Non-Nephrotic Proteinuria in Children: A Review

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Abstract
Proteinuria is defined as an increased abnormal urinary excretion of proteins. In normal conditions, few proteins are lost through the urine. Proteinuria is a problem and dilemma in pediatric practice. Non- nephrotic proteinuria is described and its follow-up is discussed in the following.

Keywords: Proteinuria; Non-nephrotic proteinuria; Nephrotic Syndrome; Child.

Introduction

Proteinuria is defined as an increased abnormal urinary excretion of albumin and/or other specific proteins, such as immunoglobulins or low molecular weight (LMW) proteins. It occurs when the kidneys leak protein in the urine. Normally few proteins are lost through the urine. Proteinuria is a challenging problem in pediatric practice (1-4).

The most common type is called albuminuria. Microalbuminuria is defined as the presence of a very small amount of albumin in the urine, and albuminuria is defined as the presence of albumin in the urine in the range of more than 30 mg/dL. Total urinary protein excretion is below 150 mg/day in normal adults and below 100 mg/m² per day in normal children. In neonates, because of reduced reabsorption of filtered proteins, normal urinary protein excretion is higher, up to 300 mg/m² (4-6).

Higher rates of protein excretion in the urine persisting beyond a single measurement need to be evaluated.

Protein should not normally appear in the urine in detectable quantities (7-9). All proteins filtered through the filtration barrier are reabsorbed in the proximal tubule, and the rest is degraded and excreted as LMW proteins.

Approximately half of normal protein excretion consists of proteins secreted by tubular epithelium;

Tamm-Horsfall protein (uromodulin) comprises 70% and albumin, transferrin, and macroglobulin comprise 30% of the secreted protein (10, 11).

Clinical manifestation, history, physical examination, and laboratory tests help determine the cause of proteinuria. Proteinuria is associated with renal and other organs disease and is a predictor of end-organ damage in patients (12, 13).

Detection of increased protein excretion in the urine is known to be of both diagnostic and prognostic values for initial diagnosis and confirmation of renal disease (14). An individual with proteinuria in the setting of a normal glomerular filtration rate (GFR) is high risk for renal function loss. If proteinuria is prevented, its complications reduce (15-17).

Many children with proteinuria have no symptoms. Although all children with proteinuria need laboratory examination; treatment is not required in most cases. Proteinuria indicates a problem with the kidneys in some children, and these patients may need special and careful management and treatment. Therefore, proteinuria is a great challenge in primary care that requires workup (18, 19).

This study discusses accidental detection of proteinuria during a routine follow-up in children who look healthy. This article will describe non nephrotic proteinuria and its pathophysiology and etiology as well as the management of patients with proteinuria.

Pathophysiology

The glomerular filtration barrier provides a mechanical barrier between the blood stream and the urinary space. This barrier is composed of the glomerular basement membrane and slit pores between the epithelial cell foot processes and the fenestrated endothelial cells.

The glomerular filtration barrier is negatively charged due to the presence of glycosaminoglycan and glycocalyx. Therefore, the nature of the particles that can cross this barrier depends on the molecular size and charge of the particle (20-22). Persistent proteinuria may be an indicator of a glomerular disease. It may also play a central role in the progression of glomerular lesions to later stages of chronic kidney disease (23, 24).

Increased urinary protein losses can result from increased filtration across the filtration barrier (glomerular proteinuria), decreased reabsorption from the proximal tubule (tubular proteinuria), or increased secretion of protein from the tubules (secretory proteinuria) (25, 26).

Epidemiology

The incidence of proteinuria is higher in girls and it is present in up to %10-15 of school-aged children on routine urine testing but decreases to 0.1% on retesting. Its prevalence increases with age and peaks in adolescence (1, 27, 28).

Definitions

Microalbuminuria

Microalbuminuria is defined as the presence of 30-300 mg protein per 24 hours or an albumin excretion rate of 20-200 µg/min in urine collection. This may occur in some diseases but standard dipsticks are negative. Values above the upper limit for microalbuminuria definition are diagnostic of macro albuminuria or overt nephropathy (29-30).

