classifies it by the level of GFR[1]. Using this definition and classification system, the estimated prevalence of CKD is 23.2 million or 11.5% of the US adult population[33, 38]. One of the criticisms of the CKD definition and classification system has been the concern for over-diagnosis and mis-diagnosis of CKD, especially in the elderly who have a higher proportion of CKD Stage 3 since the current classification system does not adequately describe CKD severity nor predict prognosis [2, 39]. For example, in a large managed care organization in the US, only about 1.3% of patients with CKD stage 3 progressed to ESRD over a 5 year follow up[3]. Similarly in another study, in the United Kingdom, only 4% of patients with CKD progressed to ESRD[4]. The implications of these criticisms are that over- or misdiagnosis may lead to unnecessary investigations and referrals, leading to excessive consumption of resources, as well as to patient anxiety

Revised classification systems: Kidney Disease Improving Global Outcomes (KDIGO convened a Controversies Conference on "Chronic Kidney Disease: Definition, Classification and Prognosis" in London, UK in October 2009 to discuss changes to the definition and classification of CKD, and particularly to review data on albuminuria as a

prognostic factor for adverse outcomes (Appendix II Table 1 and Figure 1). The conference members recommended to consider incorporating albuminuria into the classification system, in addition to GFR stages[9].

Possible mechanisms by which albuminuria will be associated with complications:

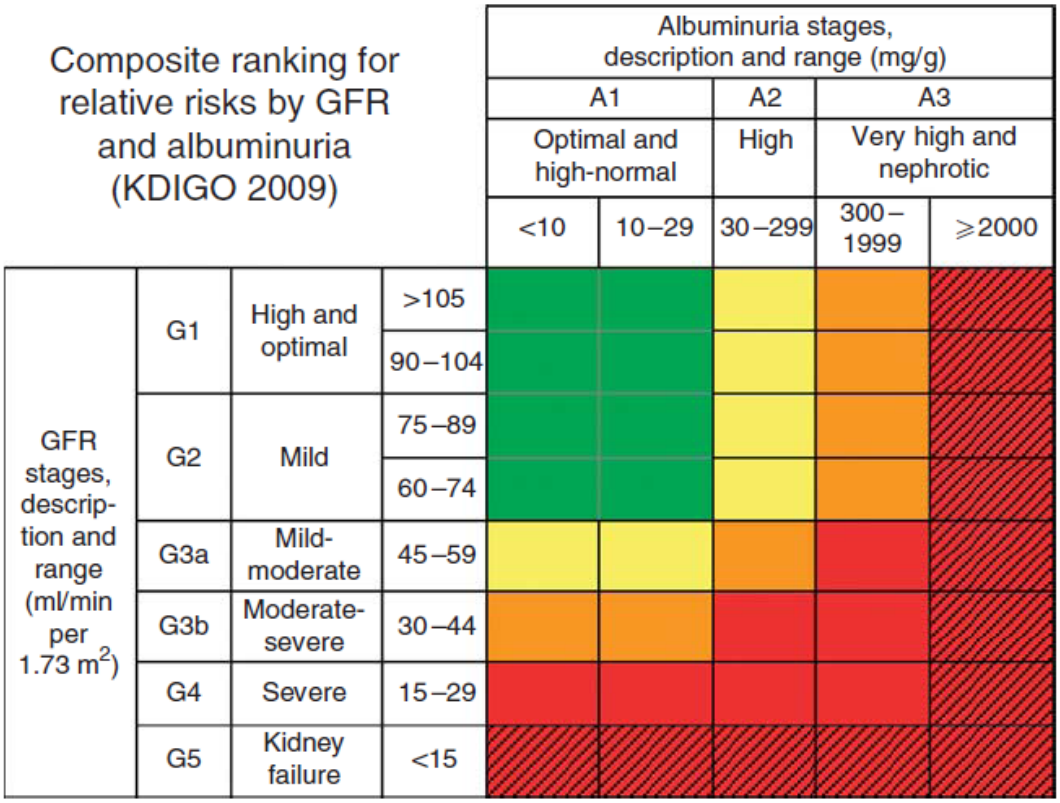
Albuminuria occurs as a result of glomerular capillary damage and subsequently leads to an increased permeability to macromolecules and loss of albumin into the urinary space, and as such, it is a biomarker of kidney damage[40] In addition, it is thought to result from generalized endothelial dysfunction[41]. Experimental models have suggested that albuminuria, regardless of etiology, can cause glomerulosclerosis and tubulointerstitial damage, which is supported by the renoprotective effect of albuminuria reduction[42, 40]. As such, there are several mechanisms by which albuminuria may be associated with CKD complications: (1) Albuminuria is a surrogate of inflammatory status, which may be a contributing cause to the development of anemia in CKD [27, 43]; (2) Albuminuria causes tubulointerstitial damage, which can cause aminoaciduria, renal tubular acidosis, and diminished erythropoietin production[44]; (3) Albuminuria is a manifestation of glomerular disease and thereby is a direct cause of the complication through the glomerular loss of erythropoietin and hormone binding proteins such as transferrin. In addition albuminuria by causing glomerulosclerosis might contribute to the glomerular loss [29, 45-46].

