Protein-Losing Kidney Disease (PLN) in Dogs

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It is devastating enough when a dog is diagnosed with chronic kidney disease, but when there is also consistent and significant protein loss in urine test results, it presents owners with a huge diet and management adaptation challenge.

The first signs of this type of kidney disease are often found in veterinary urine test reports. Protein is reported as negative, trace, 1+ to 4+, or in mg/dL. These different ways of reporting depend on the country of testing and the laboratory or vet's manner of providing results. The urine test for protein should not be confused by blood reports for protein, as the two are very different. A urine test report that states protein is at 2+ or greater is seen as significant. Results showing a trace to 1+ range should be confirmed with a more specific assay such as the ELISA-based albuminuria test. Urine protein concentration must be greater than 30 mg/dL to be detected by commercial dipstick testing, which is often done by a vet in-house. Urine dipsticks are also prone to both false positives and false negatives. This suggests the best urinalysis is conducted through an external laboratory for accuracy. A report that shows protein at greater than 50 mg/dL is equally seen as significant.

Proteinuria is the term used by vets and others to describe a dog with an excess of protein found in urinalysis test results. This condition may be short-term, which is why a vet will usually arrange for several tests to be conducted over several weeks. Transient proteinuria is the temporary excretion of protein and can be caused by strenuous exercise, a high fever, exposure to cold, stress, and other conditions. It does not involve the kidneys and does not require treatment. Trace protein found in urine test results is of little concern and is not unusual.

Over time we have learned that certain breeds have more prevalence of excessive protein loss in urine and are more frequently diagnosed with Protein Losing

Nephropathy (PLN). These include Shar Peis, Soft Coated Wheaten Terriers, Bull Terriers, Dalmatians, Samoyeds, Bernese Mountain Dogs, Doberman Pinschers, Newfoundlands, and English Cocker Spaniels.

Investigating the Causes of Proteinuria

Before a vet arrives at a final diagnosis of kidney disease with significant proteinuria, they must consider the possible alternatives that may be initiating this urinalysis result. The kidneys are only one element in renal function and it is, therefore, reasonable to consider the primary cause of high urine protein may be from any other defective or adversely affected renal system component – or from any organ or system connected anatomically to it. These can include the prostate gland, uterus, and in female dogs, the vagina. To prevent contamination while collecting a urine sample for testing, vets undertake a procedure known as cystocentesis, whereby the sample is collected using a needle to access the bladder direct (but please see my later comment about false positives).

Certain conditions cause persistent proteinuria. These conditions include infection, adverse reactions to certain drugs, diabetes, internal bleeding, inflammation (such as from tumours, stones, or polyps), or high protein in the bloodstream that consequently result in excessive amounts filtering into the kidneys. The latter is commonly identified by checking haemoglobin, globulin, and myoglobin.

Once these issues have been investigated and dealt with, the most likely cause remaining is a glomerular disease (also called glomerulonephritis) resulting from defective or underdeveloped kidneys due to trauma or congenital issues. Age-related glomerular problems are very common because, just like us, dogs suffer from wear and tear the older they become.

Underlying health conditions can also give rise to glomerular damage. These include cancer, infectious diseases (including Leishmaniosis, Lyme disease, and Ehrlichiosis), pyometra (infection in the womb or uterus), Cushing's disease, heartworm, immune-mediated (autoimmune) diseases, diabetes mellitus, and pancreatitis. These conditions cause the glomeruli to become far less effective and quickly deteriorate enough to allow large protein molecules to pass into urine.

Glomerular disease is often described by vets and others as protein-losing nephropathy (PLN), even though the latter term refers to a direct glomerular-related condition resulting in urine protein loss. Therefore what may begin as glomerulonephritis often leads to PLN. There are several different protein-losing diseases (including gastrointestinal protein loss), but this article concentrates on PLN as it is directly related to canine chronic kidney disease.

The Glomerulus

Each nephron in a dog's kidneys has a microscopic filter, called a glomerulus that is constantly filtering blood. Blood that is about to be filtered enters a glomerulus, which is a tuft of blood capillaries (tiny blood vessels). There are approximately one million glomeruli, or filters, in each healthy kidney. Glomerular filtration is the first step in making urine.

