Changing Protein Permeability with Nephron Loss; Evidence for a Human Remnant Nephron Effect.

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Abstract

Background If loss of functioning nephrons predisposes to glomerular barotrauma (a 'remnant nephron' effect) then glomerular permeability should increase as glomerular filtration rate (GFR) falls, as is observed in animal models of nephron loss.

Methods Changes in protein permeability, defined as proteinuria or albuminuria per ml/min of GFR, were measured in the setting of nephron loss due to kidney donation (ALTOLD cohort) or progressive CKD (MDRD, AASK and CRIC studies).

Results Following kidney donation renal albumin permeability increased by 31% from predonation levels ($p<0.001$). With progression of CKD a 50% loss of residual GFR was accompanied by increases in proteinuria per ml/min GFR of 1.8-, 2.1-, and 1.6-fold in the MDRD, AASK and CRIC cohorts respectively ($p<0.001$ for all), independent of systolic BP changes and ACE/ARB use. A 70% reduction in GFR was associated with permeability increases of 3.1-, 4.4-, and 2.6-fold in the same cohorts. Among MDRD participants with progression of nonglomerular primary disease, the top quartile of final protein permeability was 141mg/ml/min. This degree of permeability would have resulted in nephrotic range proteinuria had it been present at the baseline mean GFR of 40ml/min, implying the development of *de novo* glomerular pathology as GFR fell. In the absence of a fall in GFR there was no increase in permeability.

Conclusion Nephron loss is accompanied by a measurable increase in albuminuria which can be explained by increased glomerular protein permeability, even in the absence of a primary glomerular disease. This is consistent with a remnant nephron effect in human CKD.

Introduction

Animal models have demonstrated a maladaptive 'remnant nephron effect' whereby a substantial loss of nephron mass leads to glomerular hypertension within the surviving nephrons, thereby reinforcing kidney injury, resulting in nephron dropout, and further loss in GFR.[1, 2] The extent to which this phenomenon contributes to the progression of human Chronic Kidney Disease (CKD) is unclear. If loss of functioning nephron mass in humans predisposes to barotrauma from hypertension in the surviving glomeruli, then the protein leak *per nephron* should increase, as is observed in 5/6 rat nephrectomy model.[2] Single nephron protein excretion cannot be measured clinically, but proteinuria per ml/min of glomerular filtration rate (GFR) is a logical measure of glomerular permeability;[3] GFR is both the driving force for convective protein loss and a surrogate for the glomerular surface area across which protein loss can occur. We therefore studied the change in protein leak per ml/min of GFR following kidney donation (the Assessing Long Term Outcomes in Living Kidney Donors (ALTOLD) study cohort) or progressive loss of excretory function (the Modification of Diet in Renal Disease (MDRD), African American Study of Kidney Disease (AASK) and Chronic Renal insufficiency Cohort (CRIC) studies). We hypothesized that nephron loss would be accompanied by an increase in proteinuria per ml/min of GFR, even in the absence of a primary glomerular pathology affecting the filtration barrier.

Methods

Study cohorts

The inclusion criteria and data collection procedures of the ALTOLD, MDRD, AASK and CRIC studies have been reported previously.[4-7] Data were provided for this analysis by the National Institute of Diabetes, Digestive and Kidney Disease Central Repository following local Institutional Review Board Approval. The ALTOLD study ascertained the impact of kidney donation on GFR, protein excretion and blood pressure over a 3y period among 182 kidney donors and 173 healthy controls.[4] The MDRD study investigated the effect of a low protein diet and lower mean arterial blood pressure target (92 vs 107mmHg; 2x2 factorial design) on GFR loss among 840 participants with CKD.[5, 8] In the AASK study, 1094 African American patients with hypertensive nephropathy were randomized to antihypertensive regimes targeting a standard or more intensive control of mean arterial pressure (102-107mmHg vs ≤92mmHg) and based on initial treatment with ramipril, amlodipine, or metoprolol (3x2 factorial design).[6, 9] The CRIC study is an ongoing prospective observational investigation of risk factors for CKD progression and cardiovascular disease in a cohort of 3939 participants with CKD.[7, 10]

