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12-2014

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Recommended Citation

Sonderman, David, "Orthostatic proteinuria" (2014). *Kidneycentric*. Paper 8.
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Orthostatic Proteinuria

By: David Sonderman, MD

Definition:

Proteinuria in children is defined as greater than 100 mg/m² urinary protein excreted per day or greater than 4 mg/m² excreted per hour on a 24-hour urine collection (in all cases a 24 hour urine total protein should be less than 150 mg even if BSA is >1.5m²).¹ On a spot urine protein/creatinine test, proteinuria is defined as a ratio >0.2 in a child older than 2 years of age or a ratio >0.5 in a child 6-24 months old.¹ Proteinuria may be a sign of kidney disease and requires an explanation. There are numerous causes of proteinuria in the pediatric population (table 1). One cause is orthostatic proteinuria and is defined as the presence of increased urinary protein excretion in the upright or standing position, but a normal urinary protein excretion while in the supine or recumbent position. Orthostatic proteinuria rarely reaches nephrotic-range levels, which is defined as urinary protein excretion of greater than 1,000 mg/m²/day or greater than 40 mg/m²/hour on a timed urine collection.¹

Epidemiology:

In children, the prevalence of proteinuria on a single random urinalysis is generally between 5-15%.¹ The majority are found to have transient proteinuria (secondary to fever, stress, dehydration, or exercise) or orthostatic proteinuria, as opposed to the more concerning finding of persistent non-orthostatic proteinuria. Whereas past studies have estimated the prevalence of orthostatic proteinuria in the general pediatric population to be around 6%,² a more recent prospective cohort study of 91 patients aged 6-18 years demonstrated a 20% prevalence of orthostatic proteinuria.³ The mean total protein excretion of those with orthostatic proteinuria in this cohort was 170 mg/m²/24 hours (maximum 341 mg/m²/24 hours [606 mg/24 hours]). Approximately 80% of patients with orthostatic proteinuria were males and over 10 years of

age.³ Additionally, the prevalence of orthostatic proteinuria in these 91 patients increased with increasing BMI (24% with BMI <85%, 25% with BMI 85-94%, and 50% with BMI \geq 95%).³

Pathophysiology:

The underlying pathophysiology of orthostatic proteinuria remains unclear, but several theories have been proposed to offer an explanation. One theory states that orthostatic proteinuria is simply a normal variant caused by an exaggerated response of glomerular protein filtration while standing. This theory is based on the finding that, among those with normal urinary protein excretion, there still exists an increase in protein excretion while standing.⁴ A second theory states that orthostatic proteinuria is due to a glomerular abnormality that increases one's susceptibility to the effects of various hemodynamic forces on the kidney.⁴ This theory is based on findings from renal biopsies performed in 56 patients with orthostatic proteinuria.⁵ In this cohort, glomerular abnormalities were appreciated in 45% of subjects, including capillary wall thickening, focal hypercellularity, capsular thickening, and eosinophilic granules in the capsular space.⁵ Finally, a third theory states that orthostatic proteinuria is caused by the hemodynamic effects of angiotensin II resulting from renal vein entrapment. In nutcracker syndrome, there is entrapment of the left renal vein between the descending aorta and the superior mesenteric artery leading to renal vein constriction. This entrapment is exacerbated in the standing position and relieved in the supine position. The partial renal vein constriction leads to renal congestion that triggers release of angiotensin II to constrict the efferent renal arteriole and maintain an adequate GFR, which ultimately leads to an increase in orthostatic proteinuria.^{4,6,7} The true pathophysiology of orthostatic proteinuria, however, is perhaps a combination of all three theories.

Clinical Presentation:

Children with orthostatic proteinuria are asymptomatic and are usually incidentally discovered by a positive urinary dipstick performed in the office setting.

Diagnostic Evaluation:

If a child has persistent dipstick proteinuria ($\geq 1+$; $>30\text{mg/dL}$), then further evaluation should take place with a spot urine protein/creatinine ratio on a first morning void. The child is instructed to void just prior to going to sleep and should remain in the supine or recumbent position throughout the night. A first morning void should then be obtained for testing. If the spot urine protein/creatinine ratio is < 0.2 in a child over 2 years of age or < 0.5 in a child 6-24 months old, then a diagnosis of orthostatic proteinuria can be made.

Treatment:

Orthostatic proteinuria is a benign condition that does not indicate or lead to chronic kidney disease.⁸ Therefore, further laboratory and imaging studies are not necessary after making this diagnosis. However, yearly screening of first morning voids for emergence of persistent non-orthostatic proteinuria is recommended.

Table 1. Differential Diagnosis of Proteinuria in Pediatric Patients

Persistent Proteinuria	Transient Proteinuria
Nephrotic syndrome: minimal change disease, focal segmental glomerulosclerosis, membranoproliferative glomerulonephritis, dense deposit disease, membranous nephropathy, HIV associate nephropathy, congenital nephrotic syndrome, diffuse mesangial sclerosis	Orthostatic (can be persistent, but generally resolves as young adult; age <25 years old)
IgA nephropathy	Fever
Chronic kidney disease: congenital dysplasia, acquired from acute kidney injury	Exercise
Alport syndrome	Acute kidney injury: sepsis, acute post streptococcal glomerulonephritis, Henoch-Schonlein purpura
Systemic lupus erythematosus	Seizure

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