The filters act on water and nitrogenous waste materials, and non-filterable components, such as cells and serum albumins, and which exit the inner part of the glomerulus via an arteriole blood vessel. The kidneys are directly responsible for sieving good and bad elements, returning those good elements to the blood supply that are required for normal healthy bodily functions.

Normal glomeruli do not allow larger protein molecules such as albumin to pass into the urine.

It is useful to note that issues with the glomerulus tend to occur far earlier than other symptoms or blood test values for kidney disease. Left without management and treatment, glomerulonephritis can hasten worsening kidney values and speed up the route to severe illness, which typically becomes critical and fatal.

Protein Molecules

In healthy dogs, cells and large molecules like proteins are excluded by the glomeruli sieve and are thus reserved in circulation to facilitate muscle strength, weight maintenance, and body and blood fluid balance. In PLN, the sieve is compromised and protein leaks into the urine. The resulting symptoms initially include excessive thirst and urination, inappropriate fluid retention causing tissue edema, muscle wastage, and 50 to 85% of dogs with PLN also have hypertension (high blood pressure). There is also a high risk of rapid blood clotting (hypercoagulability) in severe cases.

Left without early management PLN and can rapidly develop into chronic kidney disease, and even with good management, there is an increased likelihood of this happening as time progresses. Management of PLN and glomerulonephritis requires a two-fold approach.

Management by Diet

Protein leaking into the kidney organs and then being passed out of the body through urine is a major problem. Excessive protein is toxic to the kidneys. The goal with diet is therefore to reduce this toxic load as far as it is possible and practical to do, without a dog suffering malnutrition. The amount of protein from meat, poultry, and other sources, depends on the severity and advancement of PLN.

One important point to make at this stage is all dogs with PLN and/or kidney disease should be given the highest quality of protein. Many dog food products contain low-quality proteins, and this adds to the problems. High-quality proteins for home cooking mean human-grade meat, fish, and poultry. Many dog treats are often a source of poor-quality proteins. Specialized renal dog foods often have high-quality proteins, but this must be verified with the manufacturer.

Low sodium and low phosphorous are two additional requirements for diet and particularly when chronic kidney disease has been diagnosed.

The diet of dogs that are non-azotemic (IRIS Stage 1 where there are NO excess levels of nitrogen-based substance compounds such as urea, creatinine, and other

body waste compounds in the blood) needs careful assessment of nutrient intakes such as proteins, calories, omega-3 fatty acids, and sodium. Omega-3 fatty acids are generally thought to be very useful in most chronic kidney disease cases, as they help offer some anti-inflammatory properties to the system, but they can also inhibit a decrease in proteinuria and urea concentration.

Calories need to be assessed and counted to ensure sufficient daily amounts are given for the size, activity level, and breed of the dog. A weekly weight record is useful in determining whether a sufficient amount of appropriate calories are in the diet to maintain weight and energy levels.

Excessive amounts of sodium are a problem for both PLN and chronic kidney disease dogs. Because it cannot be extracted in sufficient amounts, this mineral is returned to circulating blood and levels can build up enough to cause heart issues and an adverse imbalance occurs with other minerals. Restriction of sodium is therefore always suggested. However, some dogs with PLN and chronic kidney disease have excessively low sodium and abnormal potassium blood levels which are equally undesirable, so this is an aspect of diet that needs constant checking via blood tests.

How much Protein?

Most food products, including dog food, need to be calculated on a dry matter basis (DMB). This gives the most accurate amount of protein contained in them and allows for an equal comparison of all products under consideration. To calculate DMB divide the percentage of protein by the remaining percentage of moisture (after calculating 100 minus percentage of moisture for the product), then multiply the result by 100.

Treats should also be assessed for the DMB of protein and combined with the other meal(s) total intake. Dogs that have many treats in a day may be receiving upwards of 50% of their protein intake through them, so reducing or changing the number and type of treats may sufficiently contribute towards lowering protein loss in the early stages of PLN.