Measurements

GFR was measured by iohexol clearance (ALTOLD) or iothalamate clearance (MDRD, AASK and CRIC). Protein permeability was assessed in MDRD, AASK and CRIC participants as 24h proteinuria per ml/min GFR using urine and GFR measurements from the same study visit. Urine collections with a creatinine excretion rate of <350mg/24h or >3500mg/24h were considered implausible and not included in the analyses.[11] In ALTOLD timed urine collections were not undertaken so relative changes in permeability were assessed using spot urine albumin:creatinine ratio (ACR) per ml/min GFR. Fractional excretion of albumin was used as an additional measure of permeability in ALTOLD since any reduction in muscle

mass (thus creatinine excretion rate) following kidney donation could increase ACR independently of albuminuria. ALTOLD cohort analyses included all participants with complete GFR, ACR and blood pressure data for each timepoint (0, 6, 12, 24 and 36m). In the CKD cohorts, participants with at least 2 paired measurements of proteinuria and GFR and concomitant BP results were included.

Kidney Disease Diagnosis

A range of renal diagnostic categories were recorded for MDRD study participants. For the purposes of this analysis, the cohort was divided into subgroups with a primary glomerular disease (including membranous, membranoproliferative, focal sclerosis, mesangial proliferative, IgA and other glomerulonephritides, nonbiopsied nephrotic syndrome, immunotactoid, amyloid, Wegener's, Alport's, diabetic nephropathy), those with a diagnosis not intrinsically affecting the glomerular permeability barrier (including polycystic kidney disease, interstitial nephritis, nephrocalcinosis, lithium toxicity, previous tubular necrosis, medullary sponge kidney, hypertension, atherosclerosis), those with an unknown diagnosis and those with a secondary diagnosis of focal sclerosis in the absence of primary glomerular disease. This latter category was selected since secondary focal sclerosis is considered a manifestation of remnant glomerular hypertension. The CRIC cohort utilised 4 diagnostic categories: diabetes, hypertension, other (including glomerulonephritis) and unknown. All patients in the AASK cohort had an underlying diagnosis of hypertensive nephropathy made on clinical grounds.[12]

Statistical analyses

Fractional change in proteinuria was expressed as final permeability/baseline permeability and log transformed prior to parametric analyses. Sequential changes in GFR, ACR and permeability following kidney donation in ALTOLD were examined using repeated measures ANOVA. In the CKD cohorts, definite evidence of disease progression was defined as a reduction in GFR of at least 30% from baseline to final available assessment. Visual inspection of the data (Loess curves) identified a steeper increase in log fractional change in permeability associated with more severe relative reductions in GFR. Regression of log transformed permeability change against the square of the percentage fall in GFR was therefore undertaken. This better approximated a linear relationship (based on R^2 values and visual inspection) in all the CKD cohorts. Data are thus presented from this approach. Other variables included *a priori* were systolic BP and change in systolic BP from baseline,[13] use of ACE inhibitor or angiotensin receptor blocker, treatment arm (MDRD and AASK trials) and renal diagnosis (where applicable). Interaction between baseline GFR and percentage GFR reduction were examined using multiplicative interaction terms. Analyses were performed using SPSS version 25.0 (IBM Corp., Armonk, N.Y., USA).

Results

Participant characteristics

Characteristics of the full ALTOLD, MDRD, AASK and CRIC study cohorts have been published previously.[4, 8-10] The characteristics of those participants donating a kidney or experiencing a fall in GFR of at least 30% are shown in Table 1.

Changes in albumin permeability following kidney donation

As previously reported, following kidney donation GFR fell by a median of 26% at 3 years and ACR decreased by 10% at 3 years, but rose steadily between 6 months and 3 years. There was a progressive rise in renal albumin permeability over the 3 years following donation, to a final median increment of 31% (geometric mean 35%, 95% CI ±14% $p<0.001$, Figure 1). This was not driven by a rise in postdonation BP, since BP did not increase (Table 1) and correction for a change in MAP in the model did not affect the findings. Using fractional albumin excretion to define permeability gave the same conclusions (final permeability rise 33%, $p<0.001$). In contrast, renal albumin permeability in controls did not change (median difference +1.7%).

