ASSESSMENT OF PROTEINURIA IN PEDIATRIC PRACTICE

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OBJECTIVES

• Define proteinuria in pediatric health and disease
• Examine the mechanisms of proteinuria and distinguish sites of origin
• Interpret the clinical prognostic determinants of proteinuria in the context of pediatric practice
• Provide a paradigm for the assessment of proteinuria in pediatric practice
• Consider treatment strategies for proteinuria in children and adolescents
PROTEINURIA: PREVALENCE

- Up to 10% of children have proteinuria in a single urine sample (NKF Concensus Panel: PARADE)
- Only 0.1% have persistent proteinuria after 4 samples (Vehaskari et al 1982)
- AAP no longer advises the use of screening urinalysis at any age
DEFINITIONS

• Dipstick (albumin only):
  trace: <15 mg/dl; 1+ ≈ 30 mg/dl; 2+ ≈ 100 mg/dl; 3+ ≈ 300 mg/dl; 4+ ≈ >2000 mg/dl

• Random Urine pr/cr (mg/mg)
  Normal <100 mg/m^2/day = 0.1
  Intermediate Range >100 <1000 mg/m^2/day = >0.1 <1.0
  Nephrotic Range > 1000 mg/m^2/day = >1.0

• Microalbumin (µAlb)
  <30 µgrams/ mg creatinine
URINARY DIPSTICK

Colorimetric reaction between tetrabromophenol blue and albumin (only)

- Negative
- Trace = 15-30 mg/dl
- 1+ = 30-100 mg/dl
- 2+ = 100–300 mg/dl
- 3+ = 300–1000 mg/dl
- 4+ => 1000 mg/dl

Only >/= 1+ is abnormal

False Positives
- Alkaline urine pH>8
- Concentrated urine SG>1.025
- Gross Hematuria
- Pyuria
- Bacteriuria
- Iodinated radiocontrast dyes
- Dipstick held in urinary stream
- High-dose PCNs, Ceph, or Sulfa

Not sensitive for low molecular weight proteins which include IgG, transferrin, uromodulin
TYPES OF PROTEINURIA

- Orthostatic (Postural) Proteinuria
- Incidental Proteinuria
  - Fever
  - Exercise
- Overflow proteinuria
- Pathologic Proteinuria
  - Hyperfiltration (Diabetic; Low Nephron Mass; HT; Chronic Kidney Disease)
  - Inflammation (Glomerulonephritides)
  - Nephrotic Syndrome
MECHANISMS OF PROTEINURIA

- Loss of “net negative charge barrier”.
- Loss of fenestrated “pore barrier”.
- Filtration/generation of cytokines & noxious chemokines provoke interstitial cell proliferation and activation.
- “Overload proteinuria” from filtered albumin causes disruption of endosomal reabsorption of albumin and other proteins.
- Tubular proteinuria from ischemic/interstitial injury.
This paradigm shift implies that excreted protein represents the net effect of the interplay of glomerular permeability alterations and the saturable reabsorptive capacity of the proximal tubule.
MECHANISMS OF PROTEINURIA

Loss of “net negative charge” and pore size barrier

Loss of podocyte number and integrity

Loss of endosomal reclamation and degradation of filtered albumin
TUBULAR REABSORPTION OF FILTERED PROTEINS

- Complexes with cubulin or megalin
- Endocytic invagination with formation of endosomes and lysosomes
- Degradation of filtered proteins and reabsorption of amino acids
CHARACTERIZATION OF PROTEINURIA

• If microalbumin characterizes renal disease progression in adults; can we draw parallels with adults?

• Glomerular proteinuria is characterized by albuminuric.

• Tubular proteinuria is characterized by microglobulins (the “non-albumin component of proteinuria)

• Fractionation of Proteinuria
  • Microalbumin/Total protein ratio (µAlb/TP < 15%)
  • “Tubular Proteinuria” (microglobulins): 35%
  • Tamm Horsfall (uromodulin): 50%
USE OF SINGLE VOİDED URİNE SAMPLES TO ESTİMATE QUANTİTATİVE PROTEİNURIÂ

JAY M. GINSBERG, M.D., BRUCE S. CHANG, M.D., RICHARD A. MATARESE, M.D., AND SERAFİNO GARELLA, M.D.
(N Engl J Med 1983; 309:1543-6.)
Similar prognostic ability for each of the three methods to quantify proteinuria for characterizing a >50% decline in GFR or need for RRT based on clinically meaningful cutoffs of UP/C (Kaplan–Meier, dashed lines and Generalized Gamma, solid lines).

