

Jerry M. Bergstein

## A practical approach to proteinuria

Received: 26 May 1998 / Revised: 19 October 1998 / Accepted: 17 November 1998

**Abstract** Proteinuria is defined as urinary protein excretion exceeding 150 mg/day. It may result from nonpathological (posture, fever, exercise) or pathological (glomerular or tubular) processes. Glomerular proteinuria is an early sign of kidney disease and may also play a role in the progression of glomerular damage. Asymptomatic proteinuria is common; it may be transient or persistent. Transient proteinuria is a benign condition and requires no evaluation. Persistent proteinuria can be the first sign of kidney disease. Persistent proteinuria commonly results from disorders associated with increased glomerular permeability such as nephrotic syndrome, glomerulonephritis (e.g., post-infectious, membranous, membranoproliferative, lupus, IgA), and genetic defects (Alport syndrome, mesangial sclerosis). Tubular disorders should also be considered. Evaluation for the underlying cause is traditional. Whether the early detection and evaluation of proteinuria prevents progressive disease is unknown.

**Key words** Proteinuria · Postural · Fever · Exercise · Tubular · Glomerular

### Introduction

Proteinuria is usually detected in asymptomatic children by their primary care physician. Confirmation of persistent proteinuria leads to referral to the pediatric nephrologist for evaluation. The goals of this review are to define proteinuria, discuss the causes and significance of proteinuria, and suggest an approach for evaluating the child with proteinuria.

### Renal processing of proteins

The movement of proteins across the glomerular capillary wall is regulated by several factors, including the glomerular plasma flow rate, hydrostatic and oncotic forces, the molecular size, charge, and configuration of the protein, and the intrinsic properties of the capillary wall [1, 2]. The size barrier for filtration approximates that of albumin. Progressively smaller proteins are filtered in progressively increasing amounts. The vast majority of proteins appearing in the glomerular ultrafiltrate are reabsorbed in the proximal tubule.

### Definition and detection of proteinuria

Because normal individuals have protein in their urine, the term “proteinuria” is used to indicate urinary protein excretion beyond the upper limit of normal. In adults, that limit approximates 150 mg/day. In children, the upper limit of normal protein excretion remains to be defined. Since several variables (e.g., posture, activity, diet) can influence protein excretion and as I can find no clear evidence that protein excretion in normal children is related to body size, I use 150 mg/day as the upper limit of normal protein excretion in children as well. Approximately half of this protein derives from the plasma, albumin representing the largest fraction; the upper limit of normal albumin excretion approximates 30 mg/day. The remainder of normal urinary protein is Tamm-Horsfall protein, a mucoprotein of unknown function produced in the distal tubule.

In the urine, protein is commonly detected by the dipstick test and is reported as negative, trace, 1+ (approximately 30 mg/dl), 2+ (approximately 100 mg/dl), 3+ (approximately 300 mg/dl), and 4+ (2,000 mg/dl). Dipsticks primarily detect albuminuria and are less sensitive for (and may miss) other forms of proteinuria (e.g., low molecular weight proteins, Bence Jones protein, gamma globulins). The depth of color of the dipstick reaction increases in a semi-quantitative manner with increasing

J.M. Bergstein (✉)  
James Whitcomb Riley Hospital for Children,  
Indiana University School of Medicine, 702 Barnhill Drive,  
Indianapolis, IN 46202, USA  
e-mail: jbergste@iupui.edu  
Tel.: +1-317-274-2563, Fax: +1-317-278-3599

urinary protein concentrations. Dipsticks may be positive despite normal protein excretion when the urine is concentrated, or negative despite moderately increased protein excretion when the urine is dilute. Because the dipstick reaction cannot accurately measure protein excretion, persistent proteinuria should be quantitated by a more-precise method (e.g., sulfo-salicylic acid) in a timed (preferably 24-h) urine collection. False-positive results for proteinuria may be found with both the dipstick test (gross hematuria, contamination with chlorhexidine or benzalkonium, pH >8.0, phenazopyridine therapy) and the sulfosalicylic acid method (radiographic contrast agents, penicillin or cephalosporin therapy, tolbutamide, sulfonamides).