Changes in protein permeability in progressive CKD

In participants with progressive CKD (GFR loss ≥30%) from the MDRD, AASK and CRIC cohorts absolute proteinuria increased (Table 1), reflecting an increase in permeability. There was a linear relationship between log transformed fractional change in permeability and the square of the percentage fall in GFR (Figure 2A-C). This relationship was consistent between cohorts and remained significant following adjustment for systolic BP, change in systolic BP from baseline, ACEi/ARB use, trial diet/BP randomisation arm and diagnostic category ($p<0.001$ in all cohorts, Table 2). Increasing permeability was not dependent on the presence of progressive primary glomerular disease, since increases were similar among MDRD participants with or without glomerular disease. Even among MDRD progressors without primary glomerular disease the top quartile of protein permeability at final assessment (141mg per ml/min) would equate to protein excretion of 5.6g/24h had it been present at the baseline GFR of 40ml/min, thus well within the 'nephrotic range'. The top quartile of permeability at final assessment among AASK progressors was similar (116mg per ml/min). In contrast, in the absence of GFR loss there was no increase in permeability (median permeability changes was 0.9-, 1.1- and 1.0-fold in MDRD, AASK and CRIC respectively).

Among the small subset of nephrotic progressors (baseline proteinuria ≥3.5g/24 and serum albumin<35g/l, n=21 in CRIC and n=16 in MDRD) increasing permeability limited the resolution of the nephrotic state. In CRIC, despite a fall in median GFR from 50ml/min/1.73m^2 to 23ml/min/1.73m^2, median proteinuria only fell from 5.2g/24 to 5.1g/24h and serum albumin increased modestly from 31 to 33g/L. In MDRD, a fall in median GFR from 31ml/min/1.73m^2 to 13ml/min/1.73m^2 was accompanied by a fall in proteinuria from 5.4g/24h to 4.1g/24h and a slight rise in serum albumin from 33 to 34g/L.

Some participants with progressive CKD had no increase in permeability; 16%, 22% and 24% in the MDRD, AASK and CRIC cohorts respectively. Since upstream occlusive vascular disease might limit pressure transmission to the glomerulus, age and a history of cardiovascular disease were tested as possible negative predictors of increasing permeability. There were no significant associations with

these predictors in all CKD cohorts. An increase in permeability was also not confined to participants reaching a GFR below a threshold level; in all CKD cohorts there was no interaction between the absolute GFR and the percentage change in GFR.

Relationship to Blood Pressure

Since nephron loss has been hypothesized to leave remnant glomeruli more vulnerable to transmission of elevated systemic BP, the relationship between GFR loss, BP and permeability was studied. Increases in systolic BP of 20mmHg and 40mmHg were associated with permeability increases at final follow up of 1.5- and 2.3-fold in MDRD, 1.2- and 1.4-fold in AASK and 1.3- and 1.7-fold in CRIC ($p<0.05$ for all in adjusted models). The use of an ACE inhibitor or angiotensin receptor blocker was associated with a significantly smaller increase in permeability only in the MDRD study (0.76-fold, $p=0.007$). There was no significant interaction between GFR reduction and systolic BP or ACEi/ARB use in any cohort.

Discussion

Haemodynamic changes at remnant nephrons have been considered to play an important role in the progression of CKD of diverse aetiologies.[14] However, the animal models used to demonstrate this phenomenon undergo a sudden and drastic reduction in functional nephron mass (typically 5/6 loss through surgical ligation of renal artery branches, or surgical removal of renal tissue). In clinical practice CKD develops more slowly and may be accompanied by upstream vascular disease/remodelling that could limit the transmission of systemic arterial pressure to the glomerular microcirculation. Some cases of human CKD resulting from non-glomerular disease are accompanied by proteinuric secondary focal segmental glomerulosclerosis, suggesting that remnant glomerular barotrauma can indeed occur. Whether or not the remnant nephron effect is a frequent contributor to progression of human CKD is unclear.

We find that proteinuria increases in over 75% of cases of nephron loss, due to kidney donation or CKD progression. These data are in keeping with a model in which loss of nephron mass results in increased glomerular permeability of remnant nephrons. The top quartile of permeability among progressors without primary glomerular disease from the MDRD study would have been sufficient to cause 'nephrotic range' proteinuria had it been present at the baseline level of GFR. This implies that *de novo* glomerular injury commonly develops as GFR falls, consistent with a remnant nephron effect.

