

## Reducing Creatinine in Canine Kidney Disease

### The Role of Creatinine in Canine Kidney Disease



**Creatinine is a waste product of creatine phosphate resulting from muscle and protein metabolism. It is released at a constant rate by the canine body and this is a normal process. Two per cent of the body's creatine and phosphocreatine pool (mostly present in muscle) is converted to creatinine each day.**

The normal creatinine blood level for dogs is 1.4mg/dL or lower. When it rises to between 1.4mg/dL and 2.00mg/dL it suggests stage-1 of kidney disease, but this potential judgement needs to be considered alongside other relevant blood and urine tests so the diagnosis can be confirmed. The International Renal Interest Society (IRIS) states that urine specific gravity, the level of protein-loss (if any) in urine, high blood pressure, and other factors all collectively contribute to an accurate diagnosis.

#### **Azotaemia, GFR and albumen levels**

When blood creatinine levels are above 1.4mg/dL a dog is said to be suffering from azotaemia. This term relates to an event (acute or chronic) where the kidneys are no longer able to get rid of enough nitrogen waste. Abnormally high levels of creatinine and BUN (blood urea nitrogen) are usually due to decreasing kidney function and varying levels of damage to the organs. The organ damage may have been caused by trauma, a birth or genetic defect, a different but associated primary illness, medications, toxic substances (including human medications), poor quality or contaminated foods, severe infections, poor dental hygiene, or age-related wear and tear.

Although an abnormally high creatinine level is a major contribution to diagnosing kidney failure, there are additional factors alongside other blood and urine values that need to be taken into consideration.

Blood creatinine concentration is the most commonly used marker of glomerular filtration rate (GFR) in dogs. But despite a slow, steady and consistent rise in creatinine over years, it can remain within normal range despite a significant fall in GFR. Maintaining a good record of blood test results for comparison year on year is perhaps the best method of picking up these changes, although the Idexx SDMA (serum symmetrical dimethylarginine) test is also a very useful early indicator of problems. GFR can also be tested by vets in isolation or alongside other blood tests. Increased Urine Albumin is another early warning red-flag. Albumin is a protein that can pass into the urine when the filters in the kidneys are damaged.

### **Influencing factors for abnormal creatinine levels**

What may appear to some vets and vet technicians as abnormal creatinine levels (hypercreatininemia) can also be associated with additional factors, which when taken into consideration can make the higher blood creatinine level normal for a particular dog. Interpretation of blood levels therefore needs to be undertaken with the greatest care, diligence and expertise. Misdiagnosis can occur if these additional factors are not considered and potentially disastrous treatments and diet controls may be introduced without good reason.

Dogs that have a high muscle mass or muscle volume often have slightly higher than normal creatinine levels. These moderate apparent abnormalities are due to the consistently increased level of creatinine from muscle mass and muscle use. Breeds that fall into this category are likely to include greyhounds and other sighthounds, boxers, sled and working dogs. A veterinarian needs to physically examine a dog's muscle mass and interpret the creatinine level in light of this influencing factor. Owners can also help by maintaining a reference history of blood test results over several years despite any changes to the vet used, as this will provide an insight into the consistency of results. If creatinine has shown to be slightly raised over all historic blood results, without consistently increasing any further, then owners are likely to be safe in assuming this is normal for their breed of dog.

Different laboratories sometimes use different references for creatinine. So for example, one test may show a marker for a high result, whereas the analysis of a test by another laboratory or a vet's in-house blood test may show the same level to be within normal range. While these are often minor variances, they can be interpreted inconsistently by different vets. In addition, high concentrations of bilirubin, lipids, and glucose may lead to an overestimation of blood creatinine concentrations. While this variable is affected adversely by the Jaffé's reaction method in human laboratories, it is not widely used in veterinary blood analysis. It is of course always worth confirming the type of laboratory used to analyse blood samples by your vet, just in case.

Dehydration also plays an important role in creatinine levels. IRIS states that low extracellular fluid volume may increase blood creatinine concentration when dehydration exceeds a mere 5%. Vets need to consider this fact as it may lead them to a misdiagnosis of kidney disease in the absence of other necessary diagnostic measures being taken. Normal BUN levels in dogs seldom reach higher than 25 to 30 mg/dl, and values higher suggest dehydration. While values of 90mg/dL and higher are likely to be associated with kidney disease, these varying levels could also be the result of inadequate water intake, a bout of diarrhoea or vomiting, vigorous exercise, heatstroke, a fever or other illness. It is perhaps worth noting that dogs ordinarily require at least one fluid ounce (30mls) of water per day for each pound of body weight.