Focus on Nutrition (Vet Learn Compendium) is a useful reference for the amount of protein that should be given at different degrees of PLN. Authors Valerie J Parker, DVM, DACVIM, and Lisa M Freeman, DVM, Ph.D., DACVN, from the Tufts School of Veterinary Medicine explains that one study found that proteinuria decreased by 57% to 68% after dogs were switched from 8g/100 kcal of protein being fed to 3.3g/100 kcal. The authors suggest restricting protein amounts initially by 25% in month one and then by 50% in month two if the first action does not prove successful in reducing proteinuria to an acceptable level.

Great care needs to be taken in protein restriction. It is wise to closely observe for weight and muscle loss as these may be signs of malnutrition, and severe malnutrition is just as deadly as kidney disease. It is also important to provide some time for any newly introduced medications (particularly the use of ACEI’s) to take effect before restricting protein in the diet. These medications may prove to be enough to reduce proteinuria without the need for diet changes.

Angela Witzel Rollins, DVM, Ph.D., DACVN, offered this useful insight regarding protein in her article in Today's Veterinary Practice: *'When assessing the protein content of a diet, it is important to remember that animals require amino acids rather than protein. Feeding high-quality protein sources with well-balanced ratios of essential amino acids can lower overall dietary protein content while preventing protein malnutrition. It is also important to note that all diets currently marketed for management of CKD in dogs exceed the amounts of protein recommended by the National Research Council.'*

'Evidence currently available suggests diets providing approximately 35 g/1000 kcal of high-quality protein, combined with other dietary modifications, improve and prolong the life of dogs with Chronic Kidney Disease (stages 1 to 2) while providing adequate protein to support albumin production and maintain body weight.'

According to the Association of American Feed Control Officials (AAFCO), an adult dog's diet should contain a minimum protein content of 18 percent on a dry matter basis. Most commercial dog foods contain upwards of around 25% protein. For dogs with PLN, the first stage of protein restriction after assessing what medications might achieve should be to reduce protein to about 15% per meal (depending on the pre-PLN diagnosis diet). At the same time, supplementing with Omega-3 fatty acid and Vitamin E should help enhance improvements.

Management by Medication

The leading medications to reduce proteinuria are angiotensin-converting enzyme (ACE) inhibitors. ACE inhibitors have been confirmed by many studies over the last decade to decrease proteinuria and postpone the onset of renal failure in dogs. Benazepril and Enalapril are two ACEIs used most commonly for this purpose. However, they have an impact on blood pressure, so it is vital vets complete an accurate blood pressure check before an ACEI is started, then one week after commencement, and at least every 3 months thereafter. Dog owners need to make themselves aware of the symptoms of low blood pressure and contact their vet immediately if any are observed.

It is worth noting that my own preference is Benazepril for dogs with renal disease, because in comparison to Enalapril it is cleared 55% by the liver and only 45% by the kidneys. Enalapril is cleared 95% by the kidneys, which puts additional and often unnecessary strain on on the organs (Lefebvre et al, 1999; 2006).

Angiotensin receptor blockers (ARBs) maintain renal vasodilation (a mechanism to enhance blood flow to the kidneys). Maureen C. Carroll DVM, DACVIM, states: *'The end result is diminished proteinuria, elimination of inflammatory cell infiltration, amelioration of glomerular and tubular structural change. By selectively blocking the AT1receptor, aldosterone synthesis and secretion is reduced causing vasodilation and decreased potassium and increased sodium excretion. While plasma concentrations of renin and angiotensin-II are increased, this does not counteract the blood pressure lowering effects.'*

However, ARBs remain an uncertain medication and are not suitable for all dogs. Losartan at 0.25- 2mg/kg has been successful in some dogs with PLN, but

Irbesartan at 5 mg/kg/day has been more successful as not all dogs can convert Losartan to the required active metabolite to be useful.

A combination of ACEIs and ARBs may be considered when proteinuria worsens and is consistently stubborn to stabilize or be improved.

