Why kidney disease always gets worse; what can we do about it?

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Internal Medicine Grand Rounds

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Biographical Information

Dr. Lu is Professor of Internal Medicine (Nephrology), Graduate Program in Immunology, both at UT Southwestern Medical Center.

He graduated from Haverford College, and Harvard Medical School, was a research and clinical fellow at Brigham and Women's Hospital, and was Assistant Professor at the latter prior to joining the faculty of UT Southwestern Medical Center. He has the privilege of seeing patients with renal disease at the University Hospital St Paul and Parkland, and the privilege of learning together with residents, fellows, students, and colleagues. His research is inspired by clinical problems in renal disease. These are explored using in vitro and in vivo murine models. Currently, his laboratory is studying how renal injury triggers innate immunity. This innate immunity regulates acute kidney injury (AKI), progressive chronic kidney disease (CKD), as well as acute and chronic rejection of renal transplants.

Educational Objectives

1. To understand how the "hyperfiltration" hypothesis was formulated by bench research in rodents, and provided the theoretical basis for using ACE-INH or ARB in the treatment of CKD; how this hypothesis is an example of the translation of fundamental bench research to the bedside.
2. To understand the great clinical contribution of this hypothesis, but also its limitations.
3. To understand the role of this hypothesis in the 2013 KDIGO guidelines for the clinical care of patients with CKD.

Purpose and Overview

Chronic kidney disease leads to cardiovascular mortality and progresses to endstage renal disease that must be treated with dialysis or transplantation. The purpose of this grand rounds is to discuss how the "hyperfiltration" hypothesis forms the foundation of our current attempts slow/ prevent progression of CKD and the limitation of this hypothesis.

Introduction

Chronic kidney disease is important for every internist for the following reasons:

1) It is extremely common and affects approximately 13% of the adult population. In other words, every internist will have to manage patients with chronic kidney disease.

2) Chronic kidney disease is progressive and ultimately leads either to dialysis or death from cardiovascular disease.

3) Good therapy is available to ameliorate these complications of chronic kidney disease, and in every internist should know the published clinical guidelines. See Appendix I.

Summary of relative risks from categorical meta-analysis (dipstick included) (−, ±, +, ⩾++)

All-cause mortality

	ACR <10	ACR 10–29	ACR 30–299	ACR ⩾300
eGFR > 105	1.1	1.5	2.2	5.0
eGFR 90–105	Ref	1.4	1.5	3.1
eGFR 75–90	1.0	1.3	1.7	2.3
eGFR 60–75	1.0	1.4	1.8	2.7
eGFR 45–60	1.3	1.7	2.2	3.6
eGFR 30–45	1.9	2.3	3.3	4.9
eGFR 15–30	5.3	3.6	4.7	6.6

Cardiovascular mortality

	ACR <10	ACR 10–29	ACR 30–299	ACR ⩾300
eGFR > 105	0.9	1.3	2.3	2.1
eGFR 90–105	Ref	1.5	1.7	3.7
eGFR 75–90	1.0	1.3	1.6	3.7
eGFR 60–75	1.1	1.4	2.0	4.1
eGFR 45–60	1.5	2.2	2.8	4.3
eGFR 30–45	2.2	2.7	3.4	5.2
eGFR 15–30	14	7.9	4.8	8.1

Kidney failure (ESRD)

	ACR <10	ACR 10–29	ACR 30–299	ACR ⩾300
eGFR > 105	Ref	Ref	7.8	18
eGFR 90–105	Ref	Ref	11	20
eGFR 75–90	Ref	Ref	3.8	48
eGFR 60–75	Ref	Ref	7.4	67
eGFR 45–60	5.2	22	40	147
eGFR 30–45	56	74	294	763
eGFR 15–30	433	1044	1056	2286

Acute kidney injury (AKI)

	ACR <10	ACR 10–29	ACR 30–299	ACR ⩾300
eGFR > 105	Ref	Ref	2.7	8.4
eGFR 90–105	Ref	Ref	2.4	5.8
eGFR 75–90	Ref	Ref	2.5	4.1
eGFR 60–75	Ref	Ref	3.3	6.4
eGFR 45–60	2.2	4.9	6.4	5.9
eGFR 30–45	7.3	10	12	20
eGFR 15–30	17	17	21	29

Progressive CKD

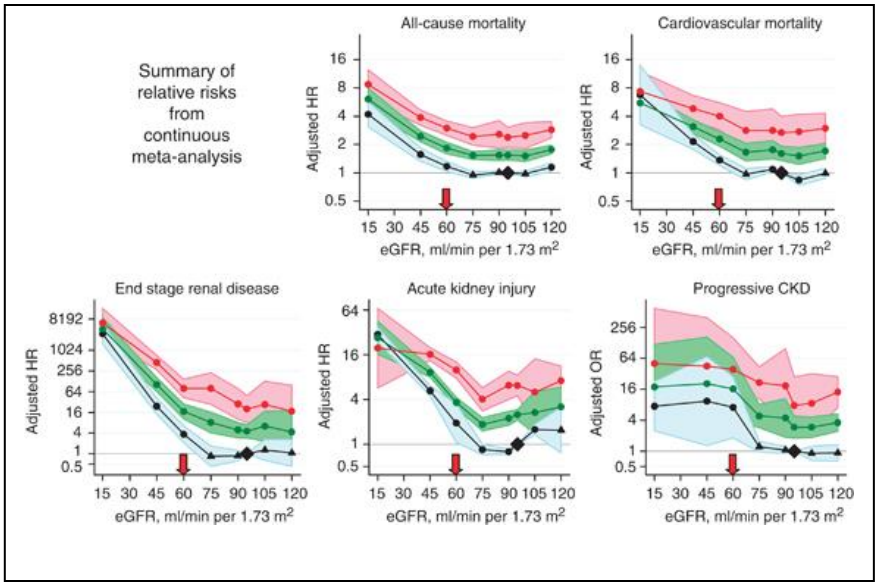
	ACR <10	ACR 10–29	ACR 30–299	ACR ⩾300
eGFR > 105	Ref	Ref	0.4	3.0
eGFR 90–105	Ref	Ref	0.9	3.3
eGFR 75–90	Ref	Ref	1.9	5.0
eGFR 60–75	Ref	Ref	3.2	8.1
eGFR 45–60	3.1	4.0	9.4	57
eGFR 30–45	3.0	19	15	22
eGFR 15–30	4.0	12	21	7.7

Although there has been great success in the management of chronic kidney disease, we still cannot completely arrest or reverse the process. We have a long way to go.

