

Introduction to Clinical Medicine - Glomerular Disorders

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Glomerular disorders are an important cause of renal disease.

Under normal conditions glomeruli filter blood, separating the cellular and protein components from the water, electrolytes and other small molecular weight molecules. Blood components with a size $<17 \text{ \AA}$ are nearly completely filtered, whereas those with a size greater than $\sim 42 \text{ \AA}$ do not cross the glomerular basement membrane. The glomerular basement membrane (GBM) is negatively charged, further decreasing the filtration of proteins because they are mostly negatively charged anionic molecules. Small amounts of protein are filtered, but are reabsorbed by the proximal tubule.

As a result, under normal conditions the urine protein content is said to be less than 150 mg/d. However, the presence of even small amounts of protein in the urine, especially albumin, is an indicator of disease, and predicts the development of either further renal disease or development of vascular disease in other parts of the body.

The urine should also be acellular. The presence of red blood cells, white blood cells or other cellular components is an indication of disease somewhere in the genitourinary tract.

Glomerular disorders can be classified into two broad categories, nephrotic and nephritic. In simplistic terms, nephrotic conditions are associated with increased urinary protein excretion, whereas nephritic conditions are associated with increased numbers of RBC in the urine.

The causes, presentations and therapies differ for nephrotic and nephritic disorders.

Nephrotic Syndrome

Clinical Manifestations

The failure of the kidneys to appropriately exclude protein from glomerular filtration and leading to increased protein excretion into the urine leads to a wide variety of complications. The major findings associated with increased urinary protein excretion include proteinuria, edema formation, hypoalbuminemia and hyperlipidemia. When these conditions are present, the patient is said to exhibit the “nephrotic syndrome.”

Proteinuria in the nephrotic syndrome is due to an increase in glomerular permeability and not to a decrease in tubular reabsorption of filtered plasma proteins. Albumin is the main constituent of urinary protein, but larger molecular weight proteins may also be excreted in excess in some patients. By definition, the urinary protein excretion exceeds $3.5 \text{ g}/1.73 \text{ m}^2/\text{day}$, and it may be greater than 20 g/day. However, the magnitude of the proteinuria varies widely and is influenced considerably by the glomerular filtration rate, the plasma concentration of albumin, and dietary protein intake. Other proteins besides albumin are lost, including IgG and clotting factors.

We now know that proteinuria is directly nephrotoxic. Uptake of filtered proteins by the proximal tubule begins a cascade of events that lead to chronic damage, with eventual tubular loss and interstitial fibrosis development.

A second component of the nephrotic syndrome is hypoalbuminemia. As a result of the proteinuria, primarily albuminuria, serum albumin decreases. Although the hypoalbuminemia was initially attributed to mass-balance loss of albumin into the urine (loss > hepatic excretion), this is not the case. Hepatic albumin synthetic capacity can exceed 25 g/d, far exceeding the albumin loss in almost all cases of nephrotic syndrome. Moreover, hepatic synthetic rates are generally either unchanged or only slightly increased in nephrotic syndrome-related hypoalbuminemia.

Edema formation is the third component of the nephrotic syndrome. Hypoalbuminemia decreases intravascular oncotic pressure, leading to increased rates of edema formation. In addition, inflammatory cytokines may increase capillary permeability to fluid transudation, increasing edema formation. *Nephrotic syndrome should be considered in every patient with edema.*

The fourth component of the nephrotic syndrome is hyperlipidemia. Hypoalbuminemia and the resulting decreased plasma oncotic pressure stimulate hepatic lipoprotein synthesis, predominantly of LDL and VLDL. Because LDL is the primary carrier of cholesterol and VLDL of triglycerides, nephrotic syndrome typically is associated with increases in both. Although argued for many years, most people agree that the hypercholesterolemia associated with nephrotic syndrome increases the risk for cardiovascular disease.

Lipiduria is also present in the nephrotic syndrome. Lipid-containing epithelial cells, degenerated renal tubular cells containing cholesterol esters, may be present.