Urinary protein excretion can be estimated semiquantitatively by measuring the ratio of urinary protein to creatinine concentrations in a random specimen [3]. Urinary creatinine excretion is relatively constant in patients with relatively normal renal function, as is urinary protein excretion in most disease states. Determination of the ratio is especially helpful in quantitating proteinuria when a timed urine collection is not practical. Ratios (mg/mg) below 0.5 in children less than 2 years of age, and less than 0.2 in older children, suggest normal protein excretion. A ratio greater than 3 suggests nephrotic-range proteinuria.

## Nonpathological proteinuria

Proteinuria may be divided into two categories (Table 1). In the first category, nonpathological proteinuria, excessive protein excretion is apparently not the result of a disease state. The level of proteinuria in this category is generally less than 1 g/day and is never associated with edema. Pathological proteinuria results from glomerular or tubular disorders.

## Postural (orthostatic) proteinuria

Children with this disorder excrete normal or slightly increased amounts of protein in the supine position. In the upright position, the amount of protein in the urine may increase tenfold or more. The proteinuria is usually discovered at routine urinalysis; its etiology is unknown [4]. Hematuria is absent and the creatinine clearance and C3 complement level are normal. Renal biopsy (not part of the evaluation) is normal or shows mild nonspecific alterations.

In the child with asymptomatic low-grade proteinuria, a study for postural proteinuria should be performed. At bedtime, the child goes to bed without voiding. After 30 min in the supine position, the child voids in this position. This urine is discarded but the time of voiding is recorded as the beginning of the supine collection. The child is then given a large glass of liquid and allowed to sleep. In the morning, the child again voids supine before rising; this ends the supine collection and begins the upright collection which is terminated at bedtime. The child may have normal daily activities, avoiding the supine position. Protein excretion is measured in the two urine collections and, for each collection, the result is calculated as milligrams of protein excreted per minute. A finding of essentially normal protein excretion in the supine collection and increased protein excretion in the upright collection establishes the proteinuria as orthostatic.

Studies in adults suggest that postural proteinuria is a benign process [5], but similar data are not available for children. Accordingly, long-term follow-up of children is necessary (unless the proteinuria resolves) in order to monitor the child for evidence of renal disease (hematuria, hypertension, diminished renal function, or proteinuria exceeding 1 g/day).

**Table 1** Classification of proteinuria<sup>a</sup>

A. Nonpathological proteinuria	
1. Postural (orthostatic)	
2. Febrile	
3. Exercise-induced	
B. Pathological proteinuria	
1. Tubular	
a. Inherited	
Cystinosis	
Wilson disease	
Lowe syndrome	
b. Acquired	
Antibiotic-induced	
Interstitial nephritis	
Acute tubular necrosis	
Heavy metal poisoning (mercury, gold, lead)	
2. Glomerular	
a. Nephrotic syndrome	
Idiopathic	
Minimal change	
Mesangial proliferation	
Focal sclerosis	
Congenital and infantile	
b. Glomerulonephritis	
Idiopathic (membranous, membranoproliferative)	
Systemic diseases (lupus erythematosus)	
Others (drugs)	
c. Hypertension	
d. Diabetes mellitus	
e. Hemolytic uremic syndrome	
f. Hyperfiltration secondary to nephron loss (with or without focal sclerosis) due to chronic pyelonephritis or other renal diseases	

<sup>a</sup> Adapted from Bergstein JM (1996) Nephrology. In: Behrman RE, Kliegman RM, Arvin AM (eds) Nelson textbook of pediatrics. Saunders, Philadelphia, p 1480

### Febrile proteinuria

Transient proteinuria may be found in children having fever in excess of 38.3°C [6, 7]. The mechanism of proteinuria associated with fever is unknown. The proteinuria does not exceed 2+ on the dipstick and may be considered benign if it resolves when the fever abates.

### Exercise proteinuria

Proteinuria, like hematuria, may follow vigorous exercise [8, 9]. The level rarely exceeds 2+ on the dipstick. The disorder can be considered benign if the proteinuria resolves after 48 h of rest.

