

Clinical Approach to Children with Proteinuria

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Proteinuria is common in pediatric and adolescent patients. Proteinuria is defined as urinary protein excretion at levels higher than 100-150 mg/m²/day in children. It can be indicative of normal or benign conditions as well as numerous types of severe underlying renal or systemic disease. The school urine screening program has been conducted in Korea since 1998. Since then, numerous patients with normal or benign proteinuria as well as early stage renal diseases have been referred to the hospital. Benign proteinuria includes orthostatic proteinuria and transient proteinuria. Most causes of proteinuria can be categorized into 3 types: 1) overflow, 2) tubular, and 3) glomerular. Although treatment should be directed at the underlying cause of the proteinuria, prompt evaluation, diagnosis, and long-term monitoring of these pediatric patients can prevent potential progression of the underlying disease process. This article provides an overview of proteinuria: its causes, methods of assessment, and algorithmic suggestions to differentiate benign from pathologic renal disease.

Key words: Proteinuria, Children, Renal disease, School urine screening

Introduction

Proteinuria is common among pediatric and adolescent patients. It can be indicative of a normal or benign condition as well as numerous types of severe underlying renal or systemic diseases. Hippocrates noted the association between “bubbles on the surface of the urine” and renal disease¹. Dr. Richard Bright first described the association between proteinuria and renal disease in the 1800s². Nowadays, in clinical practice, proteinuria is easily detectable and treatable. The school urine screening program (SUS) has been conducted in Korea since 1998³. Since then, numerous patients with normal or benign proteinuria as well as early stage renal diseases have been referred to hospitals. This article describes an overview of proteinuria, its causes, ways of assessment, and algorithmic suggestions to differentiate benign from pathologic renal diseases.

Definition of proteinuria

Proteinuria is defined as urinary protein excretion at levels higher than 100-150 mg/m²/day in children. In neonates, normal urinary protein excre-

tion is as high as 300 mg/m²/day possibly due to their reduced reabsorption of the filtered proteins⁴). Urinary proteins are composed mainly of albumin, and Tamm-Horsfall mucoproteins secreted by tubular cells; however, immunoglobulins (Ig), microglobulins as well other proteins could also be present depending on the underlying disease.

Measurement of proteinuria

Proteinuria can be evaluated using the following methods: urinary dipstick reagent, sulfosalicylic acid (SSA) turbidity tests, random or first morning urine (FMU) for spot urine protein-to-creatinine ratio (UPCR), the 24 hours urinary protein and creatinine, urine protein electrophoresis, urinary microalbumin.

The urinary dipstick reagent test is routinely used in clinical practice. It is highly sensitive solely for the measurement of albumin concentration via colorimetric reactions. Its main limitation is that it cannot detect other types of proteins such as plasma proteins, globulins, and low-molecular-weight proteins. The graded scale is stated as follows: negative (less than 10 mg/dL), trace (10-29 mg/dL), 1+ (30-100 mg/dL), 2+ (100-300 mg/dL), 3+ (300-1,000 mg/dL), 4+ (>1,000 mg/dL)⁵. False-positive results can occur with alkaline or highly concentrated urine specimens, macroscopic hematuria, pyuria, and certain detergents. Likewise, false-negative results can occur in patients with very dilute urine specimens, or in disease states where albumin is not the predominant urinary protein.

The qualitative SSA turbidity test is not routinely used in clinical practice for assessment of proteinuria. However, it has the potential to detect a broad range of urinary proteins. This turbidometric method of testing is useful in the diagnosis of multiple myeloma, characterized by the excretion of light-chain Ig. The SSA reagent is added to a fresh urine specimen, and the degree of turbidity is correlated with the amount of proteinuria based on a predetermined scale. This type of testing is disadvantageous in that it is subjective to the grading scale. Hence, this technique is rarely used for the assessment of proteinuria.

The spot UPCR is a highly used tool for the quantitative measurements of pediatric proteinuria due to inaccuracies involved in the 24 hours urine specimen collections of in-

fants or younger children, especially those that are not toilet-trained. Moreover, for quantification the UPCR can be extrapolated to and is as good as a 24 hours urine collection process⁶⁻⁸). The first morning urine (FMU) is essential due to the large degree of variability in urinary protein levels throughout the day. The normal UPCR for infants less than 6 months of age is not clearly defined, though ratio higher than 0.8-1.0 are generally considered abnormal. Ratio less than 0.5 are considered normal for children 6-24 months of age, and those less than 0.2 for children older than 24 months of age and adults⁹). Generally, pathologic proteinuria occurs in pediatrics when the ratio is higher than 1-2, though this could be considered normal in certain conditions. The UPCR is dependent on the production and excretion of creatinine, which can vary for each child's body state. For example, the ratio will be elevated in children with low muscle mass or severe malnutrition, due to the low rate of creatinine excretion¹⁰). Despite these limitations, the UPCR is a highly useful tool for quantification of proteinuria in children.