The hormone aldosterone plays a significant role in healthy kidneys by managing water, sodium levels, and potassium. Too much aldosterone can cause the kidneys to retain water and sodium and flush potassium. This initiates a cascade of adverse effects in both kidney and glomerular disease and other systems of the dog's body. An ACTH stimulation test should be performed and cortisol and aldosterone measured in both samples. This will help identify any possible Addison's disease and clarify whether there is an excessive release of aldosterone by the adrenal gland.

Aldosterone Inhibitors can be very useful when this cascade of events occurs. Maureen C. Carroll DVM, DACVIM, says: *'Studies have shown that selective re-infusion of aldosterone RESTORES proteinuria and glomerular lesions DURING blockade of the renin-angiotensin system. This suggests an independent pathogenic role for aldosterone as a mediator of progressive renal disease. Aldosterone also has fibrogenic properties in the kidney via TGF synthesis up-regulation, another reason to consider blockade of its negative effects in the glomerulus. The medication most commonly used is spironolactone. However, this medication used in conjunction with an ACEI may have a greater renoprotective effect.'*

I mentioned the danger of blood clotting when discussing the leakage of protein molecules into circulating blood above, and, to assist in the prevention of this serious event in PLN, an antithrombotic or antiplatelet medication can prove very effective. Low-dosed Aspirin, low molecular weight Heparin (Fragmin or Lovenox), or Clopidogrel, are considered the best options. Rivaroxaban is largely used in humans to prevent thrombosis. Vets will more likely appreciate that it is a highly selective direct Factor Xa inhibitor. The dosing advice for dogs is 2 mg/kg.

Calcium channel blockers are commonly used in conjunction with ACEIs to counter the 80% of dogs with PLN that suffer from hypertension. Amlodipine helps to balance out the blood flow pressure across the glomerulus, which is considered a highly effective treatment.

Immunosuppressant therapy is a very complex but potentially viable treatment, which needs careful and often specialist consideration. At the World Small Animal Veterinary Association Congress Proceedings, 2017, Shelly L. Vaden presented her work titled 'Standard Therapy and Immunosuppression of Dogs with Protein Losing Nephropathy'. In it, she stated:

'Immunosuppressive therapy should be considered in dogs that have a severe, persistent, or progressive glomerular disease and ICGN (immune-complex glomerulonephritis) documented via appropriate evaluation of a renal biopsy specimen. However, there are practical and medical reasons why a biopsy might not be performed. Sometimes veterinarians must decide about immunosuppressive therapy in dogs with glomerular disease absent a pathologic diagnosis. Immunosuppressive therapy should not be administered if there is any doubt that the

proteinuria is of glomerular origin, administration of the specific drug is medically contraindicated, or there is a high index of suspicion that the dog has amyloidosis or a non-immune-mediated familial disease.'

Treatment using any of the above medications in isolation or in combination will depend on a full veterinary assessment of the medical history, current health concerns and other illnesses, known adverse interactions of other medications being taken, comprehensive blood and urine testing, and other likely necessary tests depending on the individual dog.

A Warning about Fluid Overload

Fluid replacement therapy in the form of IV or SubQ fluids should be used with great caution in dogs with glomerular disease because they are predisposed to fluid overload. A careful assessment of the hydration and of the vascular volume of individual dogs with glomerular disease should be a priority both before and during fluid therapy. (Journal of Veterinary Internal Medicine).

Measuring GFR

Creatinine excretion has long been recognized as a marker of an impaired glomerular filtration rate (GFR), however, this is not always reliable and is easily misinterpreted. Until GFR has fallen below 30% of normal, the plasma concentration of creatinine may remain in the laboratory reference range and some vets may mistake this as confirmation of healthy kidney function. If GFR is not measured, then a valuable early opportunity to treat potentially developing PLN is missed.

The gold standard method of assessing renal function is to measure GFR by the administration of a suitable marker. Inulin has been used successfully as one such marker and is said by many to be the safest and best choice.