Bence-Jones protein

A Bence-Jones protein is an immunoglobulin light chain that may appear in multiple myeloma but is undetectable on standard dipstick testing. (31, 32).

Albuminuria

Albumin is defined as the presence of protein in the urine. However, with an increase in disease severity and a decrease in the glomerular selectivity, larger proteins such as immunoglobulins appear in the urine. Although the plasma contains both albumin and globulin, globulin is much less likely to appear in the urine.

Albumin is accurately quantified in the urine using albumin-specific immunoassays with high sensitivities that enables the recognition of subtle glomerular injury. Although varied and influenced by age, albuminuria is considered normal at a level of <30 mg/g Cr (<3 mg/mmoL), moderately increased at the levels between 30 and 300 mg/g Cr (3–30 mg/mmol), and severely increased at levels of >300 mg/g Cr (>30 mg/mmoL). Albuminuria can be used in this way along with GFR to screen, classify, and diagnose renal disease severity (33,34).

Isolated Proteinuria

Isolated proteinuria is defined as proteinuria with a normal urinary sediment without hematuria, reduced glomerular filtration rate (GFR), hypertension, and diabetes (35, 36). In all cases of isolated proteinuria, the patient is usually asymptomatic, and the presence of proteinuria is discovered incidentally by use of a dipstick during a routine urinalysis.

This benign presentation of isolated non-nephrotic proteinuria is different from that of patients with serologic markers of systemic diseases. The rampancy of isolated proteinuria detected on a routine urinalysis (urine dipstick) in schoolchildren has been shown to be 10%. Initial testing of these children usually reveals no evidence of significant renal disease in the absence of both hematuria and proteinuria (37-39).

Glomerular Proteinuria

Glomerular proteinuria is defined as an increased protein filtration (and other macromolecules) across the glomerular capillary wall (increased permeability).

This is the most common cause of proteinuria in children and is seen in glomerular diseases and other non-pathologic conditions. This condition is more common than tubulointerstitial and is caused by structural defects, negative charge loss, immune complexes, and reduced functional nephrons (40, 41).

Tubular Proteinuria

Most of the filtered proteins are reabsorbed in the proximal tubule. Tubular proteinuria occurs due to reduced reabsorption of freely filtered low - molecular weight proteins. This form of proteinuria is seen in tubulointerstitial nephritis and is often

associated with other defects of the proximal tubular function. Tubular proteinuria can be differentiated from glomerular proteinuria by the selective immunonephelometric measurement of specific low molecular weight proteins (42, 43).

A. Secretory Proteinuria: Secretory proteinuria is characterized by a very little protein secretion in the tubules (44, 45).

B. Overflow Proteinuria: The reason for overflow proteinuria is increased plasma levels of low molecular weight proteins that affect the tubular re-absorptive capacity. This form of proteinuria is rarely seen in children and is usually associated with immunoglobulin light-chain production in plasma cell dyscrasias (multiple myeloma) (46, 47).

Nephrotic syndrome
Patients with nephrotic syndrome have severe proteinuria, hypoalbuminemia, edema, and hyperlipidemia. There may also be symptoms and signs related to the underlying cause. Normal values of total urinary protein excretion are <240 mg/m^2/day in children <6 months and <150 mg/m^2/day in older children.
Nephrotic syndrome is defined as a condition in which the kidneys have large amounts of protein excretion (>40 mg/m^2/hr. or >1 gm/m^2/day in a 24 - hours urine collection or a spot urine protein creatinine ratio of >2 mg/mg) whereas excretion of >3 g/1.73 m^2/day is classified as nephrotic range proteinuria in all age groups (48-50).

Transient Proteinuria
Transient proteinuria is associated with fever, seizure, dehydration, congestive heart failure, abdominal surgery, extreme cold exposure, exercise, or stress and is not suggestive of an underlying renal disease. When predisposing conditions are removed, proteinuria is also cured. Another type of intermittent proteinuria that is important for pediatricians is orthostatic proteinuria. It may also be caused by hemodynamic alterations in the glomerular blood flow (51-53).

