Proteinuria

Goni Katz-Greenberg, MD
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Proteinuria

Goni Katz-Greenberg, MD
Transplant Nephrology Fellow
Outline and objectives

- Definition
- Screening/Masurement
- Etiology
- Treatment
Definition of Proteinuria

• Normal protein excretion < 150mg daily
• Normal albumin excretion < 30mg daily
• Moderately increased albuminuria 30-299mg daily (formerly microalbuminuria) over 3-6 months*
• Severely increased albuminuria > 300mg daily (formerly macroalbuminuria)
• Nephrotic range proteinuria > 3.5 grams daily
Measurement of Proteinuria

• Albumin excretion above 300 mg/day is considered overt albuminuria → the level at which the standard dipstick becomes positive
• Dipstick - ALBUMIN

• 24-hour urine test - gold standard, but cumbersome
• Urine protein:creatinine ratio/ spot ratio
24-hour urine collection

• The **gold standard** for measurement of protein excretion is a 24-hour urine collection (normal value <150 mg/day).
• Adults under the age of 50 years, daily creatinine excretion should be
  • 20 to 25 mg/kg of lean body weight in men
  • 15 to 20 mg/kg of lean body weight in women
• From the ages of 50 to 90 years, there is a progressive 50% decline in creatinine excretion due primarily to a fall in muscle mass
UPCR

- UPCR best done as spot first- or second-morning urine sample after avoiding exercise
- It is a RATIO, and is best when done in a steady state
- Individuals with large muscle mass, the UPCR (or UACR) will underestimate proteinuria
- In cachectic/small muscle mass patients, the UPCR (or UACR) will overestimate proteinuria
Case 1

Mr. Jones is a 69 years old male who comes to clinic complaining of increased abdominal girth and leg swelling for the past 4 weeks. His other PMHx is significant for HTN and hyperlipidemia.

Physical exam -

- Temperature 37.2C (98.9)
- BP 135/68, HR 85
- HEENT - WNL
- Chest - clear to auscultation
- Heart - S1S2, no murmurs or gallops
- Abdomen - distended, non tender
- LEs - Edema +3 bilaterally, to hip level
Case 1 - Cont’d - Differential Diagnosis

- Nephrotic Syndrome
- Cirrhosis
- Heart failure
- Myxedema
Case 1 - Cont’d - Work up

- Albumin
- BUN, creatinine
- Urinalysis
- 24-hour urine protein/ UPCR in random sample
- Serum LDL and cholesterol
- LFTs?

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
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<tbody>
<tr>
<td>Albumin</td>
<td>2.8g/dL</td>
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<tr>
<td>Creatinine</td>
<td>1.1mg/dL</td>
</tr>
<tr>
<td>BUN</td>
<td>25</td>
</tr>
<tr>
<td>Urinalysis</td>
<td>+ 4 protein, with oval fat bodies seen. Few RBC, no casts.</td>
</tr>
<tr>
<td>UPCR</td>
<td>8.5g/g</td>
</tr>
<tr>
<td>T. chol</td>
<td>310 mg/dL</td>
</tr>
</tbody>
</table>
Nephrotic Syndrome

- Urine protein exertion of > 3.5 gram/24 hours (or UPCR of > 3000mg/g)
- Hypoalbuminemia < 3.0 g/dL
- Edema
- Hyperlipidemia +/- Lipidiuria
Where is the proteinuria coming from?
Diagram of glomerular anatomy

A

Juxtaglomerular apparatus
AA Afferent arteriole
MD Macula densa
EGM Extraglomerular mesangium
EA Efferent arteriole
N Sympathetic nerve terminals
GC Granular cells
SMC Vascular smooth muscle cells

Vascular pole
US Urinary space

Bowman capsule
PE Parietal epithelium
PO Podocyte
M Mesangium
E Endothelium
F Foot process
GBM Glomerular basement membrane

Urinary pole

Proximal tubule

B

Glomerular basement membrane
Foot processes
Capillary
Capillary endothelium
Microfilaments
Mesangium
Mesangial matrix
Mesangial angle