The Relevance of Albumin Levels

Albumin is a protein made by the liver. It is the most abundant protein in a dog's body. In post glomerular proteinuria there will be excessive amounts of albumin in the urine, making this a very useful marker for testing. Albumin helps keep fluid in the bloodstream so it doesn't leak into other tissues. It also carries various substances throughout a dog's body, including hormones, vitamins, and enzymes.

Low blood albumin (hypoalbuminemia) can occur because of a loss of protein due to damage in the intestines or loss in the urine because of kidney disease, or the lack of production of it due to liver damage. A high albumin level indicates dehydration. These two extremes are both relevant to kidney issues, therefore any abnormal albumin level in testing helps identify the cause and goes a long way to forming an accurate diagnosis when taken in combination and comparison to other findings.

The standard test for albumin is usually included in a comprehensive blood chemistry test.

Why UPC Ratios are Important

Urine protein to creatinine ratios (UPC or UP:UC) are one of the most important urine test results for identifying the likelihood of PLN but need to be considered alongside other relevant test results.

It is a simple test that measures how much protein is being lost through the kidneys. In healthy dogs the UPC is very rarely above 0.5mg/dL. It should be remembered that protein can be present in urine if there is inflammation or bleeding anywhere in the urinary system. UPC levels, therefore, need to be considered alongside a urine sediment exam. A sediment evaluation will determine if there is blood or inflammation in the urine sample which will give rise to a false high UPC level. If there is no blood or inflammation, the sample can be accurately tested for the UPC Ratio.

A value greater than 1mg/dL should prompt a thorough diagnostic evaluation. A minimum of three urine samples should be taken over a week to ensure the accuracy of results (UPC can be variable so consistency is an important safeguard to diagnosis). Some studies reveal that a pooled single sample of urine combining samples over 3 separate days is adequate. When vets take or receive samples of urine for testing, the method of collection and testing should be the same as different methods can produce different results for the same sample. The temperature of the urine sample is also important, as differing temperatures create different (false) UPC results. Cystocentesis is considered the best method for collecting a urine sample to prevent contamination. Samples kept at room temperature should be processed within 4 hours or if stored at 4°C or frozen they can be analysed within 3 days of collection.

There is however one potential problem with a Cystocentesis collection of urine for sampling insofar as it can become contaminated with a small amount of blood as the needle enters the bladder. This can cause an inaccurate and protein count. It can also cause analysists to believe there is an infection, when actually there is not. These false positive readings may be best avoided by repeat testing and comparison.

In her article ‘Protein-losing Nephropathy in Small Animals ‘, Meryl P Littman, VMD, states: *‘Therapeutic intervention is recommended for nonazotemic animals at UPC greater than or equal to 2.0, but is often started at lower values if a breed-associated cause is suspected and progression is expected without early intervention. For azotemic animals, intervention is recommended at UPC greater than or equal to 0.5.’*

Importantly when considering an interpretation of UPC levels, Meryl P. Littman makes the point that … ‘*The UPC may decrease with increasing azotaemia, but this is not necessarily a good sign, because there are fewer working nephrons leaking protein.’*

Ultrasound Scans are Always Advantageous

An ultrasound is a diagnostic tool that uses sound waves to create an image of the kidney organs. A handheld probe is passed over the abdomen and, in combination

with a computer, images are captured. The procedure does not involve any invasive techniques and causes no pain.

In addition to identifying abnormal issues with the kidney architecture, an ultrasound scan and expert analysis can prove whether glomerular nephritis is evident or not and if evident then how advanced it may be. The cost is sometimes prohibitive at around $400 (£300), but it is a very valuable examination that can provide diagnostic information in advance of other test results.

Blood Transfusions, Dialysis, and Kidney Transplants

Blood transfusions are at best a temporary “fix” for certain concerns that can occur with PLN. Hypoproteinaemia where protein loss may exceed protein manufacturing by the body is one such scenario, though more commonly plasma transfusions are used to help rectify a crisis. A transfusion is sometimes also required if the vet decides it is useful to take a biopsy to assess prognosis.

