Albuminuria: A target for treatment?

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A Growing Crisis: Diabetes

The silent killer: Scientific research shows a ‘persistent explosion’ of cases—especially among those in their prime

BY JERRY ADLER AND CLAUDIA KALB

Something terrible was happening to Yolanda Benitez’s eyes. They were being poisoned; the fragile capillaries of the retina attacked from within and were leaking blood. The first symptoms were red lines, appearing vertically across her field of vision; the lines multiplied and merged into a haze that shut out light entirely. “Her blood vessels inside her eye were popping,” says her daughter, Jannette Roman, a Chicago college student. Benitez, who was in her late 40s when the problem began four years ago, was a cleaning woman, but she’s had to stop working. After five surgeries, she has regained vision in one eye, but the other is completely useless. A few weeks ago, awakening one night in a hotel bedroom, she walked into a door...
ESRD Incidence Rates* by Primary Diagnosis, 1988–1997

- Diabetes
- Hypertension
- Other
- Glomerulonephritis

*Adjusted for age, sex, and race  †Preliminary
Diabetes and Microvascular Disease

- Leading cause of end-stage renal disease (ESRD)
- Leading cause of new blindness
- Neuropathy is common, frequently unrecognized, and disabling
Albuminuria: A target for Treatment?

- Albuminuria: How, what and when
- Risk marker for CV and renal disease
- Target for renal (vascular) protection
- Combination therapy to reduce albuminuria
Albuminuria: Not so simple after all.

- Continuous variable: lessons from LIFE trial
- Immunoreactive albumin (RIA)
- immuno NON reactive albumin (HPLC)
- Albumin fragments
- Underestimation of microalbuminuric patients
Definitions of abnormalities in urinary albumin excretion

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Microalbuminuria, when and how

When
- Type 1, at puberty and at 5 years of disease
- Type 2, at presentation
- Yearly thereafter

How
- First void (or consistent) spot urine for quantitative protein and creatinine
- 24 hour or timed urine collection for Protein and creatinine
**Albuminuria: Innocent bystander or toxin?**

- Proteinuria as a Reflection of underlying glomerular disease and a contributor to renal injury

- Mechanisms of renal injury
  - Directly causes tubule damage and apoptosis
  - Activates cellular responses that lead to interstitial injury
  - Stimulates production of fibrogenic molecules such as TGF-beta and endothelin-1
Albumin handling by the kidney

- Filtered: Glomerular sieving coefficient between 0.000077-0.00062 (filtrate concentration of approximately 0.35-2.5 mg/dL) Probably about 2000 mg/day

- Protein uptake by proximal tubule cells

  Megalin and cubulin colocalize as endocytic receptors

  - Involved in protein absorption, binding albumin, hemoglobin and immunoglobulin light chains
Proteinuria induced tubule cell injury

- **Misdirected filtration**
  - Podocyte injury causes adhesions of the glomerular tuft of Bowman’s capsule followed by accumulation of the “misdirected” filtrate in the periglomerular space

- **Luminal obstruction by protein casts**

- **Tubule uptake of filtered proteins**
  - Cubulin deficient patients (Imerslund-Grasbeck Syndrome) have proteinuria but no progression or ckd
  - Rare tubulointerstitial disease in minimal change nephropathy which is a highly selective form of nephrotic syndrom
Tubulotoxicity of specific plasma proteins

- Albumin: proximal tubule cell cultures exposed to high concentrations of albumin and various plasma protein fractions
  - Variable results
  - Apoptosis, stimulation of IL-8, MCP-1, chemokines (RANTES), ROS, NF-κB stimulation
- Lipids and fatty acids bound to albumin
- Transferrin and iron
Tubulotoxicity of specific proteins

- Filtered cytokines and growth factors
  - Insulin growth factor-I filtered in nonselective proteinuria induces secretion of types I and IV collagen
  - Activation of protein bound TGF-beta in urine in rat model of DM: potent inducer of a variety of chemokines

- Complement
  - C5-9, membrane attack complex present in urine, c6 deficiency protects against tubulointerstitial injury associated with proteinuria,
Albumin: Innocent bystander or toxin?