Foot processes
Capillary
Capillary endothelium
Microfilaments
Mesangium
Mesangial matrix
Mesangial angle
# Types of Proteinuria

<table>
<thead>
<tr>
<th>Proteinuria Classification</th>
<th>Pathogenesis</th>
<th>Clinical Setting</th>
<th>Level of proteinuria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glomerular</td>
<td>Increased filtration of macromolecules (albumin)</td>
<td>Primary or systemic diseases</td>
<td>Variable</td>
</tr>
<tr>
<td>Overflow</td>
<td>Increased filtration (causing decreased reabsorptive capacity) or marked overproduction</td>
<td>Myeloma, hemolysis, rhabdomyolysis</td>
<td>Variable</td>
</tr>
<tr>
<td>Tubulointerstitial</td>
<td>Increased excretion of low molecular weight proteins (B2 macroglobulin) from decreased proximal tubule absorption</td>
<td>Interstitial inflammation/injury, heavy metal intoxication</td>
<td>&lt;3 gr/day</td>
</tr>
<tr>
<td>Post-Renal Proteinuria</td>
<td>Inflammation of urinary tract. Non-albumin protein</td>
<td>UTI’s, nephrolithiasis, GU tumor</td>
<td>&lt;1 gr/day</td>
</tr>
</tbody>
</table>
Back to Mr Jones...
Next steps of work up

- HbA1C
- Anti-PLA2R autoantibody
- ANA and dsDNA antibody
- Serum C3 and C4 levels
- HBV, HCV, HIV
- In patients older than 50 years - serum free light chains and serum protein immunofixation

→ KIDNEY BIOPSY
Nephrotic Syndrome - DD

Systemic Diseases

- Diabetes Mellitus
- Lupus Nephritis
- Amyloidosis

Primary Diseases of the Kidney

- Membranous Nephropathy
- Minimal Change Disease
- Focal Segmental Glomerulosclerosis (FSGS)
Kidney Biopsy

Membranous Nephropathy
Kidney Biopsy from a different story

Membranous Nephropathy

About 70%-80% of membranous nephropathy are classified as primary

The remaining 20-30% have secondary forms associated with autoimmune diseases, infections, drug exposure, or malignancy

Identification of the two target antigens PLA2R and THSD7A allowed the development of serologic tests for circulating anti-PLA2R or anti-THSD7A autoantibodies, and revolutionized the diagnosis and follow up.
PLA2R-Positive Membranous Glomerulonephritis: KDIGO Recommendations for Serum Anti-PLA2R Testing

KDIGO recommends serial measurement of serum anti-PLA2R antibodies (for research protocols)

Goal is to assess value of these biomarkers in determining spontaneous remission, treatment response, and prognosis

KDIGO Clinical practice guideline for glomerulonephritis.
Cancer Screening

Standard cancer screening is recommended in all patients with glomerular lesions which may be associated with malignancy.

Targeted screening tests must be additionally performed according to each patient’s specific risk factors for cancer.
Routine and targeted cancer screening in patients with glomerulopathy

**Associated glomerular lesions with cancers**

<table>
<thead>
<tr>
<th>Membranous nephropathy</th>
<th>Minimal change disease</th>
<th>IgA nephropathy</th>
<th>ANCA+/-ANCA– crescentic glomerulonephritis</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Carcinoma: lung/bronchus</em></td>
<td><em>Focal segmental glomerulosclerosis</em></td>
<td><em>IgA vasculitis</em></td>
<td><em>Kidney/lung/upper respiratory tract carcinoma</em></td>
</tr>
<tr>
<td><em>GI/prostate/kidney, bladder, breast</em></td>
<td><em>Hodgkin’s disease</em></td>
<td><em>Kidney/GI carcinoma</em></td>
<td><em>Thymoma</em></td>
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<tr>
<td><em>Melanoma</em></td>
<td><em>Thymoma</em></td>
<td><em>Hematologic malignancy</em></td>
<td><em>Membranoproliferative glomerulonephritis</em></td>
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<tr>
<td><em>(Hematologic malignancy)</em></td>
<td></td>
<td></td>
<td><em>Kidney/lung/GI carcinoma</em></td>
</tr>
</tbody>
</table>