In 2013, the International Group of Experts published the KDIGO guidelines for the treatment of chronic kidney disease. KDIGO stands for “Kidney Disease, Improving Global Outcomes.”. The KDIGO clinical practice guidelines were published in a recent supplement in Kidney International (1). In the remainder of this section I will review some of the main points of these clinical practice guidelines. In addition details are included in appendix 1, and appendix 2 of this grand rounds protocol. See also http://kdigo.org/home/ .

KDIGO defines chronic kidney disease in the following way. The patient should have one or more of the following markers of kidney damage. Albuminuria (>= 30mg/24 hours or >=30mg/g of creatinine). The patient should have urine sediment abnormalities. The patient may have electrolyte or other abnormalities do to tubular disorders. The patient may have abnormalities detected by histology. The patient may have structural abnormalities detected by imaging. The patient may have a history of kidney transplantation. Alternatively the patient may have a decreased GFR. These abnormalities should be present for 3 months or longer.

The severity of the chronic kidney disease is defined by the GFR, and the presence or absence of albuminuria. The GFR abnormalities are classified into 5 categories G1, GFR >90; G2, GFR 60-89; G3a, GFR 45-59ml/min; G3b, GFR 30-44ml/min; G4, severely decreased 15-29ml/min; and G5, kidney failure <15ml/min. The albuminuria is defined as A1, normal or <30mg/g of creatinine; A2, moderately increased 300-300mg/g of creatinine; and A3, severely increased or >300mg/g of creatinine.



These different categories of GFR and albuminuria are well correlated with the risk of the following five bad events: all cause mortality, cardiovascular mortality, kidney failure as defined by the need for dialysis or transplantation-(ESRD – endstage kidney disease); acute kidney injury; and progressive CKD. As shown in the figure, those patients with a GFR of <60ml/min and/or albuminuria of greater than 30mg/g of creatinine are of high risk for dying, having cardiovascular mortality, having kidney failure, having acute kidney injury, and having progressive chronic kidney disease. In other words a 45 year old man with a GFR of <60ml/min and >30mg of albumin/g of creatinine has the same cardiovascular risk of death as a 60 year old. This "uremic cardiomyopathy" (or cardiorenal syndrome type 4) was discussed in Dr. Chou-long Huang's recent medical grand rounds.

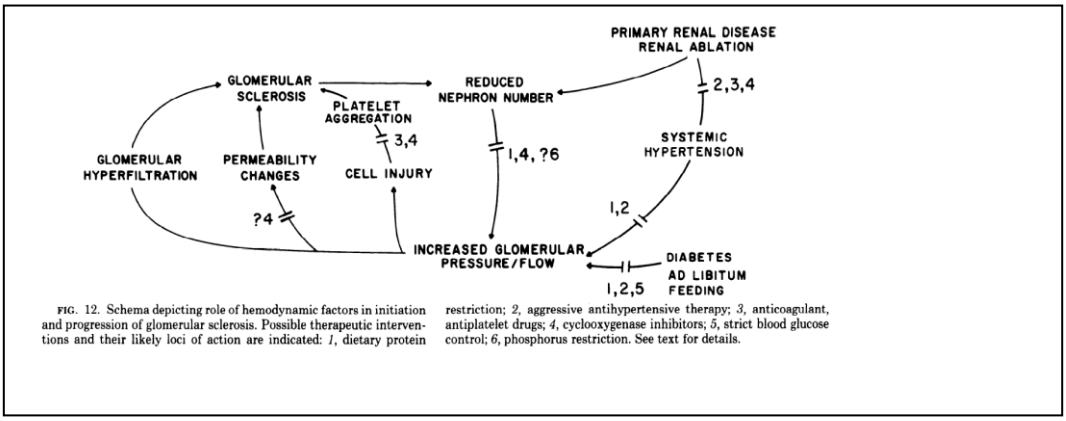


FIG. 12. Schema depicting role of hemodynamic factors in initiation and progression of glomerular sclerosis. Possible therapeutic interventions and their likely loci of action are indicated: *1*, dietary protein restriction; *2*, aggressive antihypertensive therapy; *3*, anticoagulant, antiplatelet drugs; *4*, cyclooxygenase inhibitors; *5*, strict blood glucose control; *6*, phosphorus restriction. See text for details.

Since 13% of the American population has some form of chronic kidney disease (CKD) > 3b, it is impossible for all to be for by nephrologists. Therefore each and every internist, heart specialist, GI specialist, etc. within this room will be taking care of patients with CKD. It is important that you know the most recent recommendations.

Section II: Is "Glomerular Hypertrophy/Hyperfiltration" a final common pathway for complications of CKD? The theoretical basis for ACE-INH and ARB. Hard work is bad for you.