Dana Y. Fuhrman et al. CJASN 2017;12:912-920
Collinearity between the three methods to quantify proteinuria at the index study visit, n=751.
Profiling proteinuria in pediatric patients

<table>
<thead>
<tr>
<th>Age Distribution</th>
<th>Number of Patients</th>
</tr>
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<tbody>
<tr>
<td>Infants</td>
<td>0</td>
</tr>
<tr>
<td>1-6</td>
<td>1</td>
</tr>
<tr>
<td>7-12</td>
<td>2</td>
</tr>
<tr>
<td>&gt;12-21</td>
<td>3</td>
</tr>
<tr>
<td>&gt;21</td>
<td>4</td>
</tr>
</tbody>
</table>

**Patient Disease Category by Age Distribution**

- **Glomerular Tubular Infants**: 43%
- **Tubular Disease**: 58%
- **Glomerular Disease**: 26%
- **Others**: 18%

**Urine Protein Profiles by Disease Category**

- **Infants**: 45%
- **Glomerular**: 55%
- **Tubular**: 26%
- **Others**: 18%

**Urine Protein Profiles**

- **Up/cr (mg/mg) with µAlb Fraction**

**Graphs**:

1. **Patient Disease Category by Age Distribution**
2. **Urine Protein Profiles by Disease Category**
3. **Figures and graphs showing episodes of pyelonephritis and SLE exacerbation**

**References**

DOI 10.1007/s00467-006-0103-9
CALCULATIONS FOR PROFILING RANDOM SPECIMENS

• $Upr/cr = mg/mg$ Normal \( \leq 0.2 \) (?)
• Microalbumin ($\mu Alb)/cr$
  \( \frac{mg}{mg} \times 1000 = \frac{\mu g}{mg \ Cr} \) Normal < 30 $\mu g/mg \ Cr$

• $\% \ \mu Alb = \frac{\mu Alb}{Pr} \times 100 = \text{Glomerular proteinuria}$
• $1- \ \mu Alb/Pr \times 100 = \text{Tubular Proteinuria}$
• Nephrotic Range $Upr/cr > 2.0$ (1 gram/m²/day)
Mechanisms of Orthostatic Proteinuria: Lessons From a Transplant Donor

Prasad Devarajan,²,³

P. Devarajan, Pediatric Nephrology, Yale University, New Haven, CT
(J. Am. Soc. Nephrol. 1993; 4:36–39)

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Supporting Evidence</th>
</tr>
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<tbody>
<tr>
<td>Normal Variant</td>
<td>Normal proteinuria is posture dependent</td>
</tr>
<tr>
<td></td>
<td>Both normal and orthostatic proteinuria are selective</td>
</tr>
<tr>
<td>Glomerular Abnormality</td>
<td>Capillary wall thickening and mesangial hypercellularity seen</td>
</tr>
<tr>
<td></td>
<td>Mesangial/capillary deposits of IgG, IgA, and C3 reported</td>
</tr>
<tr>
<td>Hemodynamic Abnormality</td>
<td>Animal model of angiotensin II-mediated efferent arteriolar constriction and proteinuria</td>
</tr>
<tr>
<td></td>
<td>Left renal vein entrapment syndrome</td>
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Exaggerated hemodynamic response to the upright position

Increased Angiotensin II

Renal vein entrapment

Altered glomerular permeability

No glomerular injury

"Normal" proteinuria

Subtle glomerular injury

Orthostatic proteinuria
CONCLUSIONS

• Proteinuria is an important clinical marker of renal injury.
• Quantitating and “Profiling” proteinuria may allow:
  • Predicting the need for surgical intervention
  • Assessing response to surgical and medical treatment
• Further collaborative trials in chronic kidney injury in children should include assessment and profiling proteinuria.
ORTHOSTATIC PROTEINURIA: FOLLOW-UP

Although orthostatic proteinuria does not generally persist beyond the third decade of life, testing for proteinuria on an annual basis is prudent, especially because both pathologic and physiologic proteinuria (ie, the small amount of protein normally present in urine) also has an orthostatic component. If the first-voided morning specimen has a 1+ or greater reaction for protein, further studies are indicated.
Abnormal urine dipstick protein in an afebrile child

- ≥1+
  - Obtain first AM void for urine total protein/creatinine ratio
  - Urinalysis (U/A) with microscopic exam

- ≤0.2 mg protein per mg creatinine* and normal U/A
  - Repeat dipstick on first AM void in one year

- Trace

Further evaluation:
- History (drugs, family history)
- Physical examination (blood pressure)
- Laboratory evaluation: Creatinine, BUN, electrolytes, cholesterol, and albumin
- Also consider (when appropriate): Renal ultrasonography, serum C3/C4, antinuclear antibody testing (ANA), hepatitis B and C serology, HIV testing

Evaluation abnormal

Repeat urine dipstick on at least two additional samples

Refer to pediatric nephrologist

Evaluation normal

Proteinuria persistent

Negative
CONCLUSIONS

• Persistent proteinuria predicts renal disease progression in children.

• Proteinuria should be screened quantitatively in infants & children “at risk” including those with potential low renal mass and/or excess BMI.
  • diabetes mellitus (Type 1 or 2)
  • Obesity
  • preterm birth
  • history of familial kidney disease

• Early “reno-protection” is advocated in proteinuric kidney disease