Dialysis is the standard management for human patients with kidney disease, often while awaiting the opportunity for a kidney transplant. Dialysis is also available for dogs with PLN and chronic kidney disease, but the cost is far outside most owners’ financial circumstances. Dialysis helps remove uremic toxins, correct fluid and an electrolyte disorder, restore acid-base balance, and sustains the life of the dog for some time.

However, this is largely more associated with acute renal disease. Chronic kidney disease and PLN are progressive conditions, so dialysis only offers a window of opportunity to resolve some symptoms but is unlikely to contribute to much longevity of life. Haemodialysis can stabilize a dog’s renal injury and help control azotaemia, but so much depends on the progression of PLN and the amount of architectural damage to the glomeruli. It is of course a specialized form of treatment and only available in a few veterinary centres.

The cost is prohibitive for most. The average price of dialysis and CRRT (blood purification therapy) for the first two to three treatments ranges from US $3,000 to $4,500 (£2,150.00 to £3,250.00). Subsequent treatments typically cost US $600 to $700 (£430.00 to £500.00) each.

Kidney transplants have proved most successful in humans, even though there can be problems that arise needing medical intervention and continued care along the way. The same is sadly not quite so true for dogs, despite years of transplant attempts and ongoing research into the procedure for man’s best friend. Things have certainly improved since the first attempts at canine kidney transplants began in the 1980s. The Mar Vista Animal Medical Centre in California, USA, reports about a 40% initial success rate but with very poor ongoing survival rates. But even this is only half the story.

The costs are enormous. A US $13,000 (£9,400) deposit is needed just to start the process and that assumes the dog is a suitable candidate for such a complex range of treatments and the operation itself. For example, a dog with Cushing’s disease is prohibited. A dog with cancer, heart disease, amyloidosis, or inflammatory bowel

disease is prohibited. Kidney transplantation for dogs is still considered in the investigational stage as new techniques are used to provide adequate immune suppression without complications.

And finally, there are ethical issues that would certainly prevent me from considering a kidney transplant for my dogs.

Unlike human transplantations, the owner of the ill dog is usually made responsible for identifying and obtaining a legal right to ownership or adoption of the donor dog. Also unlike humans, the healthy donor dog has no choice in being robbed of its kidney. The donor dog needs to be less than 6 years of age, healthy, and available for screening tests. In such cases, if both dogs are deemed suitable and the operation is a success, the owner walks out of the surgery with two dogs, each with only one fully functioning kidney.

Stem Cell Therapy

Stem Cell Therapy (SCT) is perhaps the most promising of all scientific research into both human and canine kidney diseases at this time. SCT is already being widely employed by veterinary agencies and clinics to help resolve conditions including age-related osteoarthritis. It is also showing promising study results for immunological, neurological, and cardiac applications.

The regenerative and renewal properties of SCT have opened up new avenues of study for the development of renal function and structural repair in kidney diseases throughout the world. The goal of these studies is to achieve normal kidney function in humans suffering from chronic and other forms of kidney disease. After that, it strikes me it is only a matter of time before the applications can be extended to our companion animals. The future looks exciting and extremely positive, but for now, all we can do as dog owners is to concentrate on the research, medications, and other interventions we and our vets currently have at our disposal.

The Aim of Intervention

While the glomerular disease is often treatable (although not usually curable), it is the fact that dogs with PLN commonly progress into chronic kidney disease and eventually renal failure that causes a likely fatal outcome. The intervention aims to deal with the initial symptoms of PLN, adapting promptly according to blood and urinalysis results, obtaining additional testing such as blood pressure checks, and being accurate and stringent about diet. Along with quickly dealing with secondary health concerns associated with PLN and kidney disease, these provide the best possible quality and longevity of life for a dog with PLN. These are further improved if diagnosed early, treated adaptively, and managed diligently.

Frequent and comprehensive blood and urine testing provide the best opportunity for achieving a slow rather than a fast deteriorating plateau, where elements such as protein loss, creatinine, and BUN are kept as low as possible to maintain adequate kidney function. Interventions are therefore aimed at maintaining the best possible kidney function despite ongoing and irreversible damage to the organs.

IMPORTANT NOTE: