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Review of Chronic Kidney Disease and Comparison Between Humans, Dogs, and Cats

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ABSTRACT

The kidney is the body's filter and when it is damaged, the body no longer functions the way it should. When enough damage has occurred to the kidney, the kidneys will slowly start to fail resulting in chronic kidney disease (CKD). There is no cure for CKD and it gets progressively worse over time. CKD affects a wide variety of animal species, including humans, dogs, and cats. We will be comparing CKD prevalence, symptoms, risk factors, and treatment modalities. There are many similarities in disease diagnosis, monitoring, and treatment between the species. There are also key differences in each species' physiology that result in different diagnostic and monitoring parameters as well as differences in the treatment options available. We compare CKD treatment options that include kidney transplantation, dialysis, hypertension, and nutrition. As part of the One Health movement, understanding these similarities and differences will help us better understand the disease process and hopefully improve treatment outcomes across species.

Chronic Kidney Disease (CKD)

Chronic Kidney Disease (CKD) is a relatively common disease seen in older animals of multiple species, especially humans, dogs, and cats. According to the CDC in 2021, 15% of US adults have CKD, and about 50% of CKD cases occur in people over 44 years of age. A CDC study from 2015-to 2018 indicates that CKD is more common in geriatric humans (65 and older) than in adults (18-44-year-olds). In addition, CKD is known to be more prevalent in women than men (*Chronic Kidney Disease in the United States, 2021*, 2021). Geriatric (older/aged) canines made up 80.6% of all CKD cases (Perini-Perera et al., 2021). In felines, about 63% of all cats older than 10 years of age (geriatric) have CKD (Bartges, 2012). There is no known difference in the prevalence of CKD in males vs females for dogs and cats (Macdougall et al., 1986; Marino et al., 2014). In addition, there is no specific breed of cat or dog that is more likely to get CKD (Macdougall et al., 1986; Marino et al., 2014). CKD in humans, cats, and dogs results in a slow, progressive decline in kidney function over time. Due to its progressive nature, CKD is often categorized by blood and urine values into different stages. In humans, urine values of interest are glomerular filtration rate (GFR) and albumin, but in dogs and cats, blood creatinine and urine symmetric dimethylarginine (SDMA) concentration levels are more commonly assessed (*IRIS Staging of CKD*, 2019; "Notice," 2013). Cystatin c is one potential new diagnostic tool in all of the species (Ghys et al., 2014). In humans and dogs, cystatin c is a new way we are starting to categorize or stage CKD, but there is not yet enough evidence in cats. In humans, there are 5 stages of CKD (Romagnani et al., 2017) but there are only 4 stages defined for cats and dogs (*IRIS Staging of CKD*, 2019). The stages for cats and dogs do not include the final category of kidney failure. Thus, while there are some similarities between the species, there are distinct differences as well.

CKD symptoms in humans, dogs, and cats have similarities, but there are also key differences. CKD most often presents with increased drinking or thirst and increased urination in all of the three species. It could also lead to hypertension, edema, growth delay in juveniles, anemia, fatigue, shortness of breath, neuropathy, and seizures (Bartlett

et al., 2010; *End-Stage Renal Disease*, 2021). In the late stages of CKD, all species are prone to weight loss, nausea, vomiting, gastric or oral ulcers, stomatitis, and cachexia (Malkina, 2021). Unique to humans is a "uremic frost", where urea from sweat crystalizes on the skin (Malkina, 2021). Because CKD is from diminished kidney function, the kidney will produce less erythropoietin than normal. Erythropoietin is a hormone that tells the bone marrow to produce red blood cells. Low erythropoietin leads to a decrease in the production of red blood cells and results in anemia (Vieth & Lane, 2014). Urine also becomes increasingly more dilute in all species because of the decreasing ability of the kidney to concentrate urine. (Bartlett et al., 2010; Romagnani et al., 2017). When it comes to dogs and cats, they have many similarities like decreased bodyweight, increased water consumption, as well as increased urine production (Bartlett et al., 2010). Hypertension from CKD could lead to heart failure in humans, while in dogs and cats it is more likely to lead to the continued progression of kidney dysfunction (Hori et al., 2018; Malkina, 2021; Tenhündfeld et al., 2009).

