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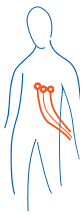

Glomerular Diseases

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INTRODUCTION

The glomerulus can be injured in a variety of disorders, and glomerular injury or disease can manifest as hematuria, proteinuria, hypertension, fluid retention, and a reduction in the glomerular filtration rate. Traditionally, glomerular diseases have been classified according to clinical presentation, including asymptomatic microscopic hematuria, the nephritic syndrome, the nephrotic syndrome, and rapidly progressive glomerulonephritis (RPGN). However, great progress has been made in unraveling the molecular causes of glomerular diseases. For instance, autoantibodies against the phospholipase A_2 receptor have been associated with membranous nephropathy, a disease that manifests clinically as nephrotic syndrome. Many glomerular diseases can manifest with more than one constellation of signs and symptoms and show more than one histologic pattern on renal biopsy. In the future, the etiologic approach to the classification of glomerular diseases will undoubtedly be expanded.

CLINICAL PRESENTATION

A detailed history and careful physical examination, with particular attention to the time of symptom onset, help to clarify the differential diagnosis of suspected glomerular disease. Blood pressure and fluid status should be recorded. Urine microscopy is a critical element of this assessment, and it may reveal hematuria, typically with dysmorphic red blood cells and casts. Hematuria due to glomerular disease is painless and often associated with brown or cola-colored urine rather than bright red; clots are rare. Other causes of brown urine include hemoglobinuria, myoglobinuria, and food or drug dyes (e.g., beetroot).

Quantitative evaluation of the degree of urinary protein excretion is essential. In adults, urine total protein excretion is less than 150 mg/24h, and urinary albumin excretion is less than 20 mg/24h. Persistent albumin excretion of 30 to 300 mg/24h reflects high albuminuria (i.e., microalbuminuria), and albumin excretion above 300 mg/24h, the level at which the standard dipstick becomes positive, reflects overt proteinuria. Levels above 3.5 g/24h are considered to be nephrotic-range proteinuria. The principal constituent of the protein excreted by these patients is albumin (up to 98% in some cases).

A 24-hour urine collection remains the gold standard, but it is cumbersome, is often collected incorrectly, and does not provide a rapid result. A protein-to-creatinine ratio measured on a spot urine sample has emerged as a useful alternative. The urine protein concentration (in mg/dL) divided by the urine creatinine concentration (in mg/dL) yields a dimensionless number that approximates the 24-hour protein excretion (in g/24h). The reliability of the protein-to-creatinine ratio is limited in patients who excrete approximately 1 g/24h of creatinine, such as in those who are severely catabolic.

Glomerular proteinuria can be classified as transient or hemodynamic (functional) (e.g., fever, exercise induced, orthostatic) or as persistent (fixed). Although functional proteinuria is benign, fixed nephrotic-range proteinuria is usually results from glomerular diseases. Total proteinuria greater than 1 g/24h in a patient with a negative urine dipstick test result (which detects only albumin) suggests that the proteinuria may be caused by light chains or low-molecular-weight proteins (e.g., retinol-binding protein, α_1-microglobulin).

CLINICAL SYNDROMES

The major clinical syndromes associated with glomerular injury are discussed in this section. In each case, general recognition and management should be pursued in parallel with efforts to define the specific mechanisms of injury.

Nephrotic Syndrome

Nephrotic syndrome is defined as persistent urinary total protein excretion greater than 3.5 g/24h, accompanied by a serum albumin concentration less than 3.5 g/dL. Edema, hyperlipidemia, and lipiduria (i.e., doubly refractile fat bodies) are common but are not required for the diagnosis.

Complications of the nephrotic syndrome include hypogammaglobulinemia, vitamin D deficiency due to loss of vitamin D–binding protein, and iron deficiency anemia due to hypotransferrinemia. Thrombotic complications such as renal vein thrombosis are more common, especially in patients with greater protein loss (>10 g/24h) and serum albumin levels less than 2 g/dL. Patients with severe nephrotic syndrome may also have acute renal failure when there is superimposed volume depletion, sepsis, interstitial nephritis, or use of nephrotoxic agents such as nonsteroidal anti-inflammatory drugs (NSAIDs).

Management of patients with nephrotic syndrome includes diuretics to control edema, regulation of blood pressure (angiotensin-converting enzyme inhibitors [ACEIs] and angiotensin-receptor blockers [ARBs] are preferred), limitation of the intake of protein to between 0.8 and 1 g/kg/day and sodium to less than 4 g/day, and control of lipid levels. Anticoagulation should be considered for patients at increased risk, especially if the nephrotic syndrome is caused by membranous nephropathy or amyloidosis.