The 24 hours urine specimen collection is still the gold standard for quantitative urinalysis. Variations in quantification can be reduced using the body surface area. This results in the followings: normal, ≤ 4 mg/m²/hour; proteinuria, 4-40 mg/m²/hour; and nephrotic-range proteinuria, >40 mg/m²/hour.

Tubular proteinuria might be underestimated with urinary dipstick testing, because of the lower levels of albuminuria. Urine protein electrophoresis should be considered when low-molecular-weight proteins are suspected in tubulointerstitial renal diseases.

More specific quantification of proteinuria is required especially in children with diabetes mellitus. Microalbuminuria is the presence of albumin above the normal but below the detectable range using the conventional urinary dipstick method. Urine albumin-to-creatinine ratio (UACR) is also calculated in a similar manner as UPCR, and its normal range is less than 20-30 mg of urine albumin per gram of creatinine using the FMU. Microalbuminuria is defined as excretion of 20-200 μ g/min/1.73m² or 30-300 mg albumin per gram creatinine a day.

Microalbuminuria is a predictive of diabetic nephropathy, cardiovascular mortality and morbidity in patients with type I or type II diabetes mellitus¹¹).

Epidemiology of proteinuria

The prevalence of proteinuria may vary based on the definition used and the number of urine specimens or evaluation time of the test. One study showed the prevalence of isolated proteinuria detected by routine urinalysis (urine dipstick method) in school children to be approximately 10%^{12,13}. Park et al. reported that a total of 1,044 school children were identified with hematuria and/or proteinuria during a mass school urine screening test in Korea. Majority of the school children had transient or orthostatic proteinuria and/or hematuria. Persistent or pathologic proteinuria ranged from 0.1% to 2%¹². The prevalence increased with increasing age and showed a peak during adolescence.

The incidence of primary nephrotic syndrome per year in the absence of systemic disease has been reported as 1.5/100,000 children¹⁴. Despite the low prevalence of persistent or pathologic proteinuria among these children, early detection and treatment of proteinuria is crucial in preventing the progression to potentially significant renal parenchymal and end-stage diseases.

Etiology of proteinuria

Proteinuria may be either asymptomatic or symptomatic (hematuria and edema), transient or persistent, and isolated or associated with other systemic symptoms. The first step in the evaluation of proteinuria is to differentiate between the pathologic and benign etiologies.

Transient proteinuria is associated with stress, fever, seizure activity, cold exposure, or strenuous exercise¹⁵⁻¹⁷. It is temporary and disappears when the inciting factor is resolved. Transient proteinuria may not be associated with any significant renal disease. Proteinuria does not exceed 1+ to 2+ in this case using the urine dipstick method. This subtype of proteinuria may be caused by hemodynamic changes in the glomerular blood flow. Although these changes result in increased protein diffusion, further evaluation or treatment for these children is unnecessary.

Orthostatic or postural proteinuria is more common in older children and adolescents, accounting for approximately 5% of proteinuria¹¹. This type of proteinuria is usually asymptomatic and can easily be detected using urinary

screening tests. This condition has the hallmark of increased protein excretion in the upright position. Other symptoms (hematuria, edema, hypertension, and renal dysfunction) must be absent. In this type of proteinuria, the total urinary protein excretion may be increased up to 1 g/day, but it rarely exceeds this level. The collection of FMU is critical for its diagnosis. The patients must fully void themselves of urine before going to bed and collect the FMU immediately after waking up. The exact etiology of orthostatic proteinuria is still unclear. Multiple factors, such as renal hemodynamic changes, partial left renal vein compression, increased permeability of the capillary walls, or circulating immune complexes have been proposed^{18,19}. Long-term studies with follow-up from 20 to 50 years have demonstrated a benign course^{20,21}. Most of the studies are not on pediatric cases, and late-onset glomerulosclerosis have been reported. Therefore, periodic monitoring of the spot FMU test and blood pressure have been recommended.