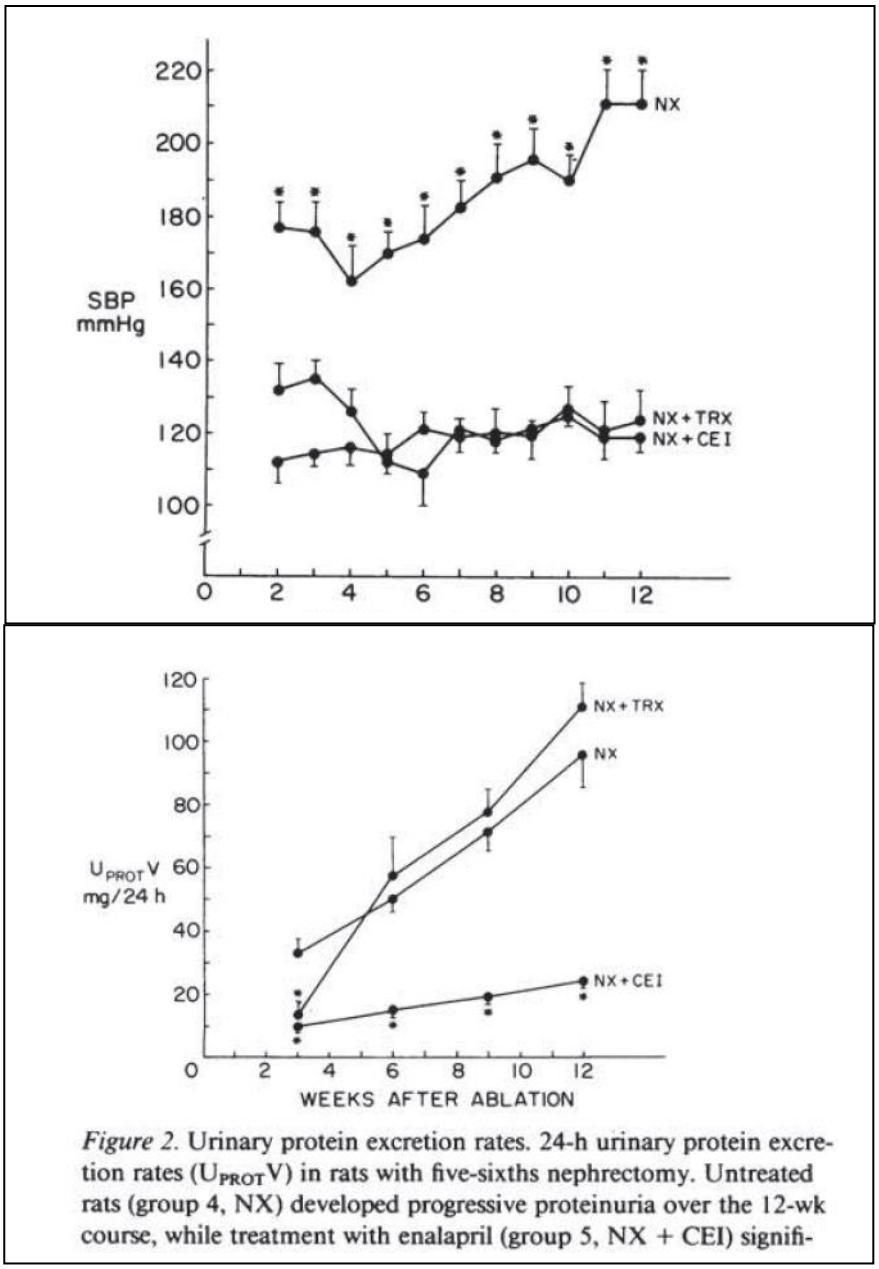


Figure 2. Urinary protein excretion rates. 24-h urinary protein excretion rates ($U_{PROT}V$) in rats with five-sixths nephrectomy. Untreated rats (group 4, NX) developed progressive proteinuria over the 12-wk course, while treatment with enalapril (group 5, NX + CEI) signifi-

As shown in the figure (previous page), this hypothesis states that any damage to nephrons will result in hypertrophy and hyperfiltration of the remaining glomeruli. This results in glomerular sclerosis and death of further glomeruli. This in turn results in reduced nephron number, further increased glomerular pressure and flow, further glomerular hyperfiltration, further glomerular sclerosis and further reduces nephron number. The vicious cycle continues until the entire kidney is destroyed.

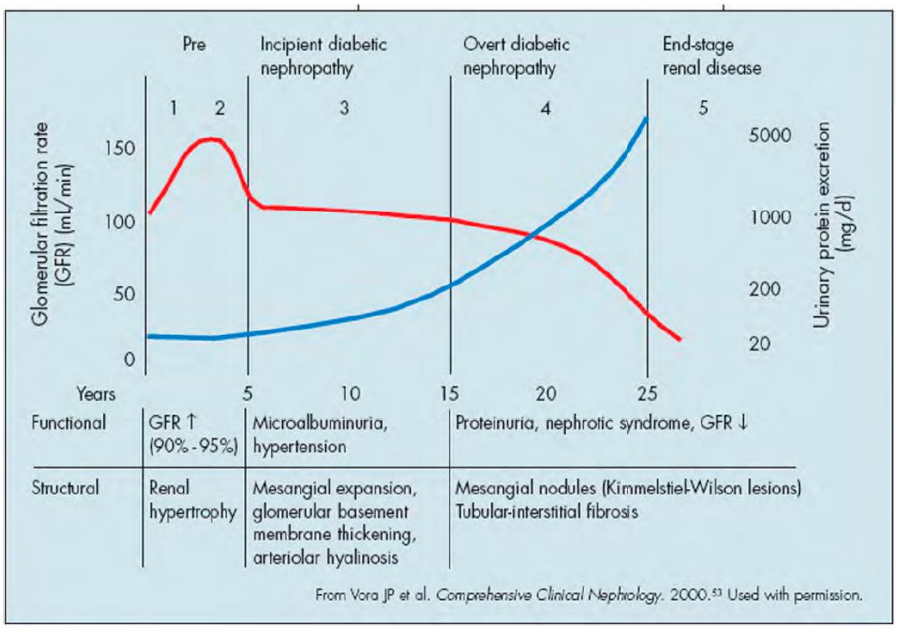
Another way of stating this hypothesis is that it illustrates a principle that we all know: hard work is bad for everyone and everything. If one has 100 nephrons, and some of them are severely injured, the remaining nephrons have to work harder. Some nephrons drop dead from overwork. The remaining nephrons have to work even harder, more nephrons drop dead from overwork, etc. etc. until all nephrons are dead. This is the reason: hyperfiltration may also be called the "doom and gloom" hypothesis.

