APPROACH TO A CASE OF PROTEINURIA

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Content

• Case scenario
• Introduction to proteinuria
• Methods of urinary protein measurement
• Causes of proteinuria
• Evaluation & Management
Case scenario

A 15 years old boy has presented to you with chief complaints of:

1. Frothy urine for one month

2. Facial puffiness for 20 days

How will you approach?

Differential Diagnosis?
Introduction

Urine analysis is an important investigation to diagnose kidney diseases.

Proteinuria is one of the earliest & most important finding of urine examination

Proteinuria can be transient due to benign renal causes or persistent due to organic renal causes.
DEFINITION

• Healthy individuals can excrete less than 150mg /d of total protein and less than 30mg/d of total albumin

• Proteinuria – Urinary protein excretion > 150mg/day

• Albuminuria- Urinary albumin excretion > 30mg/day
COMPOSITION OF NORMAL URINARY PROTEIN (150 mg/day)

- Tamm-horsfall protein (Maximum) (40%)
- Albumin (20%)
- Immunoglobulins
- Hormones, Enzymes
- Mucopolysaccharides
MEASUREMENT OF URINARY PROTEIN

Qualitative

- Urine dipstick
- Sulfosalicylic acid test
- Heat coagulation test

Quantitative

- 24-hour urinary protein
- Spot urinary Albumin/creatinine ratio (ACR)
MEASUREMENT OF URINARY PROTEIN

- Urine dipstick
  - Primarily detect albuminuria
  - Less sensitive for other forms of proteinuria (low molecular weight proteins, Bence Jones protein, gamma globulins.)
MEASUREMENT OF URINARY PROTEIN

- Urine dipstick
  - Measures albumin concentration via a colorimetric reaction between albumin and tetrabromophenol blue producing different shades of green according to the concentration of albumin in the sample
  - Negative
  - Trace — between 15 and 30 mg/dL
  - 1+ — between 30 and 100 mg/dL
  - 2+ — between 100 and 300 mg/dL
  - 3+ — between 300 and 1000 mg/dL
  - 4+ — >1000 mg/dL
MEASUREMENT OF URINARY PROTEIN

Specific Gravity
Densidad
Densidade
60 sec/seg.

pH
60 sec/seg.
Leukocytes
Leucocitos
60–120 sec/seg.

Blood/Hemoglobin/
Sangre(ue)/Hemoglobin
60 sec/seg.

Nitrite/Nitrito/Nitritos
60 sec/seg.

Ketones/
Cetónicos
60 sec/seg.

Bilirubin/Bilirrubina/
60 sec/seg.

Urobilinogen(o)/
Urobilinógeno
60 sec/seg.

Protein/Proteínas/
Proteínas
60 sec/seg.

Glucose/Glucosa/
Glicose
60 sec/seg.

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LOT

Normal
1 (17)
1 (70)
0 (148)
12 (300)
mg/dL (mmol/L)

Protein
15 (0.15)
30 (0.3)
100 (1)
300 (3)
1000 (10)
mg/dL (g/L)

Glucose
100 (5.5)
300 (17)
1000 (55)
mg/dL (mmol/L)
Pitfalls of Dipstick method

- **False positive** –
  - Very Alkaline sample pH > 7.0
  - contaminated by antiseptic agents
    - Chlorhexidine or Benzalkonium chloride
    - Iodinated radiocontrast agents.
  - Gross hematuria

- **False Negative** –
  - dilute urine (specific gravity < 1.005)
  - In which the predominant urinary protein is not albumin
MEASUREMENT OF URINARY PROTEIN

• Sulfosalicylic acid test
  • Detects all proteins in the urine including the low molecular weight proteins that are not detected by the dipstick method
  • Performed by mixing one part urine with three parts 3 percent sulfosalicylic acid, followed by assessment of the degree of turbidity
Heat and Acetic Acid Test

- If turbidity develops add 1-2 drops of glacial acetic acid
- If turbidity is due to phosphate or carbonate precipitation, it will disappear with acetic acid

  Negative: No cloudiness
  Trace: Barely visible cloudiness.
  1+: Definite cloud without granular flocculation
  2+: Heavy and granular cloud without granular flocculation
  3+: Densed cloud with marked flocculation.
  4+: Thick curdy precipitation and coagulation
Grading based on 24 hour proteinuria

< 150mg/24 hours - Normal

150-500 mg/24 hours - Functional (<1mg/24 hr)

>500mg/24 hours - Significant

>3.5gm/24 hours - Nephrotic range

>4gm/24 hours - Massive
Grading based on 24 hour albuminuria

<30mg/24 hours- Normal

30-300 mg/24 hours- Microalbuminuria

>300 mg/24 hours- Albuminuria

>2200 mg/24 hours- Nephrotic range
Grading based on Spot urinary ACR

<30mg/gram- Normal

30-300 mg/gram - Microalbuminuria

>300 mg/gram- Albuminuria

>2200 mg/gram- Nephrotic range
MECHANISMS OF PROTEIN HANDLING BY KIDNEY

- Glomerular capillary wall permits passage of small molecules while restricting macromolecules
MECHANISMS OF PROTEIN HANDLING BY KIDNEY

• Normal protein excretion affected by interplay of glomerular and tubular mechanisms
• Glomerular injury: abnormal losses of intermediate MW proteins like albumin
• Tubular damage: increased losses of low MW proteins
CLASSIFICATION OF PROTEINURIA

• Functional
• Glomerular
• Tubular
• Overflow
FUNCTIONAL PROTEINURIA

• Benign form of proteinuria
• Protein excretion is less than 500mg/day (may rise up to 1g/d)
• Includes 2 types
  1. Transient proteinuria
  2. Orthostatic proteinuria
Transient proteinuria

- If dipstick analysis shows 0 to +2 proteinuria, but subsequent dipstick tests are negative.

- Potential triggers are acute illness, exercise, fever, heart failure, and UTI.

- After potential trigger has been treated or resolved, repeat urine test is normal.
ORTHOSTATIC PROTEINURIA

- This benign condition occurs in about 3 to 5 percent of adolescents and young adults which is characterized by increased protein excretion in the upright position but normal protein excretion when the patient is supine.

- To diagnose orthostatic proteinuria, split urine specimens are obtained for comparison.

- The daytime specimen typically has an increased concentration of protein, with the nighttime specimen having a normal concentration.

There should be no hematuria.
Causes of proteinuria

- Benign
  1. Fever
  2. Strenuous exercise
  3. Acute illness
  4. Emotional stress
  5. Orthostatic proteinuria

Due to increased renal blood flow
Pathological proteinuria

- **Glomerular** - Due to increased capillary permeability of glomerulus
  - Glomerulonephritis - Primary or secondary

- **Tubular** - Due to decreased tubular reabsorption of filtered proteins
  - Tubulo-interstitial diseases

- **Overflow** - Due to increased production of low molecular weight proteins
  - Monoclonal gammopathies, Leukaemias, Lymphomas
GLOMERULAR PROTEINURIA

- Occurs due to effacement of epithelial foot process and disruption of glomerular basement membrane

- Urinary protein electrophoresis shows large albumin spike indicative of increased permeability of albumin across damaged GBM

- Presence of RBC cast/Dysmorphic RBCs

- Only proteinuria that can cause >2 g protein/24 hours with albumin:beta 2 macroglobulin ratio>1000:1
Glomerular proteinuria

Primary

- Minimal change disease
- Idiopathic membranous GN
- FSGS
- Membranoproliferative GN
- IgA nephropathy

Secondary

- Diabetes
- Connective tissue disorders - Lupus nephritis
- Amyloidosis
- Preeclampsia
- Infection - Post streptococcal, Hep B,C,HIV
- Malignancy - Lymphoma, Lung & GI cancer
TUBULAR PROTEINURIA

• Occurs due to faulty reabsorption of normally filtered proteins by the proximal tubule

• Characterised by the presence of large amounts of small proteins in urine, with normal serum protein

• Rarely exceeds 1.5-2g/day
OVERFLOW PROTEINURIA

• Excessive production of an abnormal filterable plasma protein (monoclonal gammapathies) that exceeds the tubular capacity for reabsorption

• Usually less than nephrotic range

• Examples: Multiple myeloma (Bence Jones protein), Myoglobinuria in rhabdomyolysis and hemoglobinuria in hemolysis.
Pathological proteinuria

- **Tubular**
  - Hypertensive nephrosclerosis
  - Uric acid nephropathy
  - Interstitial nephritis
  - Heavy metals
  - Sickle cell disease
  - Drugs (e.g., NSAIDS, Cyclosporin, Contrast)
  - Hypersensitive interstitial nephritis

- **Overflow**
  - Haemoglobinuria/Myoglobinuria
  - Myeloma Amyloidosis
Selective proteinuria

Only albumin and transferrin lost in urine

It is seen in Minimal Change GN
**EVALUATION OF PROTEINURIA**

**PROTEINURIA ON URINE DIPSTICK**

Quantify by 24-h urinary excretion of protein and albumin or first morning spot albumin-to-creatinine ratio

*Moderately increased albuminuria
30–300 mg/d or 30–300 mg/g

*Severely increased albuminuria
300–3500 mg/d or 300–3500 mg/g

Nephrotic range
>3500 mg/d or >3500 mg/g

RBCs or RBC casts on urinalysis

**Consider**
- Early diabetes
- Essential hypertension
- Early stages of glomerulonephritis (especially with RBCs, RBC casts)

In addition to disorders listed under *moderately increased albuminuria consider
- Myeloma-associated kidney disease (check UPEP)
  - Intermittent proteinuria
  - Postural proteinuria
  - Congestive heart failure
  - Fever
  - Exercise

Nephrotic syndrome
- Diabetes
- Amyloidosis
- Minimal change disease
- FSGS
- Membranous glomerulopathy
- IgA nephropathy