**Serology**

- PLA2R +
- TSHD7A +
- PLA2R –/TSHD7A –

**Screening for occult malignancy**

- If normal routine/targeted screening

**Screening for cancer**

**Routine screening**

- Patient/family clinical record
- Careful physical examination
- Laboratory testing
- Kidney and urinary tract ultrasound
- Standard age-specific screening for cancer
  - (gynecological examination, PAP test, mammography, fecal occult blood test)

**Targeted screening**

**Age > 60 years**

**Thrombotic event**

- Search for urine malignant cells +/- cystoscopy
- PSA test
- Abdominal ultrasound

**Smoking**

- Chest computed tomography
- Upper respiratory tract examination +/- fibroscopy
- Search for urine malignant cells +/- cystoscopy

**Alcohol abuse**

- Upper respiratory tract examination +/- fibroscopy
- Liver ultrasound, gastroscopy, serum alpha-fetoprotein

**Chronic hepatitis B and C**

- Liver ultrasound, serum alpha-fetoprotein

**Exposure to cyclophosphamide doses > 36 g**

- Search for urine malignant cells +/- cystoscopy
Thromboembolism

Patients with the nephrotic syndrome are at increased risk for venous thrombosis, particularly deep vein thrombosis and renal vein thrombosis.

There is also increased risk of arterial thrombosis and pulmonary emboli.

The risk of thrombosis is inversely related to the serum albumin levels.

Prophylactic anticoagulation?

When? Albumin < 2.5 g/dL
Who?
- Membranous Nephropathy
- Pregnant patients
Proteinuria without Nephrotic Syndrome

• Isolated proteinuria?
  • No HTN
  • No hematuria
  • No systemic disease
  • No kidney injury/azotemia
Transient Proteinuria

- Common, especially in young individuals
- Causes: fever, exercise, acute illness (eg URI), hyperglycemia
- Usually < 1 gram/ day
- Test: UACR or UPCR over 1-3 months
- Avoid exercise 24-48 hours prior to test
- Diagnosis is made when repeat test is no longer positive for proteinuria
Orthostatic Proteinuria

- Increased protein excretion in the upright position but normal protein excretion when the patient is supine
- Relatively common in adolescents (up to 5%), but uncommon in adults > 30 years old
- Usually < 1 gram/ day
- Benign, but kidney function and proteinuria should be followed yearly
- NORMAL early morning sample (<30mg), with positive PM sample within 24 hours = orthostatic proteinuria
Nephritic Syndrome

→ Glomerular Inflammation
  • Hematuria
  • Proteinuria - can be in the nephrotic range
  • HTN
  • Kidney injury
  • Involvement of other organs
Nephritic Syndrome - DD

**Systemic**
- ANCA vasculitis (pauci-immune glomerulonephritis)
- Anti-GBM disease
- SLE
- IgA nephropathy
- TMA

**Infections**
- Bacterial - Strep/ staph
- Viral - HBV, HCV, CMV
- Parasitic - Plasmodium malariae
Proteinuria - What is the big deal?

- The degree of proteinuria is prognostically important in patients with primary and secondary glomerular diseases.
- Higher degrees of proteinuria are associated with a more rapid progression to kidney failure, even in the absence of nephrotic syndrome.
Relative risks of Major Complications of CKD

### All-cause mortality

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<tr>
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<th>ACR &lt;10</th>
<th>ACR 10-29</th>
<th>ACR 30-299</th>
<th>ACR ≥300</th>
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### Cardiovascular mortality

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### Kidney failure (ESRD)

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### Acute kidney injury (AKI)

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### Progressive CKD

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<td>3.2</td>
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<tr>
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<td>4.0</td>
<td>12</td>
<td>21</td>
<td>7.7</td>
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</table>
Treatment

- Optimal HTN control: Aim BP < 130/80
- Add a diuretic for optimal HTN management
- ACEi/ARB
- Other agents that reduce proteinuria: non-dihydropyridine Ca Channel blockers, mineralocorticoid antagonists
- SLGT-2 inh