This hypothesis was initially supported by both human and rodent observations. Very careful pathologists had documented that in kidneys taken from patients with Bright's disease had some glomeruli and nephrons which were hypertrophied and other nephrons which were destroyed. This is consistent with the hypothesis: the hypertrophied glomeruli were overworking to compensate for the destroyed glomeruli.

An elegant series of laboratories experiments on rats performed in Brenner's lab by his graduate students and post-doctoral fellows, support this theory. This group performed surgery where 5/6 of the nephron mass was removed-- removal of one kidney and 2/3 of the other. These rats developed hypertension, and as predicted by the hypertrophy /hyperfiltration hypothesis the remnant kidney initially hypertrophied and then went on to sclerose and die. The rats developed hypertension.

According to this hypothesis, if one could decrease the glomerular pressure and flow then there should be less glomerular hyperfiltration, hyperfiltration, sclerosis, etc. Drugs which decrease glomerular pressure and flow are the ACE-inhibitors, and the ARBs. In rats, Brenner's group showed that controlling hypertension with conventional non ACE-inhibitors did not decrease glomerular sclerosis and progression of renal disease. However controlling blood pressure with ACE-inhibitors completely controlled the disease (2). See figures on previous page.

Section III: Clinical Application of the "Glomerular Hypertrophy/Hyperfiltration" Hypothesis – diabetic nephropathy.



From Vora JP et al. *Comprehensive Clinical Nephrology*. 2000.[53] Used with permission.

Careful studies of patients with type 1 diabetes showed the following sequence of events in some patients: Shortly after the diagnosis of diabetes, some patients had an increase in the GFR. This was due to hyperglycemia. According to the Brenner hypothesis this should lead to glomerular hyperfiltration and hypertrophy. This should stress the glomeruli, the glomeruli should be injured. This would be manifested initially as micro-albuminuria and then macro-albuminuria. The vicious cycle of glomerular hypertrophy, sclerosis, and further glomerular hypertrophy would lead to renal damage and eventually end-

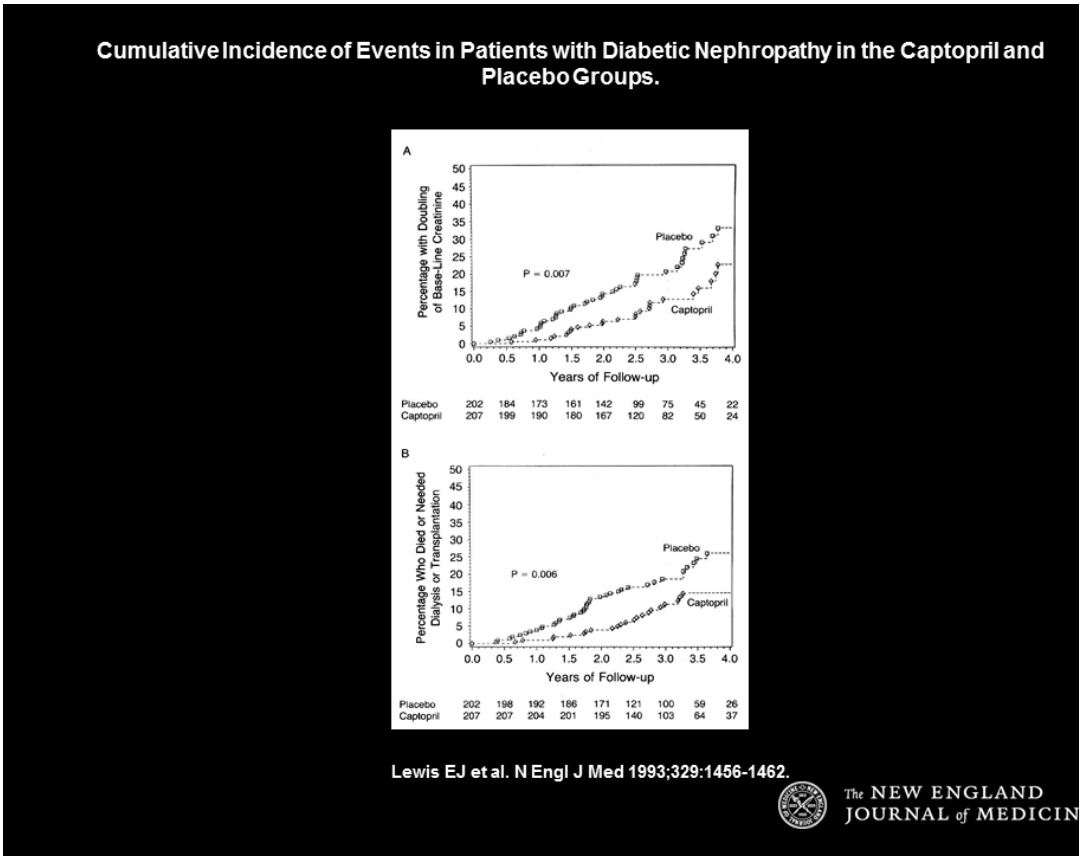
stage renal disease. All of these predictions were confirmed by careful observation in large numbers of patients with type 1 diabetes.

