

GENERAL DESCRIPTION OF GLOMERULAR SYNDROMES

Isolated Proteinuria

Proteinuria can be caused by systemic overproduction (e.g., multiple myeloma with Bence Jones proteinuria), tubular dysfunction (e.g., Fanconi syndrome), or glomerular dysfunction. It is important to identify patients in whom the proteinuria is a manifestation of substantial glomerular disease as opposed to those patients who have benign functional, transient, postural (orthostatic), or intermittent proteinuria.

Plasma proteins larger than 70 kD cross the basement membrane in a manner normally restricted by both size-selective and charge-selective barriers.^[1]^[2] The functional characteristics of the glomerular capillary filter have been extensively studied by the evaluation of the fractional clearance of molecules of different size and charge.^[3] The size-selective barrier is most likely a consequence of functional pores within the GBM that restrict the filtration of plasma proteins of more than 150 kD. There is also a shape restriction of molecules, allowing elongated molecules to cross the glomerular capillary wall more readily than globular molecules of the same molecular weight. Finally, there is a charge-selective nature of the barrier, largely a consequence of glycosaminoglycans arranged along the capillary wall. Loss of charge selectivity may be the defect in minimal change glomerulopathy,^[1] whereas a loss of size selectivity may be the cause of proteinuria in, for instance, membranous glomerulopathy.^[2]

Isolated proteinuria may occur in several conditions. These include mild transient proteinuria of less than 1 g that typically accompanies physiologically stressful conditions, including fever in hospitalized patients, exercise, and congestive heart failure.^[4] In other patients, transient proteinuria is a consequence of the overflow of proteins of low molecular weight that is a consequence of overproduction of light chains, heavy chains, or other fragments of immunoglobulins. Examples of proteinuria caused by overproduction include multiple myeloma, Bence Jones proteinuria, beta₂ - microglobulinuria, and hemoglobinuria.

Orthostatic proteinuria is defined by the absence of proteinuria while the patient is in a recumbent posture and its appearance during upright posture, especially during ambulation or exercise.^[5] The total amount of protein excretion in a 24-hour period is generally less than 1 g, but may be as much as 2 g. Orthostatic proteinuria is more common in adolescents and is uncommon in individuals over the age of 30.^[5]^[6] Two percent to 5% of adolescents have orthostatic proteinuria. Renal biopsy of patients with orthostatic proteinuria reveals that 47% have normal glomeruli by light microscopy, 45% have minimal to moderate glomerular abnormalities of a nonspecific nature, and the remainder have evidence of a primary glomerular disease.^[5] Why would proteinuria be increased during upright posture in individuals with normal glomeruli by light

microscopy? The answer to this question remains an enigma, but there are several likely possibilities. Orthostatic proteinuria may occur because of alterations in glomerular hemodynamics. It is possible that even in histologically "normal" glomeruli, where there are no identifiable structural lesions, there are subtle glomerular abnormalities, including abnormal basement membranes, or focal changes of the mesangium.^[2] Alternatively, orthostatic proteinuria has been demonstrated with entrapment of the left renal vein by the aorta and superior mesenteric artery. Thirteen of 15 children with orthostatic proteinuria had venous entrapment compared to 9 of 80 with normal protein excretion.^[8] In addition, the observation that surgical correction of a kink in an allograft renal vein resulted in the disappearance of orthostatic proteinuria gives credence to venous entrapment as a cause of orthostatic proteinuria.^[2]

There are several approaches to the diagnosis of orthostatic proteinuria. One approach is the comparison of protein excretion in two 12-hour urine collections, one recumbent and one during ambulation. Another approach is comparison of protein in a split collection of 16 hours during ambulation and 8 hours of overnight collection. Importantly, patients should be recumbent for at least 2 hours before their ambulatory collection is completed to avoid the possibility of contamination of the "recumbent" collection by urine formed during ambulation. The diagnosis of orthostatic proteinuria requires that protein excretion during recumbency be less than 50 mg during those 8 hours. As a diagnostic test for orthostatic proteinuria, no data on the usefulness of recumbent versus ambulatory urinary protein to creatinine ratio measurements are available.

Long-term follow up of orthostatic proteinuria for 30 years suggests a benign long-term course.^[6] Orthostatic proteinuria resolves in most patients. It is present in one half of patients after 10 years and in only 17% of patients after 20 years.^[6] In the absence of a kidney biopsy, an underlying glomerulopathy cannot be completely excluded, and an orthostatic component of proteinuria may be found in early glomerular disease. Thus, it is important to reassess patients yearly to be certain that the degree or pattern of proteinuria has not changed.

Fixed proteinuria is present whether the patient is upright or recumbent. The proteinuria disappears in some patients, whereas others have a more ominous glomerular lesion that portends an adverse long-term outcome. The prognosis depends on the persistence and severity of the proteinuria. If proteinuria disappears, it is less likely that the patient will develop hypertension or reduced glomerular filtration rate (GFR). These patients must be evaluated periodically for as long as the proteinuria persists.