Although there was no evidence of a threshold level of GFR below which permeability increased, much greater changes accompanied more substantial relative reductions in GFR. Thus, the increase in permeability following kidney donation was modest, consistent with the fact that loss of a single kidney does not initiate progressive injury. Glomerulomegaly and increased perfusion rather than glomerular hypertension are considered to account for postdonation hyperfiltration[15], which may increase glomerular permeability via effects of shear stress on podocytes.[16]

Average increases in protein permeability accompanying CKD progression were less than those observed in animal remnant nephron models, where permeability following 5/6 nephrectomy is often

more than 10-fold baseline.[2] Considering the observed relationship between systolic BP and permeability, if hypertension had been less well controlled then permeability increases might have been similar to those seen in the animal models, which are accompanied by severe hypertension.[17] Attenuated changes in permeability in non-hypertensive renal ablation models are similar to those we report in these cohorts.[18] Indeed, some have argued that increased vulnerability of the glomerular microcirculation to systemic arterial pressure is entirely responsible for the remnant nephron phenomenon.[17, 19, 20] Consistent with this hypothesis, a steeper relationship between systolic BP and renal albumin permeability was evident at lower eGFR in a cross sectional US population cohort analysis.[21] In the current study we did not find evidence that a lower GFR sensitized the kidney to systolic BP since there was no interaction between GFR and systolic BP in relation to changing permeability. However, the cohorts studied may have had insufficiently broad ranges of systolic BP and GFR to identify such a phenomenon. The use of ACE inhibitors and ARBs in the CKD cohorts may be another reason why permeability increases were less than those in animal models, though again there was no evidence of an interaction between ACEi/ARB use and GFR loss. It is possible that increasing permeability accompanying CKD progression reflects structural changes at sclerosing glomeruli rather than glomerular hypertension. However, previous micropuncture studies localised albuminuria to remnant glomeruli with less histological evidence of structural abnormalities.[2]

A minority of progressors experienced no increase in permeability. Whilst upstream vascular disease could limit glomerular hypertension, in exploratory analyses there was no evidence that age or cardiovascular disease predicted less increase in permeability. Nevertheless, these factors may have been poor predictors of vascular disease in the cohorts studied. (All AASK participants had hypertensive end organ damage so some degree of vascular remodelling would be expected to be universal and not necessarily predicted by age to the same extent as in other populations.) In patients with CKD due to ischaemia it would be envisaged that remnant nephron haemodynamics may not apply.

Although absolute protein excretion is used as a clinical tool, it would seem more logical to consider protein excretion in relation to GFR, given that an identical measurement of proteinuria occurring at half the GFR should reflect double the glomerular permeability.[3, 22] The clinical pathophysiological relevance of glomerular proteinuria does not reflect absolute protein loss, but rather permeability changes resulting from pathology at the filtration barrier, whether of haemodynamic, immunological, genetic or other origin. Altered tubular protein reabsorption or loss may underlie proteinuria but logically this too should be indexed to the number of nephrons across which the protein loss occurs.

A limitation of our analyses is the use of total protein rather than albumin in the CKD cohorts, so that it is not possible to distinguish glomerular versus tubular source. Our use of the term 'permeability' in these analyses should strictly be interpreted in terms of the whole nephron since protein leak could reflect reduced tubular reabsorption. However, the extent to which protein loss per ml/min GFR increases strongly implies a glomerular origin in keeping with remnant nephron physiology.

In conclusion, we find that proteinuria markedly increases with nephron loss, even in the absence of primary glomerular disease. This is can be explained by an increase in glomerular permeability of remnant nephrons, as observed in the animal models cited above. Because more than 75% of people were in the studied cohorts were affected, we suggest that haemodynamic changes in remnant glomeruli are likely to be a common feature in human CKD.

Acknowledgements

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Table 1. Characteristics of the ALTOLD Kidney Donor Cohort and of Participants with at least 30% Loss of GFR in the MDRD, AASK and CRIC Study Cohorts

	ALTOLD donors	MDRD	AASK	CRIC
N	120	371	320	193
Age at baseline, y	43 (11)	49 (12)	53 (11)	56 (12)
Duration of follow up, y	3	2.3 (0.9)	3.7 (1.5)	3.1 (1.1)
CKD diagnoses	None	Various	Hypertensive nephropathy	Various
Baseline GFR, ml/min/1.73m^2	109 (18)	27 (20, 37)	42 (30, 53)	47 (32, 58)
Diabetes, %	0	5.9	0	46.1
Final GFR, ml/min/1.73m^2	79 (14)	12 (9, 19)	19 (13, 29)	25 (17,34)
Baseline proteinuria, g/24h or ACR, mg/g	4.7 (3.3, 6.4)	0.71 (0.13, 2.18)	0.34 (0.09, 1.25)	0.68 (0.13, 2.64)
Final proteinuria, g/24h or ACR, mg/g	4.2 (2.9, 6.9)	1.00 (0.20, 2.57)	0.57 (0.15, 1.96)	0.81 (0.17, 2.96)
Baseline BP, mmHg	118(12)/70(10)	136(18)/83(9)	151(22)/96(14)	133(22)/74(14)
Endpoint BP, mmHg	118(12)/72(8)	136(19)/80(10)	136(20)/81(13)	133(22)/72(13)
Previous cardiovascular disease, %	0	12.7	49.1	26.9
On ACEi/ARB at baseline, %	Nil	37.5	35.0	73.2
On ACEi/ARB at follow up, %	Nil	38.0	40.3	73.4

Data presented as percentage, mean (SD) or median (IQR) as appropriate.