Appendix II Table 1: Proposed revised chronic kidney disease classification (KDIGO 2009)

Clinical Diagnosis	GFR stages (ml/min per 1.73 m^2)	Albuminuria stages (ACR, mg/g)
Diabetes	>90	<30
Hypertension	60–89	
Glomerular disease	45–59	30–299
Many others	30–44	
Transplant	15–29	>300
Unknown	<15	

Abbreviations: ACR, albumin-to-creatinine ratio; GFR, glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes. Adapted from[8]

Appendix II Figure 1: Composite Ranking for Relative Risks by glomerular filtration rate (GFR) and Albuminuria (Kidney Disease: Improving Global Outcomes (KDIGO) 2009).



Risk categories based on a composite ranking of 5 outcomes (All-cause mortality, Cardiovascular mortality, Kidney failure, Acute kidney injury and progressive CKD) with the colors indicating groups of patients at progressively higher risk for the outcomes. The lowest-risk categories are shaded green; moderate-, high-, and very high–risk categories are shaded from yellow to red. Adapted from[8]

Appendix III

Analysis in the Irbesartan in Diabetic Nephropathy Trial (IDNT):

We wanted to explore the possibility that albuminuria would be associated with the CKD complications across multiple etiologies of kidney disease. Since the MDRD study consisted mainly of non-diabetic kidney disease we chose to analyze the IDNT cohort in a parallel study. The preliminary results are discussed here. IDNT was a multicenter randomized controlled trial comparing irbesartan, or amlodipine, with placebo on progression of diabetic kidney disease. [47]

Methods:

The IDNT study was conducted from 1996 to 1999 and included 1,715 patients. The following inclusion criteria were used: type 2 diabetes, hypertension (systolic or diastolic blood pressure >135 or >85 mm Hg, respectively; antihypertensive medication use), baseline urine total protein level of 0.9 g/d or greater, and baseline serum creatinine level of 1.0 to 3.0 mg/dL. We excluded 139 patients that did not have all the outcome variables of interest.

Exposure Variables:

Urine protein: Both 24 hour urine protein and albumin excretion, and spot albumin-creatinine and protein – creatinine were obtained in the IDNT study. We reported analyses using both ACR and 24 hour urine protein excretion. In this analysis we used the ACR equivalents of the following clinically meaningful proteinuria cut-offs < 1 gram /day 1- 3.5 grams/day and more than 3.5 grams/day, derived using a relationship observed in the Irbesartan in Diabetic Nephropathy Trial (IDNT) where ACR =

0.396*UPro 1.007*2.45(F)*Upro-0.07 (F)[17]. The equivalent cut-offs were 590 mg/g, 590-2,200 mg/g and >2,200 mg/g.

GFR: GFR was estimated using the CKD-EPI equation [38]. The equation was developed in a diverse population of people with and without kidney disease and diabetes, and is therefore more appropriate for comparison across datasets. The equation consists of sex-specific spline transformation of log serum creatinine and two levels of race (Black vs other):): Log(GFR) = 4.95+ [α_1 × min(log(SCR/k),0)] + [α_2 × max(log(SCR/k),0)] + [0.0178 × Female] +[0.146 ×black] – [0.0071 × Age], where k = 0.9 for males and k = 0.7 for females. If serum creatinine < k, then α_1 is -0.329 and -0.411, for females and males respectively. If serum creatinine $\geq$ k, then α_2 is 1.209. Based on NKF guidelines[20] GFR was categorized into 3 categories; GFR > 60-89, 30-59 and < 29 ml/min/1.73 m^2 **.** Participants with CKD Stage 1 were excluded due to the small number of participants. Participants with CKD Stage 4 (GFR 15-29) and 5 (GFR <15) were combined to one category due to the small number of participants in stage 5.

Outcome variables:

The definitions were based on accepted cutoffs for patients with CKD[22-24]. Anemia was defined as hemoglobin less than 12 g/dL for women or less than 13.5 g/dL for men; hyperphosphatemia as phosphorus level more than 4.6 mg/dL; and hypertension was based on review of patient history or medical records. More details regarding the definition are listed in Appendix III Table 1.

Statistical Analysis:

Descriptive data were summarized according to the ACR categories and GFR stages using proportions, means and standard deviations for normally distributed continuous variables or medians and the inter-quartile range for skewed variables. The trend across the ACR categories were tested using Spearman rank correlation for continuous variables and Cochran Armitage trend test for categorical variables. Logistic regression was used to evaluate the association between ACR category and GFR stage to each of the complications of CKD. Models were initially unadjusted, but sequential models adjusted for age; age, sex, race and GFR (or ACR); and age, sex, race and GFR (or ACR).