- Unclear whether proteinuria is a cause or only a consequence of progressive renal injury.
- Probably both a reflection of glomerular injury AND acts as a specific proximal tubule cell toxin.
- Which protein, however, remains unknown?
Albuminuria: How common is it?

- Australian Diabetes, Obesity and Lifestyle study
- 11,247 adults, 1999-2000
- 25.3% with evidence of albuminuria
  - 17.8% New DM
  - 32.6% Known DM
- 21% microalbuminuria
- 4.3% macroalbuminuria
- Independent Risk Factors:
  - AGE, systolic BP, current smoking, BMI, glycated Hemoglobin

TappRT, AmJKidDis 2004;44:792
NHANES III: Type 2 Diabetic Patient Population

- 63% have hypertension
  - 40% are undiagnosed or not controlled
- 28.2% have Microalbuminuria and 7.6% have Proteinuria
- 52.9% take $\geq 3$ prescription medications
- 58% have uncontrolled diabetes
  ($\text{HbA1c} \geq 7.0$)

Harris MI. Diabetes Care. 2000; 23:754-758
What is the BIG PICTURE here?
This is, in fact, a treatable disease. The earlier you start, the better it is!
Albuminuria

- Associated with myocardial infarction and stroke
- Reflects endothelial damage
- Part of the cardiovascular dysmetabolic syndrome
- Progression of micro- to macroalbuminuria predicts progression of renal disease

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Microalbuminuria; 30–300 mg/day
Proteinuria Predicts Stroke and CHD Events in Type 2 Diabetes

Survival Curves For CV Mortality

Overall: $P<0.001$

Months

Incidence (%)

0 10 20 30 40
0 20 40 60 80 100

A: U-Prot $<150$ mg/L  B: U-Prot $150–300$ mg/L  C: U-Prot $>300$ mg/L

$P<0.001$

Stroke  CHD Events

U-Prot = Urinary protein concentration.

Microalbuminuria Increases Ischemic Heart Disease Risk

N=2,085, 10-year follow-up

Microalbuminuria Increases Ischemic Heart Disease Risk

RR of IHD

SBP <140
SBP 140–166
SBP >160

Normoalbuminuria
Microalbuminuria
Albuminuria: Risk factor for nephropathy. Lessons from RENNAL

DeZeeuw. KI 2004;65:2309
Albuminuria

From risk factor to Target
Albuminuria: RENNAL patients reaching end point depending on reduction in albuminuria at 6 months
IRMA 2 - Results
Normalization of Urinary Albumin Excretion Rates

- Placebo: 21%
- Irbesartan 150 mg: 24%
- Irbesartan 300 mg: 34%
- Total Irbesartan: 29%

Combination therapy to reduce albuminuria

- Weight loss
- Stopping smoking
- Low protein diet
- Control of blood sugar
- Blood pressure control

- ACEI
- ARB
- NHPCCB
- Aldosterone blockers
- Statins
- NSAIDS
- Others
Regression of Microalbuminuria in Type 1 DM

- Perkins BA, et al NEJM 2003;348:2285
- Joslin Diabetes Center, Boston, Mass
- 386 Type 1 diabetics with microalbuminuria followed for 8 years
- Regression (50% reduction from one 2 year period to another) incidence of 58%
- Salutary levels: HbA1c<8%, sBP<115, TC<198, TG<145 all independent effects  ACEI had NO effect
- Patients with all salutary levels: hazard ratio ratio for regression of 3.0
The Effects of Captopril on ESRD/All-Cause Mortality in Type 1 Diabetes

No. of Patients at Risk:

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Impact of ACE Inhibition on Blood Pressure and GFR:

Acute vs Chronic Effects

SBP  N=24

Baseline 1 Month 5.6 Years 1 Month off ACEI + Clonidine

GFR  N=24

Baseline 1 Month 5.6 Years 1 Month off ACEI + Clonidine

*P<0.05 compared to baseline

IRMA 2 - Results

% Reduction in Urinary Albumin Excretion

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<tr>
<th></th>
<th>DHP CCBs</th>
<th>Non-DHP CCBs</th>
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<tr>
<td><strong>Albuminuria/Proteinuria</strong></td>
<td>↑ ↔ *</td>
<td>↔ ↓ †</td>
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<tr>
<td><strong>Glomerular Scarring</strong></td>
<td>↔</td>
<td>↓</td>
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<tr>
<td><strong>Renal Autoregulation</strong></td>
<td>Abolished</td>
<td>Partially Abolished</td>
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* Long acting dihydropyridine
† Slows progression of diabetic nephropathy in long-term trials
Mean Changes in Albuminuria and MAP in Hypertensive Patients With Proteinuria

