Protein-losing Nephropathy in Small Animals

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KEYWORDS

• Proteinuria • Glomerular disease • Glomerulonephritis
• Glomerulosclerosis • Amyloidosis

The prevalence of protein-losing nephropathy (PLN) in the general population is much greater in dogs than cats but is largely unknown and probably higher than currently recognized.[1–3] Renal failure is arguably the most common organ failure in dogs and cats. The prevalence of glomerular lesions, mostly immune-mediated glomerulonephritis (IMGN), was found in 43% to 90% of random dogs.[1,3] Increased urine protein/creatinine ratio (UPC), as an indicator of glomerular disease, is a negative predictor of outcome.[4–7] Microalbuminuria (MA) is detected in about 25% of all dogs and cats, increasing with age (36% in dogs 9–11 years, 49% in dogs $\geq$12 years, 39% in cats $\geq$12 years, and 65% of cats $\geq$16 years),[8] but its clinical significance is not known. When the first insult to the nephron is at the glomerulus, proteinuria occurs, which ultimately damages the rest of the nephron. By the time end-stage renal disease (ESRD) is discovered, the initiating glomerular cause may go undetected. Because proteinuria decreases with nephron dropout and decreased glomerular filtration, hypoalbuminemia may no longer exist or it may be masked by dehydration. Therefore, glomerular disease as the initiating cause of ESRD may go unrecognized.

Renal biopsy results may not settle the question of chicken-or-egg regarding whether glomerular versus tubular damage (chronic interstitial nephritis) was the primary cause, because both are often seen in end-stage kidney samples. Even when renal biopsies are taken earlier in the disease process, pathologists' interpretations using routine histopathology techniques do not necessarily agree.[9] There is inherent subjectivity with visual analysis of membrane thickening or mesangial cell numbers present. Tissue sections traditionally cut at 5 to 6 μm for light microscopy are too thick for careful examination of renal lesions. Therefore, the incidence of subtypes of glomerulonephritis reported may not be accurate, and treatment protocols that might work for a particular subset (for instance, steroids or cyclosporine) may not seem beneficial because these cases were not properly identified.

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With the advancement of technology, there are now sensitive and specific methods to detect and monitor proteinuria and abnormalities can be identified earlier in the disease process. The source of proteinuria can be localized and the cause characterized via diagnostic tests; the trend can be followed and stability or disease progression can be monitored. Kidney biopsies can be safely taken percutaneously with ultrasound guidance, sophisticated methodology can be used with light microscopy (LM) examination of thin (3–4 μm) tissue sections, and the glomerular lesions can be characterized by transmission electron microscopy (TEM), immunofluorescence (IF), and immunohistochemistry (IHC). Specific treatments may be recommended for specific causes, as well as symptomatic and supportive therapies to reduce proteinuria, hypertension, risk of thromboembolic events, edema/effusions, and progression of renal failure.

NORMAL GLOMERULAR STRUCTURE AND FUNCTION

The normal glomerulus is a complicated, elegant sieve, filtering 20% of the cardiac output, producing liters of ultrafiltrate per day, allowing water and small molecules to cross the fenestrated vascular endothelial barrier by the force of transcapillary pressure, to penetrate the glomerular basement membrane (GBM), traverse the podocyte slit diaphragm (SD), and enter into the glomerular filtrate while holding back larger molecules based on their size and electrical charge. The endothelial cell glycocalyx is negatively charged; the underlying supportive GBM is made up of collagen type IV, laminins, nidogen, and negatively charged glycosaminoglycans.[10] Podocyte foot processes are attached to the GBM via cell membrane receptors (α3β1 integrans linked to talin, vinculin, and paxillin, and α- and β-dystroglycans linked to utrophin).[10] Recently the structure and function of a myriad of molecules in the glomerular filtration barrier of the SD (ie, the 25- to 40-nm wide pore between the foot processes) have been reviewed (**Fig. 1**).[11] Produced by podocytes, these molecules work in concert to form a dynamic three-dimensional complex at the SD; they translate outside-inside signaling, control calcium influx, and rearrange the actin cytoskeleton within the podocytes to cause their contraction and modification of their morphology as well as the intricate architecture of their interdigitating foot processes and SD aperture, thus sensing and reacting to a changing environment. Normally very few proteins with molecular weight of albumin (69,000 Da) or higher get passed into glomerular filtrate, especially if they are negatively charged as is albumin. The few proteins that do pass through into the glomerular filtrate are normally reabsorbed and degraded by tubular cells and their lysosomes, but this work can cause tubular cell damage.[12]

GENETIC ABNORMALITIES ASSOCIATED WITH PLN

Genetic mutations producing 1 or more abnormal molecules at the SD or GBM may lead to immediate malfunction of the integrity of the permselective barrier, or to a susceptibility to injury by environmental triggers, or allow increased entrapment of circulating immune complexes (CIC), which may cause later onset proteinuria. Although not yet discovered in dogs and cats, more than 100 different mutations have been identified in NPHS1, the gene for *nephrin* (the major SD transmembrane adhesion protein of the immunoglobulin superfamily)[13]; more than 40 mutations in NPHS2, the gene for *podocin* (a stomatin family member closely associated with nephrin at the SD); and various mutations in other genes including NPHS3 (phospholipase Cε1), ACTN4 (α-actinin 4), CD2AP (CD-2 associated protein), TRPC6 (transient receptor potential cation channel 6), WT 1 (WT 1 protein), LAMB2 (laminin β-2), the NEPH 1-3 complex, several mitochondrial genes, MYH9 (nonmuscle myosin11A