Table 2. Renal protein permeability changes and their association with GFR loss in MDRD, AASK and CRIC study participants with progressive CKD.

	MDRD all	MDRD nonglomerular disease	MDRD glomerular disease	MDRD focal sclerosis	AASK	CRIC
N	371	251	71	32	320	193
Baseline protein permeability, mg/ml/min	23.7 (4.4, 79.0)	10.1 (2.6, 44.5)	76.7 (32.3, 132.1)	79.1 (59.1, 120.5)	7.9 (1.7, 32.6)	13.6 (2.6, 52.7)
Final protein permeability, mg/ml/min	74.5 (14.2, 194.8)	41.7 (8.5, 141.1)	154.6 (69.7, 287.1)	259.8 (148.0, 394.8)	27.1 (5.9, 115.7)	27.9 (5.1, 121.1)
Permeability fold change per 30% fall in GFR*	1.23 (1.16, 1.31)	1.24 (1.15, 1.32)	1.28 (1.08, 1.53)	1.37 (1.16, 1.61)	1.31 (1.22, 1.41)	1.19 (1.06, 1.33)
Permeability fold change per 50% fall in GFR*	1.79 (1.51, 2.13)	1.79 (1.47, 2.20)	2.00 (1.24, 3.24)	2.39 (1.51, 3.78)	2.12 (1.72, 2.62)	1.61 (1.18, 2.22)
Permeability fold change per 70% fall in GFR*	3.14 (2.26, 4.41)	3.16 (2.13, 4.68)	3.90 (1.52, 10.00)	5.53 (2.24, 13.56)	4.39 (2.91, 6.62)	2.56 (1.38, 4.77)

*Adjusted for final systolic BP, change in systolic BP from baseline, ACE/ARB use, diagnosis category (CRIC only) and study intervention arm (MDRD and AASK). Protein permeability presented as median (IQR) and fold-change as adjusted coefficient (95% CI).

Figure Legends

Figure 1. Changes in GFR, albuminuria and albumin permeability following kidney donation in the ALTOLD cohort.