Hypercoagulability is frequently seen in the nephrotic syndrome. Clotting inhibitors, such as antithrombin III, protein S and protein C, can be lost into the urine. The hypoalbuminemia and decreased oncotic pressure stimulate hepatic synthesis of fibrinogen and other procoagulant proteins. Renal vein thrombosis is a classic complication of the nephrotic syndrome.

Causes

Etiology	Clinical feature	Screening test(s)
Minimal change disease	Most common cause in children Associated with Hodgkin’s disease or NSAIDs in adults	Selective proteinuria (almost exclusively albuminuria)
Membranous glomerulonephritis	Most common cause in Caucasian adults May be associated with cancer	None
Focal segmental glomerulosclerosis (FSGS)	The most common cause in African-American adults. Frequently associated with hypertension. Frequently progresses to ESRD (end-stage renal disease)	None
IgA nephropathy	Associated with hematuria. Common in young adults.	Hematuria

Etiology	Clinical feature	Screening test(s)
Membranoproliferative glomerulonephritis	Associated with chronic infections, particular hepatitis C	Hepatitis B and C serology
Membranous lupus nephritis	Combination of SLE with nephrotic syndrome	ANA, C3, C4, ESR
Diabetic nephropathy	Hyperglycemia Diabetic retinopathy generally present	Fasting blood glucose

Glomerulonephritis

Glomerulonephritis refers to conditions that cause glomerular hematuria.

Urinary RBC's in glomerular hematuria typically show evidence of damage from crossing the glomerular basement membrane. Helmet cells are classically seen. RBC casts may also be seen, but are less common.

The term "acute nephritic syndrome" refers to the combination of glomerular hematuria, edema and hypertension.

Glomerulonephritis is almost always associated with significant glomerular disease, and frequently leads to loss of glomerular filtration and the development of either chronic renal insufficiency or failure.

Hypertension is frequently associated with nephritic conditions, and may reflect microvascular disease in vascular sites other than the kidney.

If the disease is limited to the kidney, it is termed "primary glomerulonephritis," whereas if it is a component of a systemic disease it is termed "secondary glomerulonephritis."

The response of most causes of glomerulonephritis to treatment is related to how early treatment is instituted. Excessive delay in beginning therapy may lead to irreversible disease. If renal function is deteriorating rapidly then a renal biopsy should be obtained urgently and therapy begun quickly.

Evaluation in all patients should include a twenty-four hour urine collection for creatinine clearance and protein excretion and a renal ultrasound.

Etiology	Clinical features	Screening tests
IgA nephropathy	Most common cause in young adults May have associated proteinuria	

Etiology	Clinical features	Screening tests
Membranoproliferative glomerulonephritis	Frequently preceded by a vague systemic illness (often described as similar to a “flu”)	Hepatitis C antibodies
Anti-GBM disease	Acute nephritic syndrome. Pulmonary hemorrhage may be present, termed “Goodpasture’s Syndrome (anti-GBM antibodies cross react with alveolar basement membrane)	Anti-GBM antibodies
Wegener’s granulomatosis or microscopic polyarteritis nodosa (PAN)	Acute nephritic syndrome. Associated with systemic vasculitis symptoms, such as fever, malaise and weight loss. Wegener’s granulomatosis may be associated with granulomas in sinuses or lungs	Anti-neutrophilic cytoplasmic antibodies (ANCA)
Diffuse proliferative lupus nephritis	Systemic manifestations of SLE Acute nephritic syndrome.	ANA, C3, C4, ESR
Post-infectious glomerulonephritis	Acute nephritic syndrome. Classically occurs 8-14 days following streptococcal pharyngitis or skin infection, but may be as long as 28 days after a skin infection. Can occur with any infectious process, particularly untreated endocarditis, abscesses or osteomyelitis	ASO (anti-streptolysin O) titer Blood cultures WBC

Renal biopsy is necessary to accurately define the glomerular disease and direct appropriate therapy.