---

## Pathological proteinuria

### Tubular proteinuria

Healthy individuals filter large amounts of proteins of lower molecular weight than albumin (e.g., lysozyme, light chains of immunoglobulin,  $\beta_2$ -microglobulin, insulin, growth hormone); these are normally reabsorbed in the proximal tubule [10, 11]. Injury to the proximal tubules results in diminished reabsorptive capacity and the loss of these low molecular weight proteins in the urine. Such proteinuria rarely exceeds 1 g/day and is not associated with edema. Tubular proteinuria (Table 1) may be seen in acquired and inherited disorders and may be associated with other defects of proximal tubular function, such as glucosuria, phosphaturia, bicarbonate wasting, and aminoaciduria. Tubular proteinuria rarely presents a diagnostic dilemma because the underlying disease is usually detected before the proteinuria. Asymptomatic patients having persistent proteinuria generally have glomerular rather than tubular proteinuria. In occult cases, glomerular and tubular proteinuria can be distinguished by electrophoresis of the urine. In tubular proteinuria, the low molecular weight proteins migrate primarily in the  $\alpha$  and  $\beta$  regions and little or no albumin is detected, whereas in glomerular proteinuria the major protein is albumin [12].

### Glomerular proteinuria

The most-common cause of pathological proteinuria is increased permeability of the glomerular capillary wall. The amount of glomerular proteinuria may range from <1 to >30 g/day. Glomerular proteinuria may be termed selective (loss of plasma proteins of molecular weight up to and including albumin) or nonselective (lost of albumin and larger molecular weight proteins such as IgG). Most forms of glomerulonephritis are accompanied by nonselective proteinuria. Selective proteinuria is seen primarily in minimal-change nephrosis where it increases the likelihood of corticosteroid responsiveness. The

determination of urinary protein selectivity is generally of little clinical value due to considerable overlap of selectivities among various forms of renal disease.

Glomerular proteinuria is an early sign of kidney disease. Although the proteinuria is the result of kidney disease, it may also play a role in the progression of kidney damage [13]. The abnormal passage of proteins across the glomerular capillary wall and through the mesangium may promote glomerular injury. The filtration of large amounts of protein may then expose the proximal tubules to agents (e.g., transferrin, complement components, lipoproteins) that are directly toxic to tubular cells. In addition, overloading the proximal tubular cells with proteins may activate a number of genes, leading to the production of growth factors, vasoactive (endothelin-1) and inflammatory (monocyte chemoattractant protein-1, RANTES, integrins) agents that may also lead to tubulointerstitial lesions [14–16]. Indeed, the level of proteinuria is associated with outcome in several disease states [17, 18]. Whether the early detection of proteinuria prevents or delays the progression of disease is unknown. It seems possible that the early detection of proteinuria could lead to early disease recognition and appropriate management strategies (antihypertensive therapy, immunosuppressive drugs, anti-proteinuric agents such as angiotensin converting enzyme inhibitors, angiotensin II receptor antagonists, and/or nonsteroidal anti-inflammatory agents) [19–22].

Recent studies suggest that microalbuminuria is a more-sensitive marker for kidney disease than proteinuria. The importance of asymptomatic microalbuminuria as a risk factor for progressive kidney and cardiovascular disease is emphasized by the initiation of the Proteinuria, Albuminuria, Risk Assessment, Detection, and Elimination (PARADE) program by the National Kidney Foundation of the United States [23]. The goals of this program include education of the general public and physicians about albuminuria and universal screening for albuminuria.