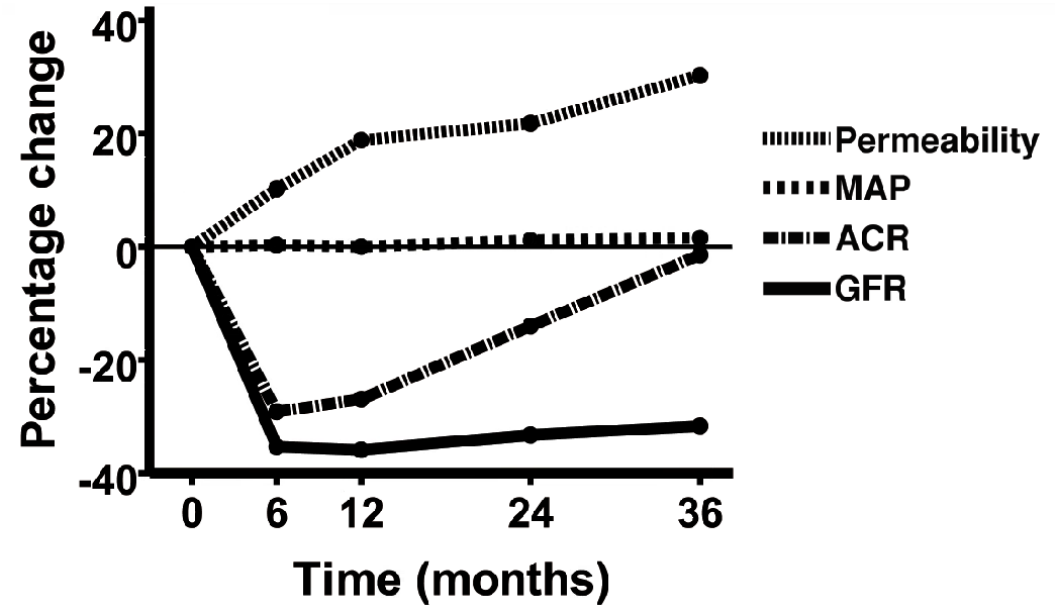
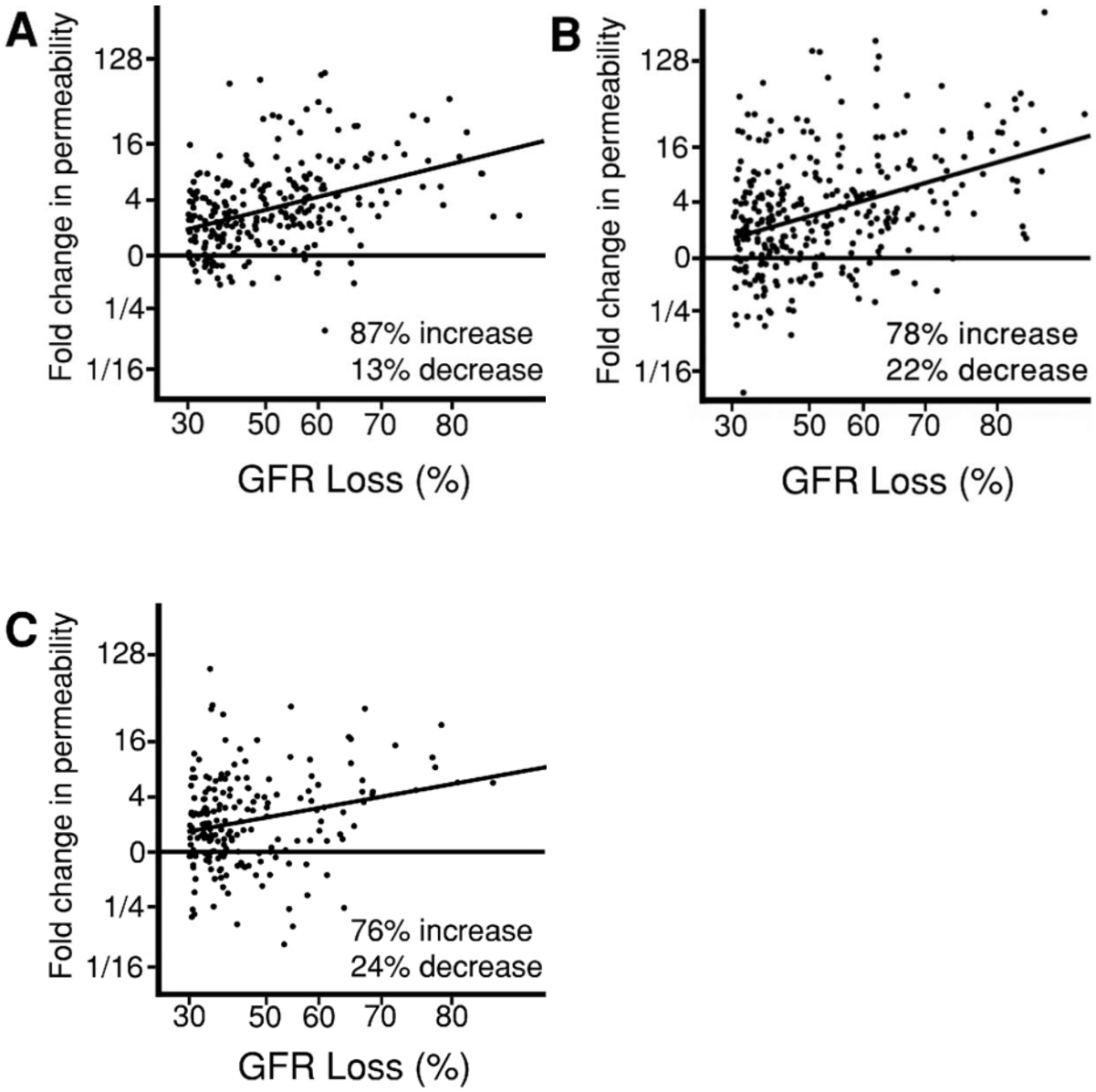


Figure 2. Changes in protein permeability in relation to percentage reduction in GFR in A) MDRD study participants with nonglomerular primary disease, B) AASK study participants and C) CRIC study participants.



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