Fixed proteinuria is defined as FMU that shows $\geq 1+$ on dipstick reagent test with UPCr of ≥ 0.2 or with a urine specific gravity > 1.015 . Fixed proteinuria may be indicative of underlying renal pathology. Therefore, if fixed proteinuria on FMU is found after three or more urinalysis performed every few weeks, these patients required close follow-up and should be further evaluated.

Pathophysiology of proteinuria

Significant amount of proteins present in urine could result from different pathophysiologic processes. First, the passage of large proteins, such as albumin, across the glomerular barrier is restricted. The components of the glomerulus basement membrane do not only serve as physical barriers but also electrical charge barriers due to the presence of glycosaminoglycans and glycocalyx attached to the plasma proteins²². The restriction of the basement membrane is mediated by charge-repelling primarily negatively charged proteins, such as albumin, and the pore size. This combination is the reason why little amounts of albumin appear in the Bowman's space as part of the ultrafiltrate (albumin concentration in the proximal tubule is about 1-10 mg/L). Second, the filtered low-molecular-weight proteins are reabsorbed in the proximal tubule by endocytosis

at the luminal membrane. Third, the proximal tubules also secrete proteins into the urine from the blood. Normally, excreted proteins comprise approximately of 40% albumin, 40% Tamm-Horsfall proteins secreted from the ascending loop of Henle, and 20% smaller proteins such as beta-2 microglobulin, retinol binding protein and N-acetyl-D-glucosaminidase filtered and reabsorbed by the proximal tubules. Increase in the excretion of these proteins is the hallmark of tubular disease.

Most causes of proteinuria can be categorized into 3 groups as follows: 1) overflow 2) tubular, and 3) glomerular. Large amounts of filtered proteins overwhelm the tubular reabsorptive capacity during marked increase in these abnormal Ig and other low-molecular-weight proteins. Multiple myeloma is the most common cause of overflow proteinuria. Another example of overflow proteinuria is found in pediatric patients with myoglobinuria. In tubular diseases, such as Fanconi syndrome, interstitial nephritis, and sickle cell disease nephropathy, this reabsorptive capacity is impaired, leading to increased low-molecular-weight proteins in the urine. The amount of tubular proteins excreted in tubular diseases is generally smaller than that in glomerular proteinuria, which is less than 2 g/day. Dent's disease is an X-linked recessive disorder of the proximal tubules characterized by hypercalciuria, low-molecular-weight proteinuria, and nephrolithiasis. Most of the cases of Dent's disease have mutations that inactivate the voltage-gated chloride transporter named CLC-5. Patients with Lowe syndrome (also called the oculocerebrorenal syndrome of Lowe), generally have proximal tubulopathy, bilateral cataracts, and hypotonia.

Glomerular proteinuria is caused by the increased permeability of the glomerular capillary wall. This can be classified as selective (proteins with molecular weights up to that of albumin and transferrin) or nonselective (proteins with larger molecular weights such as IgG). Minimal change disease also called lipoid nephrotic syndrome can be mostly seen in selective proteinuria pediatric patients. Most forms of glomerulonephritis are followed by nonselective proteinuria. This degree of selectivity can be determined by measuring albumin and other proteins of higher molecular weights such as transferrin or IgG. Highly selective proteinuria may have an IgG: albumin ratio of <0.1. Glomerular proteinuria may result from renal diseases, though this

type of proteinuria can play an important role in their progression²³. The abnormally high passage of proteins across the glomerular capillary wall and mesangium may aggravate glomerular injury. Large amounts of filtration may expose the proximal tubular cells to toxic agents (e.g., complement components, lipoprotein, and transferrin). Moreover, overloading proteins in the proximal tubules activate genes resulting in the production of inflammatory agents (such as RANTES signaling pathway, integrins, monocyte chemoattractant protein-1), growth factors, and vasoactive agents (endothelin-1) which also promote renal tubulointerstitial lesions^{24,25}. Early detection of proteinuria may facilitate early recognition of renal diseases and the proper management using medication.

Persistent proteinuria often indicates underlying renal pathology. Glomerular causes for proteinuria are more common than tubulointerstitial causes of proteinuria. The causes of proteinuria have been listed in Table 1^{26,27}. Nephrotic syndrome is one of the important causes of glomerular diseases. Nephrotic syndrome is characterized by hypoalbuminemia, edema, hyperlipidemia, and nephrotic-range proteinuria (40 mg/m²/hour in a 24 hours urine collection or >2 of UPCR). Minimal-change nephrotic syndrome (MCNS) is most common in children and shows a good response to corticosteroid therapy. Patients with MCNS were aged 2-7 years and predominantly males²⁸.