Sensitivity Analyses:

We repeated the analyses using different cut-offs of ACR that were obtained by rank order.

Results:

Baseline Characteristics:

The baseline characteristics of the study population according to the ACR categories are listed in Appendix III Table 2. 1576 participants who had all data on all the variables of interest were included in the main analysis. The mean age (±SD) of the cohort was 59 ± 8 years. Sixty seven percent of patients were male and 86% were white. The underlying kidney disease was presumed to be diabetic nephropathy and all the participants had hypertension. The mean systolic and diastolic blood pressures (±SD) were 159 (±20) mm Hg and 87 (±11) mm Hg. The mean GFR (±SD) was 46 ± 17 ml/min/1.73m^2, median (IQR) ACR was 1477 mg/g (1935) and median (IQR) proteinuria was 2929 mg/g (3465). Patients with higher ACR were younger and had lower GFR.

Albuminuria:

The overall prevalence of anemia and hyperphosphatemia was 49% and 11% respectively. Across the three albuminuria categories there was a monotonic increase in the prevalence of anemia and hyperphosphatemia with increasing levels of albuminuria (Appendix Table 3). In multivariable models adjusted for age, sex race and eGFR, ACR greater than 2200 mg/g was associated with higher odds (95% CI) of anemia 1.33 (1.07-1.66) and hyperphosphatemia 1.85 (1.31-2.62) when compared to ACR levels 590-2200 mg/g. (Appendix III Table 4).

eGFR:

Across the three eGFR stages there was a monotonic increase in the prevalence of anemia and hyperphosphatemia with decreasing levels of eGFR (Appendix III Table 5). In multivariable models adjusted for age, sex race and ACR, eGFR less than 29 ml/min/1.73 m^2 was associated with higher odds (95% CI) of anemia 5.53 (3.93-7.80) and hyperphosphatemia 2.32 (1.41-3.81) when compared to GFR levels 60-89 ml/min/1.73m^2 (Appendix III Table 6).

Sensitivity Analysis:

The results were similar to the primary analysis when ACR were categorized by rank order (Appendix III Table 7). In age and multivariable adjusted models higher levels of albuminuria were associated with a significant trend with anemia (p-trend 0.02) and hyperphosphatemia (0.01). In multivariable models adjusted for age, sex race and eGFR, ACR greater than 3366 mg/g was associated with higher odds (95% CI) of anemia 1.57 (1.16-2.13) and hyperphosphatemia 2.20 (1.35-3.57) when compared to ACR levels less than 1059 mg/g.

Appendix III Table 1: Complications to be studied and the variables defining them

Complication	Variable	Definition	NKF/KDIGO Guideline Source
Anemia	Hemoglobin	< 13.5g/dL in males < 12g/dL in females	Anemia 2006
Mineral bone disorders	Serum Phosphorus	>4.6 mg/dL	Bone Metabolism and Disease 2003 and 2008

References[20-22]

Appendix III Table 2: Baseline Characteristics in the IDNT study stratified by Proteinuria

	Overall	**Urine Protein Excretion g/24-h (ACR mg/g)**			**p-trend**
		<1 (590)	**1.0-3.5 (590-2200)**	**>3.5 (2200)**	
Total no. of patients n (%)	1576	99 (6)	812 (52)	665 (42)	
Age (y)	59 (8)	61 (6)	60 (7)	58 (8)	<0.0001
Men (%)	67	70	66	67	0.98
White n (%)	86	91	86	86	0.60
Body mass index (kg/m2)	30.9 (5.8)	30.6 (5.2)	30.5 (5.6)	31.5 (6)	0.01
Coronary Artery Disease %	46	45	43	50	0.05
SBP (mm Hg)	159 (20)	152 (17)	157 (19)	162 (20)	<0.0001
DBP (mm Hg)	87 (11)	84 (11)	86 (11)	88 (11)	0.03
Serum Glucose (mg/dL)	187 (80)	183 (76)	183 (81)	192 (79)	0.05
Serum albumin (g/dL)	3.8 (0.4)	4.1 (0.2)	3.9 (0.3)	3.6 (0.5)	<0.0001
Serum creatinine (mg/dL)	1.7 (0.6)	1.5 (0.4)	1.6 (0.5)	1.8 (0.6)	<0.0001
Potassium (mEQ/L)	4.6 (0.5)	4.6 (0.4)	4.6 (0.5)	4.6 (0.5)	0.73
GFR (ml/min/1.73 m2)	46 (17)	51 (15)	49 (17)	43 (16)	<0.0001
GFR 60-89 n (%)	369 (23)	25 (25)	230 (28)	114 (17)	<0.0001
GFR 30-59 n (%)	888 (56)	65 (66)	447 (55)	376 (57)	<0.0001
GFR <29 n (%)	319 (20)	9 (9)	135 (17)	175 (26)	<0.0001
Urine total protein (g/d)$	2929 (3465)	917 (148)	2015 (1174)	5715 (3826)	<0.0001
ACR (mg/g)$	1477 (1935)	381 (219)	953 (798)	2884 (2126)	<0.0001
Hemoglobin (g/dL)	12.9 (1.9)	13.5 (1.5)	13.1(1.9)	12.6 (1.9)	<0.0001
Phosphorus (mg/dL)	3.8 (0.7)	3.6 (0.5)	3.7 (0.6)	3.9 (0.7)	<0.0001