- Treatment for glomerular disease - IS
ACEi and ARB Therapy

- Proteinuria is independent risk factor for CKD progression
- Tight BP control reduces proteinuria and reduces GFR decline
Mechanism of ACE-inhibitors

Renin-angiotensin system

- **Renin release from kidney**
  - Renin acts on angiotensinogen to form **angiotensin I**.
  - ACE (angiotensin-converting enzyme) release from lungs
  - ACE acts on angiotensin I to form **angiotensin II**.
- Angiotensin II acts on the adrenal gland to stimulate release of aldosterone.
- Aldosterone acts on the kidneys to stimulate reabsorption of salt (NaCl) and water (H2O).
- Angiotensin II also acts directly on blood vessels, stimulating vasoconstriction (narrowing).

NSAID vs ACEI/ARB on Kidneys

- **NSAIDs**
  - Constrict Afferent arteriole
  - Afferent arteriole Arrives at glomerulus
  - Potential kidney damage
  - Efferent arteriole Exits the glomerulus

- **ACEI/ARBs**
  - Dilate Efferent arteriole
  - Kidney protection
  - Afferent arteriole Exits the glomerulus

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Spironolactone/Eplerenone

- Metanalysis (*CJASN 2009*) looked at MCA (Spironolactone 25mg daily) with ACEi compared to ACEi alone
- Proteinuria and HTN control improved significantly more with MCA + ACEi group
- No difference in GFR preservation between groups
- Higher risk Hyperkalemia with MCA+ACEi
SLGT-2 inhibitors

- CREDENCE trial (NEJM 2019) double blind randomized trial, type II DM + albuminuria + CKD
- Canagliflozin 100mg daily or placebo
- All patients GFR 30-90, treated with RAAS blockade

- Diabetic patients with >300mg albuminuria despite ARB/ACEi should start a sodium-glucose co-transporter (SGLT-2inh)
SLGT-2 inhibitors
Take home message

- Even within the normal range, higher amounts of albuminuria are associated with an increased risk of cardiovascular disease
- For patients who are very likely to have nephrotic-range proteinuria due to diabetic nephropathy, biopsy can be deferred
- Treat underlying cause/risk factors: obesity/DM/HTN/smoking/HL
Take home message - 2

• Start RAAS blockade: don’t wait! can start in CKDG1-G3b safely. Expect 30% rise in creat which stabilizes
• With treatment, aim to reduce albuminuria as much as possible by up-titrating RAAS blockade to achieve maximum effect to delay CKD progression
• For type 2 DM, with eGFR > 45, and > 300mg albuminuria, NOT on insulin/sulfonylurea, START SGLT-2 inh at lowest dose. Expect 30% rise in creatinine which stabilizes
"NEPHROTIC WHAT?!"... Understanding Primary Nephrotic Syndrome

TIP: Don’t be intimidated by the disease names; they are just descriptions of how the kidney tissue looks under a microscope.

Nephrotic Syndrome (NS) is not a disease, but an umbrella term for the collection of signs and symptoms that occur when the kidney filters (glomeruli) leak protein into the urine.

Some symptoms of NS include:
- Proteinuria ('leaking' protein into the urine)
- Edema (swelling)
- Hypertension (increased blood pressure)
- Hypoprothrombinemia (low blood protein)
- Hypercholesterolemia (high cholesterol)

Someone who is experiencing these symptoms but has not had a kidney biopsy is diagnosed with Nephrotic Syndrome.

To learn more about what is causing a patient’s Nephrotic Syndrome, doctors may choose to perform a kidney biopsy. After a biopsy, a patient is usually diagnosed more specifically, based on what can be seen under the microscope.

The most common diagnoses are:

Focal Segmental Glomerulosclerosis (FSGS)
Some sections of kidney filters show scarring.

Minimal Change Disease
Kidney tissue shows very little change from normal kidney tissue.

Membranous Nephropathy
Kidney tissue has a thicker than normal filtering barrier or glomerular basement membrane.

For more information, please visit www.NephCure.org/LivingWithKidneyDisease
Thank you!

• Questions?