Some creatine in meat is converted to creatinine during cooking, so if an owner home cooks for their dog on a regular basis the blood creatinine may be slightly higher because of it. The term applied to this is intestinal absorption of exogenous creatinine and it is certainly something worth discussing with your vet.

Some medications and typically certain antibiotics are likely to temporarily raise creatinine. The same is true of a recent meal, which makes fasting for 8 hours an ideal prerequisite for taking the blood sample. Recent exercise can also raise creatinine levels. IRIS report, for example, that creatinine commonly rises in greyhounds by about 20% in the 60 minutes following exercise.

Young puppies commonly have slightly elevated serum creatinine levels and this is perfectly normal. By the time they reach one year old, creatinine ordinarily subsides to the appropriate range for adult dogs. Old-age has little or no influence on creatinine in otherwise healthy dogs. The level should be about the same as younger adult dogs.

### **The importance of fluid therapy**

Fluids are the priority first-line treatment for lowering abnormally high blood creatinine levels. While clean fresh water should always be made available and drinking encouraged, this alone is unlikely to prevent creatinine rising during the course of canine kidney disease. When two-thirds of the nephrons have been lost in the kidney organs a dog is no longer able to conserve water and passes larger amounts of dilute urine. When levels of creatinine are significantly high, two or three days of intravenous fluids given by a vet should kick-start a reduction in the blood level. The type and dose of fluid depends on a number of factors and not least whether there is any heart condition, notably severe murmurs and/or congestive heart disease. Fluids also have to be moderated if anaemia is evident and the type of fluid needs to reflect other blood values including abnormal potassium, sodium and calcium.

While intravenous (I/V) fluids are important and often essential as the first line of treatment, little will be gained without a continuation of fluid therapy from subcutaneous (SubQ) fluids given under the skin. SubQs can be likened to ongoing maintenance that flushes toxins and rehydrates the cellular structure, and subsequently fights against rising creatinine and BUN.

The aim of SubQs is to achieve a point where creatinine plateaus ... where it remains stable without falling or significantly rising over three consecutive blood tests. Damaged kidneys are unlikely to achieve a normal range for creatinine regardless of treatment or management of the disease. However, finding the creatinine plateau achieves the best possible kidney function despite the organ damage. SubQ fluids should be undertaken daily with a reduction in dose once the level of creatinine has fallen. Many kidney dogs require this treatment for the remainder of their life.

SubQ fluids can be given by the owner at home with veterinary support. This saves cost and relieves some of the stress that some dogs suffer when visiting the vet. The rule of thumb on dosing is to provide 10mls to 15mls of fluid for every pound of dog weight per day.

Rebecca Robinson writing in Vet Times (a UK veterinary professional journal) states: 'Maintenance fluid rates are the subject of debate, but for dogs, these are quoted to be between 40ml/kg/day to 60ml/kg/day.' My personal favourite reference for fluids comes from Dr Sean Smarick (an emergency and critical care specialist and the Hospital Director at AVETS) whose article on fluid therapy in Veterinary Practice News suggested using the formula  $[30 \times (\text{weight in kg})] + 70$ . If only moderate fluids are required, I usually omit the +70 from the calculation.

There are more accurate dosing calculations that a vet may be able to provide and fluid therapy should never be commenced without veterinary approval and guidance. Most dogs become accustomed to this treatment over several days but may yelp initially when the first few needle jabs are made. To help ease this discomfort, I recommend the use of Terumo Thin Wall needles gauge 22 to 26. The lower the gauge, the easier and faster it is to inject the fluid. The higher the gauge, the slower fluids can be injected but the less painful it is for the dog.

On the rare occasions that intensive IV and follow-up SubQ fluids fail to reduce creatinine, advanced renal therapies (e.g., peritoneal dialysis, haemodialysis) may be necessary. Signs that indicate these therapies should be considered include a dangerously high potassium level, fluid in the lungs, or lack of improvement in laboratory results while a dog receives IV fluids. Both peritoneal dialysis and haemodialysis are generally very expensive.