Means and SD unless mentioned, $ Median (IQR) SBP Systolic blood pressure DBP diastolic blood pressure GFR Glomerular Filtration Rate ACR albumin-creatinine ratio

Appendix III Table 3: Prevalence of complications across Proteinuria (ACR) categories

	Overall	**Proteinuria g/24-h (ACR mg/g)**			
		<1 (590)	**1.0-3.5 (590-2200)**	**>3.5 (2200)**	**p-trend**
Total no. of patients n (%)	1576	99 (6)	812 (52)	665 (42)	
Anemia n (%)	49	29	45	57	<0.0001
Hyperphosphatemia n (%)	11	4	8	16	<0.0001

Means and SD unless mentioned

Appendix III Table 4: Association of CKD complications by level of Albumin-Creatinine Ratio (ACR) adjusted for age, sex, race, GFR and kidney disease etiology

Complication	**Adjustment**	**Proteinuria g/24-h (ACR mg/g)**			**p-trend**
		<1 (590)	**1.0-3.5 (590-2200)**	**>3.5 (2200)**	
Anemia	Age	0.54 (0.35-0.83)	1 (ref)	**1.59 (1.29-1.96)**	**<0.0001**
	MV	0.57 (0.36-0.90)	1 (ref)	**1.33 (1.07-1.66)**	**0.02**
Hyperphosphatemia	Age	0.65 (0.27-1.54)	1 (ref)	**1.91 (1.37-2.66)**	**<0.0001**
	MV	0.71 (.30-1.71)	1 (ref)	**1.85 (1.31-2.62)**	**0.01**

MV: Adjusted for age, sex, race and GFR continuous

Appendix III Table 5: Prevalence of complications across GFR Stages

	Overall	GFR ml/min/1.73 m2			
		60-89 (n=382)	30-59 (n=916)	<29 (n=344)	p-trend
Total no. of patients n (%)	1576	99 (6)	812 (52)	665 (42)	
Anemia (%)	49	32	49	69	<0.0001
Hyperphosphatemia (%)	11	8	10	21	<0.0001

Means and SD unless mentioned

Appendix III Table 6: Association of CKD complications by level of Glomerular Filtration Rate adjusted by age, race, sex, ACR and kidney Disease etiology

Complication	Adjustment	GFR ml/min/1.73 m2			p-trend
		60-89 (n=382)	30-59 (n=916)	<29 (n=344)	
Anemia	Age	1 (ref)	**2.20 (1.70-2.84)**	**5.34 (3.88-7.36)**	**<0.0001**
	MV	1 (ref)	**2.23 (1.71-2.91)**	**5.53 (3.93-7.80)**	**<0.0001**
Hyperphosphatemia	Age	1 (ref)	1.42 (0.91-2.22)	**4.07 (2.54-6.50)**	**<0.0001**
	MV	1 (ref)	1.14 (0.72-1.79)	**2.32 (1.41-3.81)**	**<0.0001**

MV: Adjusted for age, sex, race and ACR continuous

Appendix III Table 7: Association of CKD complications by level of Albumin-Creatinine Ratio (ACR) adjusted for age, sex, race, GFR and kidney disease etiology, categorized by rank order in the IDNT study

Complication	Adjustment	24-hour Albuminuria, mg/g			p-trend
		<1059 (n=388)	**1059-3366 (n=769)**	**> 3366 (n=419)**	
Anemia	Age	1 (ref)	**1.43 (1.12-1.83)**	**2.10 (1.58-2.78)**	**<0.0001**
	MV	1 (ref)	**1.32 (1.02-1.72)**	**1.57 (1.16-2.13)**	**0.02**
Hyperphosphatemia	Age	1 (ref)	1.44 (0.92-2.26)	**2.50 (1.57-3.98)**	**<0.0001**
	MV	1 (ref)	1.29 (0.81-2.04)	**2.20 (1.35-3.57)**	**0.01**

MV: Adjusted for age, sex, race and eGFR continuous

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