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The Nephrotic Syndrome

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The Nephrotic Syndrome

Jeffrey Komisarof, MD

The glomerulus with its intricate network of delicate capillary loops is one of the most elegant structures in the human body. When the glomerulus is damaged by disease, a range of disparate effects can occur, including pathologic clotting of the blood, an increase in cholesterol and other lipid molecules to abnormally high levels, hypertension, and ultimately, uremia and certain death without dialysis or transplantation. Interestingly, many seemingly different disease processes and environmental stressors cause glomerular pathology. These include malignancies of many types (liquid tumors such as leukemia and solid tumors such as those of the lung [paraneoplastic syndrome]), infections (group A Streptococcus, leprosy, syphilis, HIV, malaria, and Schistosomiasis [parainfectious syndrome]), inflammatory conditions (ranging from systemic lupus erythematosus to an idiosyncratic reaction to a bee sting [parainflammatory syndrome]), medications (from commonly used over-the-counter nonsteroidal anti-inflammatory drugs to seldom used immunomodulators such as gold and penicillamine), and lastly diseases that do not fall neatly into these categories, such as diabetes mellitus, obstructive sleep apnea, and primary systemic amyloidosis. The endocrine-inflammatory, hormone-cytokine milieu induced by these various disease processes appears to have a common final pathway: glomerular damage accompanied by degrees of cellular inflammation. Such damage results in loss of albumin and other small protein molecules through the normally highly size- and charge-selective structure of the capillary loops, and this loss of proteins along with other events, some rooted in altered transcription at the genomic level, ultimately cause the sequelae known as the nephrotic syndrome.

OVERVIEW OF CLINICAL SEQUELAE

The nephrotic syndrome is associated with the classical clinical quartet of (1) albuminuria in excess of 3 to 3.5 g daily, (2) hypoalbuminemia with serum levels less than 3 g/dL, (3) peripheral edema, and (4) hyperlipidemia, most commonly hypercholesterolemia and less

often hypertriglyceridemia. The hypoalbuminemia is predominantly due to the heavy albuminuria, which can range from a few grams to 20 g/day. Hepatic synthesis of albumin is appropriately increased in response to urinary loss. What is intriguing is that the liver can produce up to 25 g of albumin per day, far greater than the amount lost in the urine, yet serum albumin levels often remain low in patients with the nephrotic syndrome. It is likely that inflammatory cytokines (eg, interleukin-1) that are present in many disease states that induce the nephrotic syndrome concomitantly reduce hepatic albumin synthesis, causing the serum concentration to fall.¹

The peripheral edema is believed to result from a combination of factors that likely vary among patients. Most important perhaps is increased sodium retention, which may result from primary renal retention and possibly reduced sensitivity to atrial natriuretic peptide.² Although studied extensively, the contribution of decreased serum oncotic pressure to the development of edema remains unclear. What must be kept in mind is that the driving force for edema formation is not just serum oncotic pressure, but the gradient between serum and interstitial tissue oncotic pressure. Both of these pressures likely fall in parallel, suggesting that hypoalbuminemia by itself does not contribute greatly to edema formation.

The hyperlipidemia may also be multifactorial. Hypercholesterolemia seems to result from both upregulation of hepatic production of lipoproteins triggered by hypoalbuminemia, low plasma oncotic pressure, or low plasma viscosity,³ and decreased catabolism and clearance of lipoproteins.⁴ Decreased catabolism and increased synthesis also likely cause hypertriglyceridemia.⁴ Interestingly, it has been postulated that the increase in lipoprotein is composed largely of apoprotein B, which has a greater effect on oncotic pressure than other lipoproteins.³

It is important to distinguish between nephrotic glomerular disease and nephritic glomerular disease. Nephrotic disease generally presents with significant proteinuria but usually does not cause generalized renal dysfunction evidenced by a rising serum creatinine level. Conversely, nephritic glomerulopathies often do present with general renal dysfunction with an