### **Why diet plays a critical role**

Creatinine is a waste product that compromised kidneys struggle to eliminate. When creatinine reaches the first abnormally high increase in blood levels the kidney organs have already lost 75% of viable filtering function nephrons (Washington State University), so controlling this element is vitally important to prolonging life and reducing the acceleration of further damage. A renal diet consisting of low phosphorous, low sodium and high-quality human-grade protein has shown repeatedly in numerous studies to slow the progression of kidney disease and prolong life. Using blood creatinine as a measure of kidney function, the levels are lower in those diseased dogs fed a renal diet and effective supplements compared with control group diseased dogs fed a normal diet. Furthermore, the survival time has been

shown to improve by 50% between the two groups (NCBI 'Effect of Dietary Supplements in Reducing Probability of Death for Uremic Crises in Dogs Affected by Chronic Kidney Disease').

While high-quality protein in diet is much easier for the kidneys to deal with, recent science has shown that reduced protein diets are not always helpful despite many articles and veterinarians suggesting this course of action. The reality is that so much depends on the stage of illness and the type of kidney disease. Moreover, excessive reductions in protein can cause severe malnutrition and a loss of muscle mass in all dogs along with other lifethreatening repercussions. Reducing the volume of protein does help those dogs in later stages of the disease, because the kidneys then don't have quite as much work to do and have a chance at eliminating some of the by-product toxin. But that reduction needs to be undertaken with care as too much will cause weight-loss and malnutrition. Sometimes this is a difficult balance to achieve and getting a veterinary nutritionist on-board can prevent greater issues arising.

More severe reductions in protein are essential when a urinalysis shows protein levels in urine samples of 3+. This suggests the glomerular architecture of the organs to be severely damaged (protein-losing nephropathy) and normal levels of the toxic waste products from protein simply cannot be filtered, resulting in further accelerating deterioration.

Hypoalbuminemia (low blood albumen) can occur from reducing protein in the diet. Under such circumstances it is useful to provide some supplemental protein, ideally as hard-boiled egg whites (albumin). Each large egg white provides 6 grams of protein. In addition, giving angiotensin converting enzyme inhibitors (for example, Enalapril) have been shown to reduce proteinuria in dogs suffering from this particular form of kidney disease.

It is always a good idea to aim for reducing the volume of food fed while increasing the frequency of meals. While not all owners are able to achieve this due to other commitments, the less food that can be fed at one time helps reduce the work and therefore the stress on the kidneys. Feeding tiny meals six times a day is much better than feeding one or two larger meals, for example, as long as the total amount for the day equates to the volume of food and nutrients required for the size and breed of dog.

It is worth noting that creatinine blood levels always increase after a meal, so a fasting of 8 hours is usually advised before a sample is taken by the vet for testing. Repeating this protocol for every blood test allows for accurate and consistent historic references over the course of the illness.

### **Omega-3 as a supplement**

There is research study history that provides evidence of improved renal health with dietary added omega-3 fatty acids for dogs with kidney disease. The improvements are not substantial, but are nonetheless significant. In addition, many studies show that omega-6 fatty acids have a detrimental effect on kidney function. A small 1998 study ('beneficial

effects of chronic administration of dietary omega-3 polyunsaturated fatty acids in dogs with renal insufficiency') published in The Journal of Laboratory and Clinical Medicine was probably amongst the first to recognise it. The paper states: 'We conclude that supplementation with omega-6 polyunsaturated fatty acids enhanced renal injury; supplementation with omega-3 polyunsaturated fatty acids was renoprotective.'

This conclusion has been unchanged by the passage of time. An article by Dr. Angela Witzel Rollins DVM, PhD, a Diplomate and former President and Chair of the Board for the American College of Veterinary Nutrition in Today's Veterinary Practice (2020) states: 'Diets high in omega-3 fatty acids have been shown to reduce glomerular capillary pressure and proteinuria and to abate the decline of glomerular filtration rate in dogs with experimentally induced CKD.'

Omega-3 fatty acids, notably eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are known to be beneficially anti-inflammatory. Their assistance in reducing the adverse effects of kidney disease allows for improved filtration and elimination of toxic substances, thus reducing the level of creatinine. However, it is worth pointing out that owners should not merely add omega-3 indiscriminately to a dog's diet as too much can prove disastrous. A dosage of 40 mg/kg EPA combined with 25 mg/kg of DHA q24h has been recommended for dogs with CKD (Cline M. 'Nutritional management of chronic kidney disease in cats & dogs'). One of the richest sources of omega-3 is from natural organic salmon oil. Owners that use this for their dogs should add a vitamin E supplement at a canine suitable dose, because salmon oil depletes this vitamin in a dog's body.