*Moderately and severely increased albuminuria were previously termed “microalbuminuria” and “macroalbuminuria,” respectively.*
CLINICAL EVALUATION- HISTORY

• Proteinuria is usually detected during a routine screen in asymptomatic patients

• Symptoms with duration (history of recent fever with sore throat, periorbital puffiness progressing to anasarca, frothy urine, high coloured urine, oliguria, nausea, vomiting, abdominal pain, joint pain etc)

• Past history-Diabetes, hypertension, renal disease, systemic illnesses

• Drug history-NSAIDS, Cyclosporin, exposure to heavy metals

• Family history of renal disease
PHYSICAL EXAMINATION

• Blood pressure, body weight

• Edema – particularly facial (around eyes), pedal edema, ascites

• Fundoscopic examination
Investigations

• Baseline investigations –
  1. Complete blood count
  2. Renal function test
  3. Urine dipstick
  4. Urine routine examination
  5. 24 hour urinary protein
  6. Spot urine ACR, PCR(albumin / protein to creatinine ratio)
  7. Renal USG
# Diagnostic Evaluation of Proteinuria

1. When proteinuria is found on a dipstick urinalysis, the urinary sediment should be examined microscopically

<table>
<thead>
<tr>
<th>MICROSCOPIC FINDING</th>
<th>PATHOLOGIC PROCESS</th>
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<tbody>
<tr>
<td>Fatty casts, free fat or oval fat bodies</td>
<td>Nephrotic range proteinuria (&gt; 3.5 g per 24 hours)</td>
</tr>
<tr>
<td>Leukocytes, leukocyte casts with bacteria</td>
<td>Urinary tract infection</td>
</tr>
<tr>
<td>Leukocytes, leukocyte casts without bacteria</td>
<td>Renal interstitial disease</td>
</tr>
<tr>
<td>Normal-shaped erythrocytes</td>
<td>Suggestive of lower urinary tract lesion</td>
</tr>
<tr>
<td>Dysmorphic erythrocytes</td>
<td>Suggestive of upper urinary tract lesion</td>
</tr>
<tr>
<td>Erythrocyte casts</td>
<td>Glomerular disease</td>
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<tr>
<td>Waxy, granular or cellular casts</td>
<td>Advanced chronic renal disease</td>
</tr>
<tr>
<td>Eosinophiluria*</td>
<td>Suggestive of drug-induced acute interstitial nephritis</td>
</tr>
<tr>
<td>Hyaline casts</td>
<td>No renal disease; present with dehydration and with diuretic therapy</td>
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* A Wright’s stain of the urine specimen is necessary to detect eosinophiluria
Other tests

1. Fasting lipid profile
2. Hba1c
4. ANA
5. Serum C3/C4
6. Hepatitis B/C
7. Renal biopsy
<table>
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<tr>
<th>TEST</th>
<th>INTERPRETATION</th>
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<tr>
<td>Antinuclear Antibody</td>
<td>Elevated in SLE</td>
</tr>
<tr>
<td>Antistreptolysin O Titre</td>
<td>Elevated after streptococcal GN</td>
</tr>
<tr>
<td>Complement C₃ &amp; C₄</td>
<td>Levels low in RPGN</td>
</tr>
<tr>
<td>ESR</td>
<td>If normal help to rule out infection or inflammation</td>
</tr>
<tr>
<td>Fasting Blood sugar</td>
<td>Elevated in Diabetes Mellitus</td>
</tr>
<tr>
<td>Hemoglobin, Hct</td>
<td>Low in CRF</td>
</tr>
<tr>
<td>HIV, VDRL &amp; Hepatitis serology</td>
<td>All are associated with glomerular proteinuria</td>
</tr>
<tr>
<td>S. Electrolytes (Na⁺, K⁺)</td>
<td>Screening for any abnormalities consequent to renal disease</td>
</tr>
<tr>
<td>Serum &amp; Urine protein</td>
<td>Abnormal in multiple myeloma</td>
</tr>
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<td>Electrophoresis</td>
<td></td>
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<tr>
<td>Serum Urate</td>
<td>Elevated urates can lead to tubulointerstitial disease and stones</td>
</tr>
<tr>
<td>USG KUB</td>
<td>For structural renal disease</td>
</tr>
<tr>
<td>Chest X Ray</td>
<td>Systemic diseases like sarcoidosis</td>
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MANAGEMENT

Treat the underlying cause -

- Blood pressure control, Glycemic control
- Edema - diuretics, sodium restriction
- ACE inhibitors, ARB’s
- Lipid control
- Specific immunosuppressive therapies for primary glomerular diseases
Most common cause of nephrotic range proteinuria in adults is

1. Minimal change GN

2. Amyloidosis

3. Diabetic nephropathy

4. PSGN
Glomerular proteinuria can be differentiated from nonglomerular proteinuria by

1. Proteinuria < 1 g/day
2. RBC cast
3. Type of protein excreted is Tam-Horsfall protein
4. Albumin/Beta 2 macroglobulin ratio of 100:1
Thank you for your attention