If the Brenner hypothesis were true then giving these patients ACE-inhibitors would result in a marked diminution in the rate of progression of diabetic nephropathy, proteinuria, end-stage renal disease, and death. A number of clinical trials showed in a spectacular fashion that this was true.

The first clinical trial was in Type I diabetes. The progression of the disease, the mortality, and the end-stage renal failure all were decreased. However it is worth noting that the patients did eventually develop end-stage renal disease and death. However these end points were markedly delayed. (3).

In a similar fashion, ARBs were found to decrease the progression to end-stage renal disease and cardiovascular death in patients with type 2 diabetes. (4).

It is on the basis of these studies, that KDIGO recommends ACE-inhibitors and ARBs for the treatment of patients with albuminuria and diabetic nephropathy. See appendix for details.



There are three practical problems in giving these agents to patients with renal failure.

1) ACE-inhibitors or ARBs both can cause hyperkalemia. Paradoxically, those patients with severe diabetic nephropathy, and possibly a type 4 RTA, need ACE or ARBs the most, are those who are most likely to develop significant hyperkalemia with these drugs. Fortunately in compliant

patients it should be possible to give ACE-inhibitors and ARBs. The patient should be placed on a low potassium diet. Potassium excretion by the kidney should be increased by giving loop diuretics. A slight metabolic alkalosis might be enhanced by giving sodium bicarbonate, and the sodium bicarbonate may also prevent hypokalemia. This is discussed in an editorial in the New England Journal by Dr. Biff Palmer in our renal division (5).

2) Another problem when giving ACE-inhibitors is that the serum creatinine may rise. If it rises to a marked degree and the patients become uremic, it may not be possible to give these drugs. However a rise of 10-15% is usually well tolerated by our patients. Indeed it indicates that the glomerular hyperfiltration is being inhibited by the drugs in a desirable fashion.

3) The question arises as to how aggressive one should be in controlling hypertension in these patients. This is a particularly critical question, because new data suggests that subclinical episodes of acute kidney injury due to hypotension may actually exacerbate diabetic nephropathy. Thus if patients receive sufficient hypotensive agents to develop orthostatic syncope on occasion in the morning, they may actually accelerate the loss of their renal function. The issue of acute kidney injury resulting in progressive chronic kidney injury will be discussed later in this grand rounds (6). Current blood pressure targets are reviewed in the KDIGO appendix of this protocol.

Table 6. Assessing criteria for diabetic kidney disease

Inclusion	Exclusion
Pre-existing diabetes, impaired glucose	Other systemic disease process
Persistent albuminuria, proteinuria	Rapid increase in proteinuria, nephrotic syndrome
Elevated creatinine, decreased GFR	Rapid decrease in GFR
Normal to large kidneys on ultrasonography	Presence of active urinary sediment
Diabetic retinopathy or neuropathy	Refractory hypertension
	Greater than expected drop in GFR with ACEs/ARBs

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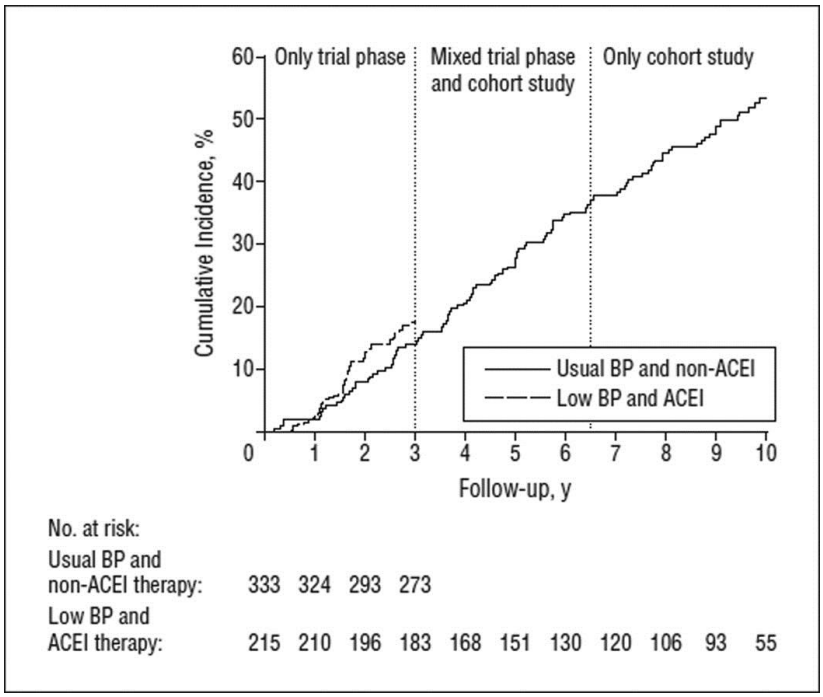
Section IV: "Glomerular Hypertrophy/Hyper-filtration" hypothesis - - right drugs; wrong rationale? wrong pathology?

The pathology for diabetic nephropathy, particularly type 1 diabetic nephropathy has become very well defined.