It is important here to mention that omega-3 and other fish oils should be stopped during any flare-up of pancreatitis, as fats in the diet schedule exacerbate the inflammation.

### **Rehmannia glutinosa as a supplement**

A study (Rehmannia glutinosa ameliorates the progressive renal failure induced by 5/6 nephrectomy) published in the Journal of Ethno pharmacology concluded that the renoprotective effect of Rehmannia glutinosa might be mediated by suppressing the expression of angiotensin II and AT(1) receptor and by regulating TGF-beta1 and type IV collagen expression. This is just one of multiple studies that suggest creatinine reduction may be partly achieved by the introduction of Rehmannia glutinosa as a dietary supplement. The steamed root of the Scrophulariaceae family has been widely used in Asian countries for the treatment of renal diseases for centuries. It is only in recent years that Rehmannia extracts have been produced as potentially beneficial products intended for dogs with kidney disease, making this supplement worth considering as part of a combined therapy.

### **The role played by potassium**

A large amount of the mineral potassium is lost when urine production becomes excessive. Urgent, frequent and nocturnal urination is very typical in dogs with kidney disease. Low

potassium blood test levels have also been shown to further reduce kidney function, thereby increasing creatinine levels. A potassium supplement replaces the loss of nutrients and helps maintain kidney function.

While it is better to have potassium blood levels on the higher side of normal, it is equally important not to allow potassium to rise into abnormal levels and therefore develop into hyperkalaemia. High levels of potassium increase acidity in a dog's blood which can have a direct impact on the heart's ability to function normally.

It is worth mentioning that certain types of fluid given by IV or SubQ can incrementally increase potassium blood levels, so always check with a vet whether the type and amount of fluid being given is suitable for a dog with existing abnormally high potassium levels in kidney disease.

### **Immunosuppressive therapy**

Immunosuppressive therapy can be an effective line of treatment for those dogs that have protein-losing glomerular disease. The improvement achieved often helps reduce progression to chronic kidney disease and consequentially rising creatinine and BUN.

The American College of Veterinary Internal Medicine published an IRIS Canine GN Study Group paper 'Consensus recommendations for immunosuppressive treatment of dogs with glomerular disease based on established pathology' in 2013. It concluded mycophenolate or chlorambucil alone or in combination with azathioprine should be given on alternating days. Therapeutic effectiveness should be assessed serially by changes in proteinuria, renal function, and serum albumin concentration. In the absence of overt adverse effects, at least 8 weeks of the rapidly acting nonsteroidal drug therapy and 8-12 weeks of slowly acting drug therapy should be provided before altering or abandoning an immunosuppressive trial.

### **CoQ10 as a creatinine reducing agent**

Various studies have concluded that supplementing with CoQ10 can reduce some kidney values including creatinine by improving a dog's metabolic profile. In 2018 a systematic review and meta-analysis of Randomized Controlled Trials (RCTs) were conducted to determine the effects of coenzyme Q10 (CoQ10) supplementation on metabolic profiles of patients diagnosed with Chronic Kidney Disease (CKD), published by PubMed. The review concluded: 'Overall, the current meta-analysis demonstrated that CoQ10 supplementation significantly improved metabolic profile in patients with CKD by reducing total cholesterol, LDL-cholesterol, MDA and creatinine levels, yet it did not affect fasting glucose, insulin, HOMA-IR, and CRP concentrations.'

### **Liver disease and its influence on creatinine**

Creatine is a natural compound generated in a dog's liver. It's transported to the muscles where it's used for energy. Unused creatine that's not used as energy gets converted into

the waste product creatinine. When a dog with kidney disease appears to be improving with good and adaptive management and treatment, as assessed by falling serum creatinine amongst other test results, it is vital to confirm this is not a false-positive due to liver damage.

As the liver fails, so creatine production also fails, and reduced volumes of creatinine enter circulating blood. The liver and kidneys perform sympathetic roles in the management of waste products so when the kidneys fail this puts additional stress on the liver. Abnormal blood values for liver enzymes in routine testing are not at all uncommon in canine kidney disease. One possible way of preventing this from occurring is to add a Milk Thistle herbal remedy as a supplement to diet. The silymarin in Milk Thistle is valued for its known protection of the liver and has been used for centuries for its antioxidant, antiviral and anti-inflammatory properties.