Orthostatic Proteinuria
Orthostatic proteinuria (also referred to as postural proteinuria) is described as normal urine protein on a spot urine test of the first morning void (after being in the supine position throughout the night) and increased urine protein after being upright for at least 4-6 hours. It is the most frequent etiology of isolated proteinuria in children, especially adolescents. Orthostatic proteinuria is common in older children and adolescents, especially males, with a prevalence of 2–5%.
The cause of orthostatic proteinuria is not recognized; however, anatomic compression of the left renal vein has been suggested. Long-term studies with significant follow-up have demonstrated a good prognosis (53-56).

Symptoms of Persistent Proteinuria
Proteinuria is usually asymptomatic except in severe proteinuria. Although patients may complain of some 'frothiness' in their urine, there may be vigorous edema, ascites, hydrocele, and pleural effusion as a result of decreased oncotic pressure in more severe cases (such as patients with nephrotic syndrome) (57, 58).

Detection of protein in urine
Screening for proteinuria can be performed in three ways: (1) 24--hours urine collection, (2) dipsticks, and (3) the protein-creatinine ratio on a spot urinary sample.
For careful assessment, urinary protein should be measured quantitatively and expressed as the protein/creatinine ratio or should be measured based on a 24--hours urine collection and expressed as mg/m2/day (1, 3, 49).

Dipstick
The test is very sensitive and is associated with a color change following the reaction of tetra bromophenol with amino acids. A urine dipstick primarily detects albumin not LMWP. The color changes from yellow to green to blue with an increase in the amount of protein in the urine, for example, negative (<20 mg/dL), trace (30-20 mg/dL), 1+ (>30 mg/dL), 2+ (>100 mg/dL), 3+ (>300 mg/dL), and 4+ (>1000 mg/dL). False negative results can be seen in very dilute urine samples, especially when the specific gravity is <1.002 and with LMW proteinuria. False positive results may be seen in highly concentrated urine samples, alkaline urine specimens (pH > 8.0), after iodinated contrast, and after using antiseptics prior to urine collection. A reading of 1+ requires rechecking and if the positive result is confirmed, timed urine collections will be suggested (1, 3, 49, 9).

Timed Collection
Twenty-four-hour urine collection for protein quantification is a gold standard test, but it may be very difficult in children. 24--hour or timed urine

collections are often difficult to perform, particularly in children, with lack of accuracy in this age group (1, 3, 18, 19).

Protein/Creatinine ratio

A very quick method for quantifying proteinuria is to measure the spot/random urine protein creatinine ratio (mg/mg) when the urine dipstick shows persistent proteinuria (1+ and above). Many studies have shown a good correlation between the spot urine protein creatinine ratio and 24-hour urine collection. Urinary protein excretion and more importantly spot urine protein-creatinine ratio can help the physician to assign the patients need further work-up for proteinuria.

The normal random urine protein creatinine ratio is below 0.2 and the nephrotic range is above 2 when both urine protein and creatinine are measured in mg/dl. However, when the spot protein creatinine ratio is between 0.2 and 2, it is advisable to obtain a 24 -hour. urine collection. (1, 3, 18, 19).

Approach to a Patient with Proteinuria
History

As with any medical problem, a thorough history is critical in evaluating the patient. History should include symptoms of swelling, headache, hematuria, joint pain, rashes, elevated blood pressure, urinary tract infections, recent throat or skin infections, loss of appetite, decreased energy, weight loss, and intake of medications. Family history including cystic kidney disease, deafness, visual disturbances, renal disease, renal failure, and dialysis is also important (3, 5, 18, 19).

Physical Examination

Growth is an important clue for chronic kidney diseases and needs to be controlled. Blood pressure should be measured and the signs of renal diseases including flank pain, fluid overload, edema, organomegaly, rashes, joint swelling, anemia, and evidence of osteodystrophy should be examined (18, 60).

Tests and Diagnosis

The pediatrician can diagnose proteinuria on a urine test. Proteinuria may be found during a routine urine test for screening or other reasons. If the first test reveals protein in the urine, more tests are required to find out whether proteinuria is serious.

Among glomerular causes (Table 1), nephrotic syndrome is one of the important ones but tubular proteinuria commonly includes LMW proteinuria and is generally mild. Tubular proteinuria rarely presents with early diagnostic symptoms because the underlying disease is usually detected before proteinuria (1, 3).