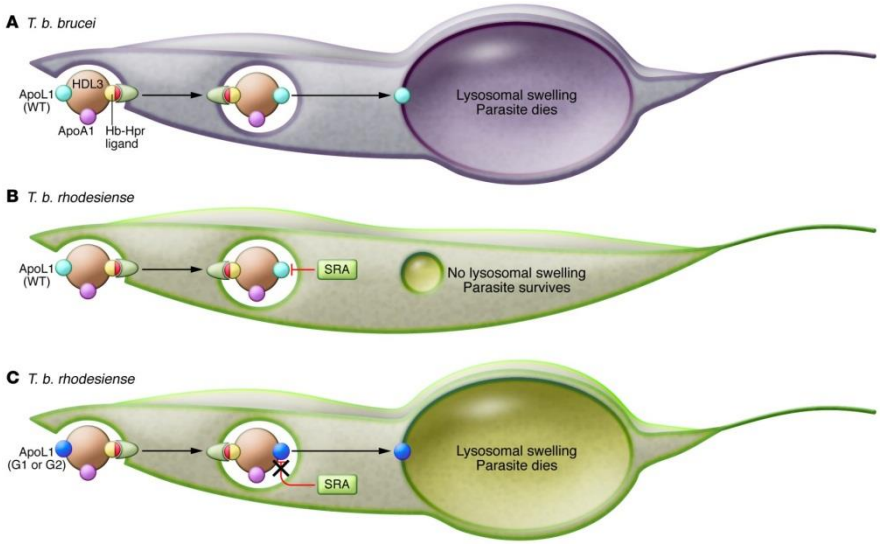
Diabetic kidney disease has been separated into four progressive classes (7). Class 1 is isolated glomerular basement membrane thickening. Class 2 A and B is mesangial expansion mild and greater than

25% of the glomeruli. B is mesangial expansion, severe and involving greater than 25% of glomeruli. There should be no nodular sclerosis. Class 3 is glomeruli with nodular sclerosis (Kimmelstiel-Wilson), greater than one glomerulus with nodular increase in mesangial matrix. Class 4 is global glomerulosclerosis in greater than 50% of glomerular lesions from classes 1-3.



However in a model rodents of the Brenner group, the major feature was focal segmental glomerulosclerosis.

Clinical aside: The clinicians often confronted with the question whether a patient with diabetes and progressive renal disease should be biopsied. This issue is addressed in the figure above. It is of note that approximately 60% of patients in the United States are thought to develop end-stage renal disease secondary to diabetes. However biopsy studies suggest that only 60% of patients with the clinical diagnosis of diabetic nephropathy actually have a biopsy which shows diabetic nephropathy or shows diabetic nephropathy plus other pathology. However, in most cases, the more accurate pathologic diagnosis may not have changed therapy.



Section V: "Glomerular Hypertrophy/Hyperfiltration" hypothesis - "hypertensive nephrosclerosis" in African Americans. Progression with minimal albuminuria. AASK and APOL 1.

It has long been known that there are important clinical and historiological differences between hypertensive nephrosclerosis in African Americans versus European Americans. The former

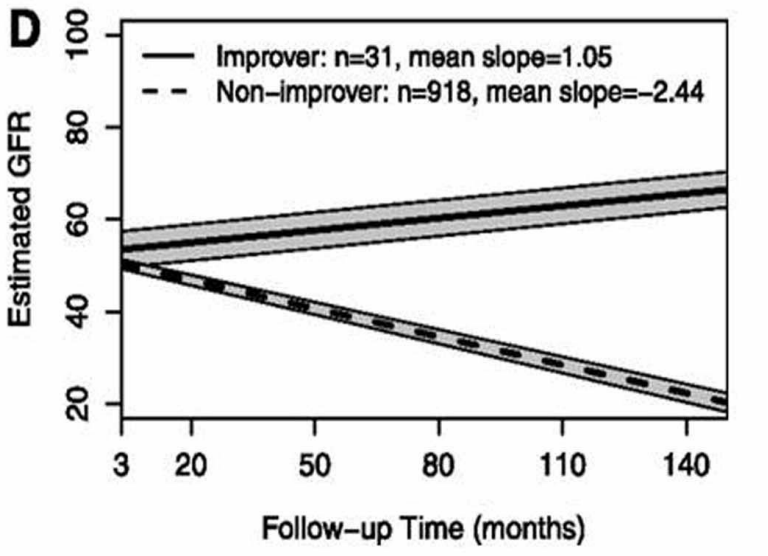
develop end-stage renal disease earlier in life than the latter. In addition treatment of hypertension is more affective in European Americans than African Americans. The pathology is also different. African Americans have greater degrees of solidified glomerulosclerosis and arteriolonephrosclerosis. On the other hand European Americans have greater amounts of obsolescent and collapsed glomeruli. It is now known that these differences may be related to genes. (8).

Large scale studies of African Americans (9) (10) show disappointingly little difference between the use of ACE-inhibitors and other hypotensive medications in delaying the progression of chronic kidney disease to end-stage kidney disease, and decreasing mortality. There was a small improvement in prognosis with the use of ACE-inhibitors, but the not the dramatic effects seen in diabetic nephropathy, nor in rodents with 5/6th nephrectomy. This suggests that there is a different etiology of progressive CKD in some African americans. See figures, previous page.

It is now clear that African Americans with a specific mutation of APOL 1 have a markedly increased risk for developing chronic kidney disease. The relative risk is approximately 7-10. This genetic variant protects African Americans from sleeping sickness (11). See figure, previous page.

Clinical aside: What is hypertensive nephrosclerosis? Does hypertension cause renal disease? Does renal disease cause hypertension? Or, does hypertension exacerbate renal disease and vice versa (12, 13)

Section VI: "Glomerular Hypertrophy/Hyperfiltration" hypothesis - hard work is actually good for you!



There are several situations where some individuals with chronic kidney disease do not progress, but either stabilize or actually improve their renal function. These exceptions to the rule are important because they indicate that it may be possible for the kidney to recover, and for the physician to aid such recovery.

One example of such recovery is a detailed study of eight patients (14) (15). These eight patients had type 1 diabetes mellitus and received a pancreas transplant, but no kidney transplant. The patients had micro-albuminuria. They were followed and had renal biopsies at five years and 10 years after their pancreas only transplant. These patients had regression/ improvement of their

diabetic nephropathy after their diabetes was "cured" by the pancreas transplant. This is a striking example of reversal of chronic kidney disease.

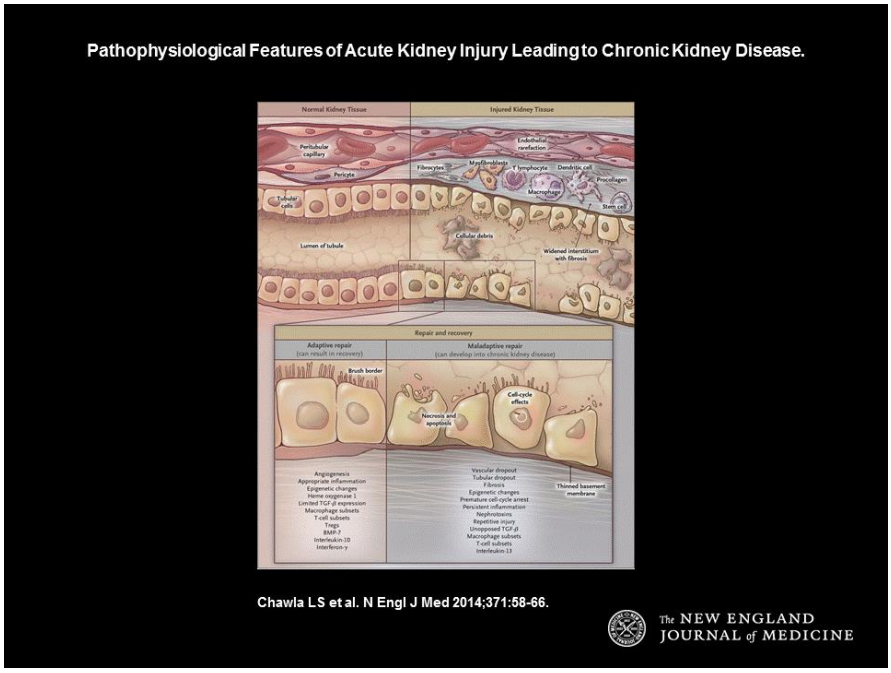
An additional study (16) found that although 918 patients in the AASK study had progression after CKD, 31 of these patients improved. (None of the patients were biopsied.) This is an improvement incidence of 3.3%. See figure, previous page. In another study of 406 patients with various types of chronic kidney disease, 15.3% improved. (17).

Studies in rodents similarly show improvement in established advanced diabetic nephropathy. (18) (19). In an additional model of progressive renal disease after 5/6th nephrectomy in rats, there was improvement after aggressive treatment with ACE-inhibitors. (20).

These mice, rats, and rare patients know a secret – the "cure" for progressive chronic kidney disease. This secret needs to discovered by further research.

Section VII: "Glomerular Hypertrophy/Hyperfiltration" hypothesis – tubular injury sustained during acute kidney injury causes, and exacerbates, chronic kidney disease.

The above discussion has focused entirely on the glomerulus as the instigator and victim of chronic kidney disease. The interstitium consisting of tubules, pertubular capillaries, and interstitial fibroblasts and leukocytes was ignored until recently. However a convergence of outcome studies in large numbers of patients, and bench-studies on rodents now unequivocally show that tubular damage also leads to progressive chronic kidney disease. Thus, "acute tubular necrosis", now known by its politically correct name of "acute kidney injury" (AKI), which is the most common acute kidney disease, leads to progressive chronic kidney disease. A kidney that recovers to its baseline function after AKI is still in bad trouble (6).



“Glomerular Hypertrophy/Hyperfiltration” hypothesis as “a”, but not “the”, cause of progressive chronic kidney disease.

In the 1980’s the Brenner group formulated the “Hyperfiltration hypothesis.” This was a “paradigm shifting” view of chronic progressive kidney disease and provided the theoretical basis for essentially all of our progress in the treatment of patients with this disease. This was an example of “bench” research translated to the “bedside” with spectacular results. However, this hypothesis does not explain important aspects of progressive chronic kidney disease, nor progressive disease in all patient populations. Treatment based on this hypothesis slows but does not cure the disease. New insights are needed and will come from bench research that is translated to the bedside.

Appendix I

Table 5. Summary of KDIGO CKD recommendations/suggestions for CKD management in adults with prior KDIGO recommendations for comparison

Area	2013 KDIGO CKD Recommendation	Prior KDIGO Recommendation or Suggestion
Hypertension	Target BP ≤140/90 mmHg if albuminuria <30 mg/d Target BP ≤130/80 mmHg if albuminuria ≥30 mg/d	Target BP ≤140/90 mmHg if albuminuria <30 mg/d Target BP ≤130/80 mmHg if albuminuria ≥ 30 mg/d
ACEI or ARB	Diabetes: use ACEI or ARB if albuminuria ≥30 mg/d Nondiabetes: use ACEI or ARB if albuminuria ≥300 mg/d	Diabetes: use ACEI or ARB if albuminuria ≥30 mg/d Nondiabetes: use ACEI or ARB if albuminuria ≥30 mg/d in nondiabetic adults in whom treatment with BP-lowering drugs is indicated[a]
Glycemia	Target HbA1c approximately 7% Do not treat <7% in patients at risk for hypoglycemia Target >7% if significant comorbidities or limited life expectancy and risk of hypoglycemia	NA, although recommendations are currently the same as the KDOQI diabetes guidelines
Sodium intake	Lower salt intake to <2 g sodium per day (5 g NaCl), unless contraindicated	Lower salt intake to <90 mmol (<2 g) per day of sodium (corresponding to 5 g of sodium chloride), unless contraindicated
Protein intake	Lower protein intake to <0.8 g/kg per day with appropriate education, if GFR <30 ml/min per 1.73 m^2 Avoid high protein intake >1.3 g/kg per day in adults with CKD at risk of progression	NA
Healthy lifestyle	Undertake physical activity compatible with cardiovascular health and tolerance (aiming for at least 30 min, 5 times/wk) Achieve a healthy weight (BMI 20–25 kg/m^2) Stop smoking	Achieve or maintain a healthy weight (BMI 20–25 kg/m^2) Undertake an exercise program compatible with cardiovascular health and tolerance, aiming for at least 30 min, 5 times per week. Limit alcohol intake to no more than 2 standard drinks per day for men and no more than 1 standard drink per day for women
CKD-MBD	Routine prescription of vitamin D supplements or vitamin D analogs in the absence of suspected or documented deficiency to suppress elevated PTH concentrations in people with CKD not on dialysis is not suggested	Suggest use of calcitriol or vitamin D analogs in stage 3–5 CKD (not on dialysis) when PTH is progressively rising and remains persistently above the upper limit of normal for the assay despite correction of modifiable risk factors[b]

Reprinted with permission from Kidney Disease Improving Global Outcomes (KDIGO) CKD Work Group: KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Int Suppl* 3: 1–150, 2013. KDIGO, Kidney Disease Improving Global Outcomes; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CKD-MBD, CKD-mineral and bone disorder; PTH, parathyroid hormone; NA, not applicable.

[a]Kidney Disease Improving Global Outcomes (KDIGO) Blood Pressure Work Group: KDIGO Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease. *Kidney Int Suppl* 2: 337–414, 2012

[b]Kidney Disease Improving Global Outcomes (KDIGO) CKD-MBD Work Group: KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). *Kidney Int Suppl* 76: S1–S130, 2009

Appendix II

Table 2. Summary of equations

Method	Considerations
MDRD study equation $GFR = 175 \times (Scr)^{-1.154} \times (age)^{-0.203} \times 0.742$ (if female) or $\times 1.212$ (if black)	Underestimates GFR when GFR >60 ml/min per 1.73 m^2 Less accurate with near normal GFR, extremes of age and weight, amputation, pregnancy and cirrhosis More accurate and less biased than CKD-EPI when GFR <60 ml/min per 1.73 m^2
CKD-EPI creatinine equation Female (Scr $\leq$ 0.7): $144 \times (Scr/0.7)^{-0.329} \times 0.993^{Age} \times 1.159$ (if black) Female (Scr > 0.7): $144 \times (Scr/0.7)^{-1.209} \times 0.993^{Age} \times 1.159$ (if black) Male (Scr $\leq$ 0.9): $141 \times (Scr/0.9)^{-0.411} \times 0.993^{Age} \times 1.159$ (if black) Male (Scr > 0.9): $141 \times (Scr/0.9)^{-1.209} \times 0.993^{Age} \times 1.159$ (if black)	Decreased sensitivity for diagnosis of CKD relative to the MDRD formula Increased specificity for diagnosis of CKD relative to the MDRD formula Less likely than MDRD to misclassify individual with CKD whenGFR close to 60 ml/min per 1.73 m^2 in general populations Overestimates CKD in older individuals Overestimates GFR in individuals with CKD More accurate and less biased than MDRD when GFR >60 ml/min per 1.73 m^2
CKD-EPI cystatin C equation Female or male (Scys $\leq$ 0.8): $133 \times (Scys/0.8)^{-0.499} \times 0.996^{Age} \times 0.932$ (if female) Female or male (Scys > 0.8): $133 \times (Scys/0.8)^{-1.328} \times 0.996^{Age} \times 0.932$ (if female)	Lack of standardization among different laboratories An international standard has been developed May be helpful in more accurately classifying CKD in older individuals May be more accurate in individuals with malnutrition and decreased muscle mass
CKD-EPI creatinine–cystatin C equation Female (Scr $\leq$ 0.7 and Scys $\leq$ 0.8): $130 \times (Scr/0.7)^{-0.248} \times (Scys/0.8)^{-0.375} \times 0.995^{Age} \times 1.08$ (if black) Female (Scr $\leq$ 0.7 and Scys > 0.8): $130 \times (Scr/0.7)^{-0.248} \times (Scys/0.8)^{-0.711} \times 0.995^{Age} \times 1.08$ (if black) Female (Scr > 0.7 and Scys $\leq$ 0.8): $130 \times (Scr/0.7)^{-0.601} \times (Scys/0.8)^{-0.375} \times 0.995^{Age} \times 1.08$ (if black) Female (Scr > 0.7 and Scys > 0.8): $130 \times (Scr/0.7)^{-0.601} \times (Scys/0.8)^{-0.711} \times 0.995^{Age} \times 1.08$ (if black) Male (Scr $\leq$ 0.9 and Scys $\leq$ 0.8): $135 \times (Scr/0.9)^{-0.207} \times (Scys/0.8)^{-0.375} \times 0.995^{Age} \times 1.08$ (if black) Male (Scr $\leq$ 0.9 and Scys > 0.8): $135 \times (Scr/0.9)^{-0.207} \times (Scys/0.8)^{-0.711} \times 0.995^{Age} \times 1.08$ (if black) Male (Scr > 0.9 and Scys $\leq$ 0.8): $135 \times (Scr/0.9)^{-0.601} \times (Scys/0.8)^{-0.375} \times 0.995^{Age} \times 1.08$ (if black) Male (Scr > 0.9 and Scys > 0.8): $135 \times (Scr/0.9)^{-0.601} \times (Scys/0.8)^{-0.711} \times 0.995^{Age} \times 1.08$ (if black)	Performs better than MDRD, CKD-EPI, and CKD-EPI cystatin C in estimating GFR More accurately classifies CKD stage when GFR is 45–74 ml/min per 1.73 m^2 May be helpful in more accurately classifying CKD in older individuals May be more accurate in individuals with malnutrition and decreased muscle mass

MDRD, Modification of Diet in Renal Disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; Scr, serum creatinine; Scys, serum cystatin C.

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