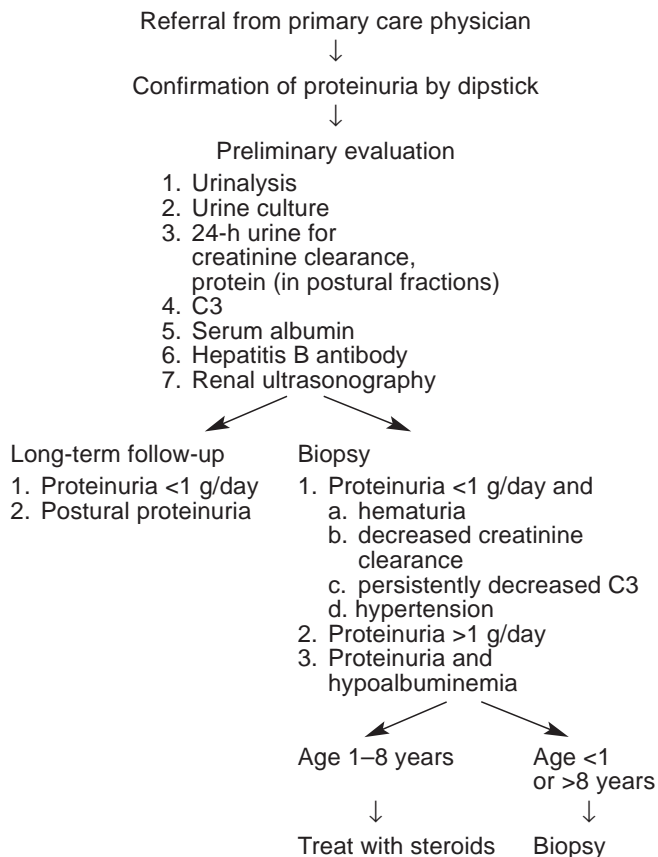
---

### Persistent asymptomatic proteinuria

Asymptomatic proteinuria may be transient or persistent. Transient proteinuria is that which disappears on subsequent urine examinations. It seems to be a benign condition and no evaluation is necessary.

Persistent asymptomatic proteinuria is defined as proteinuria in an apparently health child that occurs without hematuria and persists for 3 months. The prevalence in school-aged children may be as high as 6% [24–26]. The amount of proteinuria is usually <2 g/day; it is never associated with edema. Causes include postural proteinuria, membranous and membranoproliferative glomerulonephritis, hepatitis B infection, pyelonephritis, hereditary nephritis, developmental anomalies, and “benign” proteinuria.

The evaluation of the child with persistent asymptomatic proteinuria is summarized in Fig. 1. The evaluation should begin with a complete history and physical exam-



**Fig. 1** Laboratory evaluation of the child with asymptomatic proteinuria

ination, focusing on the manifestations of the diseases noted in the differential diagnosis. Important features of the history might include hematuria, frequency, dysuria, weight gain, swelling, hearing loss, and the family history. A list of medications is important. Drugs that can cause proteinuria include nonsteroidal anti-inflammatory agents, gold, penicillamine, and angiotensin converting enzyme inhibitors. On examination, evidence of edema, flank masses, and hypertension should be sought.

If the laboratory studies are normal except for low-grade proteinuria (150–1,000 mg/day), renal biopsy is not indicated, because evidence for a progressive disease is rarely found. Such patients should have an annual re-evaluation consisting of a physical examination and blood pressure determination, urinalysis, creatinine clearance, and 24-h protein excretion. Indications for renal biopsy include persistent asymptomatic proteinuria in excess of 1,000 mg/day or the development of hematuria, hypertension, a low C3, or diminished renal function in the patient with low-grade proteinuria.