Diagnosis of proteinuria

As with any medical problem, a thorough history is very crucial in evaluating patients with proteinuria. History should include symptoms of hypertension, oliguria, polyuria, weight loss, skin lesions, joint symptoms, recent infections, previous abnormal urinalyses, and recent intake of medications (such as NSAIDs, gold, angiotensin converting enzyme inhibitors (ACEi), and penicillamine). Family history of hypertension, renal disease, autoimmune disease, and visual impairment or deafness should also be considered. Growth is an important clue for chronic diseases such as renal disease and needs to be measured. Blood pressure also needs to be routinely measured²⁹. Signs of edema, flank pain, fluid overload, organomegaly, rashes, anemia, joint swelling, and symptoms of osteodystrophy should be

examined. Table 1 illustrates common conditions associated with persistent proteinuria to guide the physical examination for rare medical conditions.

The first step is to confirm that the children have fixed proteinuria on FMU. If the children have fixed proteinuria on FMU on three separate occasions, the following evaluation is required. A complete urinalysis evaluation of the children with fixed proteinuria is required to determine the absence or presence of hematuria with dysmorphic or eumorphic red blood cells, pyuria, urine eosinophils, or crystals. Laboratory tests, such as electrolyte balance, renal function test, complete blood count, tests for serum albumin, and complement 3 or 4 (C3 or C4) activity levels should also be examined. The anti-streptolysin O titers, antinuclear antibody levels, and DNase B titers may also be considered in certain situations, 24 hours urine specimen collection may be necessary for this step. Chest x-ray and kidney ultrasound imaging should be performed to determine volume overload or renal structural abnormalities. Further studies may include hepatitis B and C tests, more specific laboratory studies on vasculitis or autoimmune diseases as well as the type of proteinuria. Possible indications for percutaneous renal biopsy have been listed in Table 2.

Persistent asymptomatic proteinuria

This is the type of proteinuria not associated with hematuria but proteinuria persists on FMU for more than 3 months. The prevalence of persistent proteinuria in children may be as high as 6%³⁰⁾. This type is not associated with edema, and the average amount of proteins excreted is approximately <2 g/day. Causes of persistent asymptomatic proteinuria include membranous and membranoproliferative glomerulonephritis, pyelonephritis, developmental anomalies, hereditary nephritis, hepatitis B infection, and “benign” proteinuria. The algorithm for evaluating this proteinuria and differential diagnosis has been illustrated in Fig. 1. The evaluation should start with thorough history and physical examination. If the results of the laboratory

Table 2. Possible Indications for Percutaneous Renal Biopsy in Patients with Persistent Proteinuria

Elevated serum creatinine concentration
Persistent macroscopic or microscopic hematuria or heavy proteinuria (>1 g/day)
Hypertension
Persistent hypocomplementemia
Consider with frequently relapsing, steroid-dependent and steroid-resistant nephrotic syndrome
Family history of chronic renal disease or end-stage renal disease
Parental anxiety

Table 1. Causes of Persistent Proteinuria

Glomerular	Tubulointerstitial
Primary glomerulopathy	Inherited
Minimal change nephrotic syndrome	Proximal renal tubular acidosis
Focal and segmental glomerulosclerosis	Cystinosis
Membranous nephropathy	Galatosemia
Membranoproliferative glomerulonephritis	Lowe syndrome
Congenital nephrotic syndrome	Dent’s disease
Secondary glomerulopathy	Wilson disease
IgA nephropathy	Tyrosinemia
Infections (Hepatitis B and C, HIV, CMV, malaria, syphilis, streptococcal)	Acquired
Henoch-Schönlein nephritis and systemic lupus nephritis (SLE)	Acute tubular necrosis
Alport syndrome	Toxins (gold, lead, copper, and mercury)
Thin basement membrane disease	Pyelonephritis
Hemolytic uremic syndrome	Interstitial nephritis (penicillins and other antibiotics, NSAIDs, and penicillamine)
Diabetes	
Hypertension	
Reflux nephropathy	
Malignancies	
Toxins	

tests are within normal range with the indication of low grade proteinuria (150-1,000 mg/day), renal biopsy is not recommended, as it is rare to find evidence for progressive renal disease. These patients should be subjected to annual evaluation including physical examinations, routine blood pressure monitoring, and laboratory tests like urinalysis, 24 hours urine specimen collection, and creatinine clearance¹⁰.