### **Muscle wastage influence**

Creatine is considered to improve strength, increase lean muscle mass, and help the muscles recover more quickly during exercise. Muscle wastage is a common physiological symptom of advanced kidney disease in dogs. When there is less muscle, less creatine is released by the liver and lower amounts of creatinine are measured in circulating blood as a direct result.

Hyporexia (decreased appetite) is considered to play an important role in muscle wastage during the degeneration of chronic kidney disease. Vets and dog owners need to consider the fact that reduced creatinine blood levels may not be entirely due to other contributing treatments, particularly if there are signs of muscle wastage or weakness. Proprietary renal diets tend to be unpalatable (but very necessary in stages 3 and 4) and taken together with other common symptoms of nausea and acid-reflux it is little wonder hyporexia occurs. Ensuring a dog eats regularly, appropriately and sufficiently is therefore a crucial goal. Various therapies and treatments may help achieve this including anti-nausea and appetite stimulant medications.

### **Urine Creatinine Ratio (UPC) testing**

A creatinine (UPC) ratio greater than 0.5 in a dog indicates there is significant protein loss through the kidneys, and a diagnosis of primary kidney disease is confirmed, although it is necessary to prove that the protein loss through the kidney is an ongoing problem and not something transitory. An abnormal UPC above the threshold is a condition termed proteinuria. The recommendation by VCA Animal Hospitals in the USA and Canada is to repeat the protein:creatinine ratio (with complete urinalysis) on at least three consecutive urine samples taken at 2-week intervals. The protein:creatinine ratio only helps to establish that a problem exists and is useful in assessing and adapting ongoing treatment and management, but serum creatinine and BUN remain important primary tests along with other kidney values and physical examinations.



## **The relevance of creatinine in staging canine kidney disease**

Creatinine levels are one of the multiple elements involved in staging the severity of kidney disease in dogs. While creatinine levels provide a rough estimate of the stage, it would be inappropriate to use them in isolation. It is also prudent to note that staging is not always a one-way process. A dog that is diagnosed at stage 3, for example, may actually drop back to stage 2 with the introduction of adaptive, appropriate and rapid treatment and management.

Stage 1 kidney disease: Creatinine less than 1.4 mg/dL (<125 umol/L). SDMA <18.

Stage 2 kidney disease: Creatinine 1.4 – 2.8 mg/dl (125 to 250 umol/L). SDMA 18 to 35.

Stage 3 kidney disease: Creatinine 2.9 - 5.0 mg/dl (251 – 440 umol/L). SDMA 36 to 54.

Stage 4 kidney disease: Creatinine greater than 5.0 mg/dl (440 umol/L). SDMA >54.

(IRIS modified in 2023).

## **Medications that can falsely raise blood creatinine levels**

High blood glucose, vitamin C supplements and certain antibiotics (cephalosporins) can falsely raise creatinine readings, depending on how the blood sample is tested. When the margin of diagnostic creatinine is small and suggests kidney disease at around 1.4mg/dL, it is worth remembering that dehydration, stomach antacids, antibiotics, heart and blood pressure medications, and arthritis medications, all have the capacity to cause slight increases in normal serum creatinine levels.

In the Journal of Internal Medicine, Andreev E, Koopman M, Arisz L (Medical University Sofia, Sofia, Bulgaria and University of Amsterdam, Amsterdam, The Netherlands) confirmed in 2001 that 'Several drugs can induce a rise in plasma creatinine concentration, interacting with different aspects of creatinine physiology whilst not decreasing GFR.' Some of these medications include NSAID's, Cimetidine, Trimethoprim, Pyrimethamine, Salicylates, Phenacemide, Corticosteroids, Vitamin D derivatives, Calcitriol, and Alfacalcidol. Antibiotics called aminoglycosides seriously and adversely affect the kidneys and consequentially creatinine levels, when a dog is dehydrated.

## **And finally ...**

There is a whole raft of companies promoting natural and formulated supplement products that claim to reduce creatinine levels, but other than those already mentioned above, I am not aware of any that have been independently scientifically studied and peer-reviewed to a point of proven success. I would therefore suggest scepticism, caution and meticulous scrutiny before owners procure any such product.

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