Angiotensin II Formation

Angiotensinogen → Renin → Angiotensin I → ACE → Angiotensin II → Angiotensin II Receptors

Alternate Pathways:
- t-PA
- Cathepsin G
- Tonin
- CAGE
- Cathepsin G
- Chymase

* The clinical significance of the alternate pathway is unknown

ACEI + ARB in renal disease

- Combination treatment of ARB and ACEI in non-diabetic renal disease (COOPERATE): a randomized trial
- 263 Japanese patients with glomerular disease
  - Randomized to receive:
    - Losartan 100 mg/day
    - Trandolapril, 3 mg/day
    - Combination of Losartan and Trandolapril
## COOPERATE Study: Demographics

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<th>Trandolapril</th>
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<td><strong>n</strong></td>
<td>n=89</td>
<td>n=86</td>
<td>N=88</td>
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<td><strong>Age yrs</strong></td>
<td>44.8(4.8)</td>
<td>45.9(5.8)</td>
<td>45.2(4.9)</td>
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<td><strong>Sex (M/F)</strong></td>
<td>48/41</td>
<td>46/40</td>
<td>47/41</td>
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<tr>
<td><strong>GFR ml/min</strong></td>
<td>38.4(4.0)</td>
<td>37.9(3.7)</td>
<td>37.5(3.9)</td>
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<tr>
<td><strong>Protein exc gr/day</strong></td>
<td>2.4(1.1)</td>
<td>2.5(1.2)</td>
<td>2.5(1.1)</td>
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<td><strong>Systolic BP</strong></td>
<td>130(9.3)</td>
<td>129.9(10.2)</td>
<td>130.3(10.5)</td>
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<td><strong># BP meds</strong></td>
<td>3</td>
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<td><strong>Low responders%</strong></td>
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COOPERATE study: Proportion of patients reaching endpoint (doubling Scr, ESRD, death)

Months after randomization

Lancet 2003;361:117
Multifactorial Intervention and Cardiovascular Disease in Patients with Type 2 Diabetes

- Steno-2 Study (Steno Diabetes Center, Copenhagen, Denmark)
- Randomized, Parallel trial
  - 80 Patients who had conventional treatment
  - 80 Patients who had intensive treatment
- Composite End Point: death from cardiovascular disease, nonfatal MI, nonfatal stroke, revascularization, amputation
Percentage of Patients who reached the Intensive-Treatment Goals at a Mean of 7.8 years
Multifactorial Intervention in Type 2 DM

RESULTS:

- Intensive-therapy group v Conventional-therapy group

Relative Risks

- Cardiovascular Disease, 0.47 (p<0.008)
- Nephropathy, 0.39 (p<0.003)
- Retinopathy, 0.42 (p<0.02)
- Autonomic neuropathy, 0.37 (p<0.002)
- Peripheral neuropathy, 1.09 (p=0.66)

Target-driven, long-term, intensified intervention reduces risk of cardiovascular and microvascular events by 50%
Treatment of Hypertension in Diabetes: NKF recommendations

- Blood pressure goal: 130/80 mm Hg
- Target blood pressure: 125/75 for patients with proteinuria
- BP lowering medications should reduce both:
  - blood pressure + proteinuria
- Both reduce:
  - Renal disease progression and incidence of ischemic heart disease
A Call to Action

- ADA recommends screening in all type 2 diabetics at time of diagnosis and annually thereafter
- 30% to 40% prevalence of microalbuminuria in type 2 diabetes
- Microalbuminuria a marker of small blood vessel disease in both the kidney and the heart
- Combinations of interventions necessary in all diabetics to normalize urinary albumin excretion