Treatment of proteinuria

The treatments should be directed at the underlying causes of the proteinuria. If the patient is confirmed to have transient or orthostatic proteinuria, no treatment is required. However, regular follow-up is recommended until the condition persists. For patients with isolated proteinuria, treatment recommendations range from none to protein lowering agents like angiotensin receptor blocker (ARB) or ACEi. ARB or ACEi medications can be used as adjunctive or primary treatments in patients with high grade proteinuria and those with abnormal levels of microalbuminuria with type I or type II diabetes mellitus. Although most of the patients tolerate these medications, some suffer electrolyte abnormalities, bone marrow suppression, and renal functional changes, requiring routine periodic monitoring. Patients experiencing volume depletion because of the intrarenal glomerular mechanism

should discontinue the intake of these medications. In addition, ARB or ACEi medications produce teratogenic effect; hence, patients who are pregnant or are considering pregnancy, should immediately discontinue this medication. ACEi and ARB also reduce proteinuria in patients with chronic kidney diseases, irrespective of their systemic blood pressure-lowering effects³¹. The main mechanism of these medications is to reduce glomerular hypertension due to the efferent arteriole vasodilatation^{32,33}. Other suppressive mechanisms include a) glomerular basement membrane hyperpermeability and b) renal fibrosis induced by transforming growth factor-beta 1. Reports show that ARB specifically prevents nephron damage in glomerular slit diaphragms³⁴.

Prevention of proteinuria

Although, there are no recommendations to prevent proteinuria, prompt evaluation, diagnosis, treatment, and long-term monitoring of these pediatric patients can significantly prevent potential progression of the underlying disease process. Dietary protein restriction is rarely recommended to avoid harmful effects on their growth and development. Hence, pediatric patients must receive the proper daily protein intake depending on their ages. A positive treatment response to proteinuria is not only an indicator of good prognosis but also a predictor of high renal func-

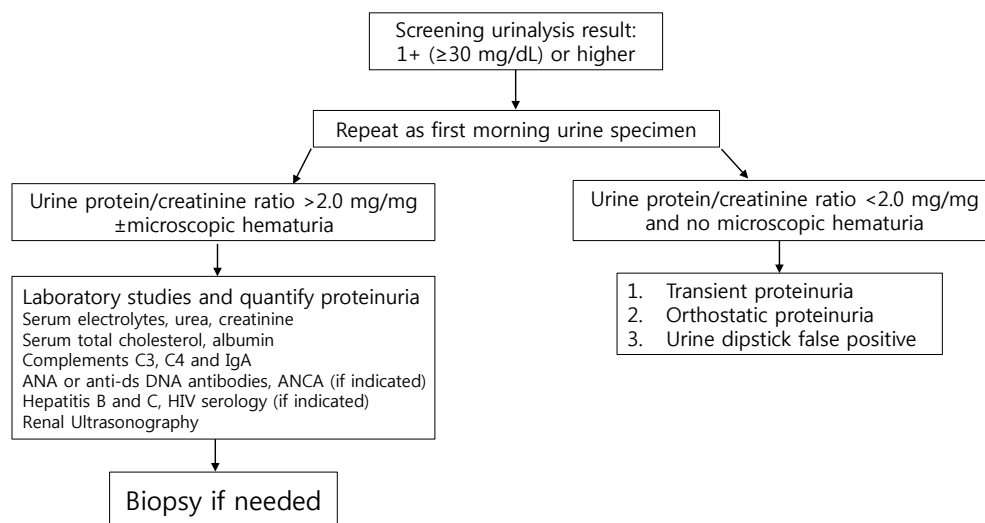


Fig. 1. Clinical approach of the child with proteinuria.

tional survival rate as well as subsequent changes in glomerular filtration rate.

Conclusion

The first step in the evaluation of proteinuria is to differentiate between the pathologic and benign etiologies. Persistent proteinuria may be indicative of underlying renal pathology and the treatments should be directed at the underlying causes of the proteinuria. Although, there are no recommendations to prevent proteinuria, prompt evaluation, diagnosis, treatment, and long-term monitoring of these pediatric patients can significantly prevent potential progression of the underlying disease process.

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

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