Table 1. Causes of persistent proteinuria

Glomerular	Tubulointerstitial
Diabetes	**Acquired** Acute tubular necrosis, Toxins (gold, lead, copper, and mercury), Pyelonephritis, Interstitial nephritis (penicillins and other antibiotics, NSAIDs, and penicillamine)
Hypertension	
Reflux nephropathy	
Primary glomerulonephropathy conditions: Minimal change nephrotic syndrome, Focal and segmental gomerulosclerosis, Membranous nephropathy, Membranoproliferative glomerulonephritis, Congenital nephrotic syndrome	**Inherited** Proximal renal tubular acidosis, Cystinosis, Galactosemia, Lowe syndrome, Dents disease, Wilson disease, Tyrosinemia
Secondary glomerulonephropathy conditions: IgA nephropathy, Infections (Hepatitis B and C, HIV, CMV, malaria, syphilis, streptococcal), Henoch-Schonlein nephritis and systemic lupus nephritis (SLE), Alport syndrome, Thin basement membrane disease, HUS	
Malignancies	
Toxins	

It is very important to know if proteinuria is transient, orthostatic, or persistent (1, 36). In a patient who is asymptomatic with isolated proteinuria, urine dipstick needs to be repeated at least two times a week to establish that proteinuria is not transient. If proteinuria disappears on repeated testing, then it is likely to be temporary, and the family can be reassured, but urine dipsticks should be repeated within 6- 12 months (1, 3, 4).

Persistent proteinuria should be further investigated with a complete history, including a family history of renal disease, recent upper respiratory infections or other infections, gross hematuria, weight changes, and changes in the urine output. Physical examination should include height, body weight, and blood pressure measurement, identification of edema, ascites and skin pallor, and palpation of the kidneys in infants.

A urinalysis should be performed, and blood samples should be collected to evaluate electrolytes, blood urea nitrogen, creatinine, total protein and albumin levels, as well as a complete blood cell count, lipid profile, antistreptolysin-O (ASO) and C3 and C4 complements (1).

Quantitative assessment of urinary protein excretion should be done, using either a 24-hour collection or a random urine sample for the first morning UPr/Cr ratio (3, 36).

If orthostatic proteinuria is diagnosed, the child should be followed with annual office visits, including the UPr/Cr ratio determination. If fixed isolated proteinuria is ascertained, thework-up depends on the degree of proteinuria. If total protein excretion is less than 1000 mg/day, twice-yearly visits, later extended to annual visits, with determination of the UPr/Cr ratio are sufficient. If proteinuria persists beyond one year, renal biopsy should be considered (36, 50). If the total protein excretion is more than 1000 mg/day, a urinalysis should be performed and blood samples should be obtained to measure electrolytes, blood urea nitrogen, creatinine, total protein and albumin levels, lipid profile, ASO, C3 and C4 complements, and a complete blood cell count. In young children, renal ultrasonography may be helpful for detecting anatomical or congenital abnormalities. The existence of an antecedent streptococcal infection may be investigated by measuring ASO and anti-deoxyribonuclease B titers.

Postinfectious glomerulonephritis is usually self-limited, and a renal biopsy is not indicated. If urinary protein excretion is in the nephrotic range, even in the absence of edema, idiopathic nephrotic syndrome is likely, and a trial of corticosteroid therapy is warranted (1, 48, 50).

Renal biopsy is not indicated unless the patient has other abnormal laboratory test results, such as hematuria, increased blood urea nitrogen and creatinine levels, or hypocomplementemia. Further evaluation will include a renal function test, determination of the UPr/Cr ratio, and workup based on the etiologies (1, 3, 36).

Dietary protein supplementation is not recommended but avoiding excessive salt intake is desirable. In some patients with a glomerular disease resulting in heavy proteinuria unresponsive to corticosteroids or cytotoxic agents, therapy with an angiotensin converting enzyme (ACE) inhibitor or receptor blocker can cause a significant reduction in proteinuria. The use of ACE inhibitors or receptor blockers in the treatment of renal disease may reduce the glomerular filtration rate and hyperkalemia (1, 3, 4, 50).

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