## References

1. Kanwar YS (1984) Biophysiology of glomerular filtration and proteinuria. *Lab Invest* 51:7–21
2. Comper WD, Glasgow EF (1995) Charge selectivity in kidney ultrafiltration. *Kidney Int* 47:1242–1251
3. Abitbol C, Zilleruelo G, Freundlich M, Strauss J (1990) Quantitation of proteinuria with urinary protein/creatinine ratios and random testing with dipsticks in nephrotic syndrome. *J Pediatr* 116:243–247
4. Devarajan P (1993) Mechanisms of orthostatic proteinuria: lessons from a transplant donor. *J Am Soc Nephrol* 4:36–39
5. Springberg PD, Garrett LE Jr, Thompson AL, Collins NF, London RE, Robinson RR (1982) Fixed and reproducible orthostatic proteinuria: results of a 20-year follow-up study. *Ann Intern Med* 97:516–519
6. Jensen H, Henriksen K (1974) Proteinuria in non-renal infectious disease. *Acta Med Scand* 196:75–82
7. Marks MI, McLaine PN, Drummond KN (1970) Proteinuria in children with febrile illnesses. *Arch Dis Child* 45:250–253
8. Campanacci L, Faccini L, Englaro E, Rustia R, Guarnieri GF, Barat R, Carraro M, De Zotti R, Micheli W (1981) Exercise-induced proteinuria. *Contrib Nephrol* 26:31–41
9. Poortmans JR (1985) Postexercise proteinuria in humans. *JAMA* 253:236–240
10. Maack T, Johnson V, Kau ST, Figueiredo J, Sigulem D (1979) Renal filtration, transport, and metabolism of low-molecular-weight proteins: a review. *Kidney Int* 16:251–270
11. Waller KV, Ward KM, Mahan JD, Wismatt DK (1989) Current concepts in proteinuria. *Clin Chem* 35:755–765
12. Alt JM, Von der Heyde D, Assel E, Stolte H (1981) Characteristics of protein excretion in glomerular and tubular disease. *Contrib Nephrol* 24:115–121
13. Williams JD, Coles GA (1994) Proteinuria – a direct cause of renal morbidity. *Kidney Int* 45:443–450
14. Burton C, Harris KPG (1996) The role of proteinuria in the progression of chronic renal failure. *Am J Kidney Dis* 27:765–775
15. Peruzzi L, Trusolino L, Amore A, Gianoglio B, Cirina P, Basso G, Emancipator S, Marchisio PC, Coppo R (1996) Tubulo-interstitial responses in the progression of glomerular disorders: albuminuria modulates  $\alpha\beta$  integrin. *Kidney Int* 50:1310–1320
16. Zoja C, Donadelli R, Colleoni S, Figliuzzi, Bonazzola S, Morigi M, Remuzzi G (1998) Protein overload stimulates RANTES production by proximal tubular cells depending on NF- $\kappa$ B activation. *Kidney Int* 53:1608–1615
17. Perna A, Remuzzi G (1996) Abnormal permeability to proteins and glomerular lesions: a meta-analysis of experimental and human studies. *Am J Kidney Dis* 27:34–41
18. Ruggenti P, Perna A, Mosconi L, Pisoni R, Remuzzi G (1998) Urinary protein excretion rate is the best independent predictor of ESRF in non-diabetic proteinuric chronic nephropathies. *Kidney Int* 53:1209–1216
19. Ichikawa I (1996) Will angiotensin II receptor antagonists be renoprotective in humans? *Kidney Int* 50:684–692
20. Ihle BU, Whitworth JA, Shahinfar S, Cnaan A, Kincaid-Smith PS, Becker GJ (1996) Angiotensin-converting enzyme inhibition in nondiabetic progressive renal insufficiency: a controlled double-blind trial. *Am J Kidney Dis* 27:489–495
21. Remuzzi G, Ruggenti P, Benigni A (1997) Understanding the nature of renal disease progression. *Kidney Int* 51:2–15
22. Maschio G, Alberti D, Janin G, Locatelli F, Mann JFE, Motolese M, Ponticelli C, Ritz E, Zucchelli P, and the Angiotensin-Converting-Enzyme Inhibition in Progressive Renal Insufficiency Study Group (1996) Effect of the angiotensin-converting-enzyme inhibitor benazepril on the progression of chronic renal insufficiency. *N Engl J Med* 334:939–945
23. Lore G (1998) The NKF launches its own PARADE – a bold new initiative to detect, evaluate and treat proteinuria. *Contemp Dial Nephrol* 19:20–22
24. Dodge WF, West EF, Smith EH, Bunce H III (1976) Proteinuria and hematuria in school-age children: epidemiology and early natural history. *J Pediatr* 88:327–347
25. Vehaskari VM, Rapola J (1982) Isolated proteinuria: analysis of a school-age population. *J Pediatr* 101:661–668
26. Yoshikawa N, Kitagawa K, Ohta K, Tanaka R, Nakamura H (1991) Asymptomatic constant isolated proteinuria in children. *J Pediatr* 119:375–379