There are many different risk factors for CKD in humans, dogs, and cats. Obesity is a major risk factor for CKD in all three species, where extreme weight gain can cause high blood pressure (Hall et al., 2004; Novellas et al., 2010). In humans, diabetes is one of the major risk factors for CKD and both type 1 and 2 diabetes can contribute to CKD development. In addition, infants born preterm are more likely to develop CKD during their lives than the regular human population. In canines, aging is a major risk factor with 80.6% of CKD cases occurring in geriatric animals. Risk factors for dogs include inflammatory and infectious diseases (such as Leptospirosis), history of anesthetic-surgical procedures, heart disease, neoplasms, endocrinopathies, and exposure to nephrotoxic drugs (Perini-Perera et al., 2021). Leptospirosis is something that affects humans, cats, and dogs. Leptospirosis is a bacterial disease that can and is spread usually through wild animals to pets or humans through urine. Leptospirosis is a bacterium that targets the kidney and can cause both acute and chronic infections in the kidney (Yang, 2007). While felines have an increased risk of CKD with age like dogs, they are three times more likely to develop CKD than dogs (Bartges, 2012). The reasons for this increased prevalence are still unknown. In pets, there are also poisonous plants that are risk factors for CKD. Shamrocks (*Oxalis sp.)* and lilies (*Lilium sp.*) are known to be nephrotoxic. Shamrocks contain calcium oxalate crystals, which can harm the kidney function when consumed in large quantities (*Keep Lilies Away From Your Cats | FDA*, n.d.; *Oxalis (Clover, Good Luck Plant, Lucky Clover, Oxalis, Shamrock, Shamrock Plant, Sorrel, Wood-Sorrel) | North Carolina Extension Gardener Plant Toolbox*, n.d.). Cats are particularly susceptible to lily poisoning, which is especially common in Easter or other spring bouquets and can be fatal if not treated swiftly (*Keep Lilies Away From Your Cats | FDA*, n.d.; Muir, 2003). Any part of a lily can be dangerous, including the pollen that cats can get on their fur and then lick off since they are a grooming species (*Keep Lilies Away From Your Cats | FDA*, n.d.). Dogs may become nauseous or vomit due to lily ingestion, but are not known to develop nephrotoxicity. On the other hand, raisins and chocolate have been reported to cause renal failure in dogs (Cortinovis & Caloni, 2016). While all three species may have CKD associated with infectious or metabolic disease, pets are more prone to developing CKD associated with dietary indiscretions.

The four biggest challenges in CKD are hypertension, dialysis, kidney transplantation, and nutrition. All of these challenges are present in humans, dogs, and cats. However, advanced treatments are often less utilized in companion animal species than in humans.

Section 1: High Blood Pressure/Hypertension

High blood pressure in humans, dogs, and cats is also known as hypertension. About one in three human adults in the US have high blood pressure, with about 30% undiagnosed (Ong et al., 2007). That number is even higher in people known to have CKD (*Chronic Kidney Disease in the United States, 2021*, 2021). Indeed, hypertension has been reported to occur in 85%-95% of patients with CKD (Rao et al., 2008). Not only is hypertension a major risk factor for CKD, but it is also a risk factor for cardiovascular disease (Tedla et al., 2011). Epidemiologic human data has consistently suggested that hypertension is more highly correlated with the occurrence of cardiovascular and stroke events (Kannel et al., 1971). High blood pressure is associated with a greater risk of cardiac failure later on (Levy et al.,

1996). Humans with hypertension and CKD are often prescribed anti-hypertensive medications to lower their risk for heart attack and stroke (Nielsen et al., 2017). In humans, hypertension often develops due to separate underlying health issues such as diet. Hypertension can be influenced by sodium intake (most commonly a problem in humans) as well as sodium retention due to loss of kidney function. Excess sodium leads to increased fluid consumption, increased blood volume, and increased perfusion of peripheral tissues (Ku et al., 2019). This stimulates the body to narrow the blood vessels which reduces blood flow and increases pressure in the blood vessels. Reduced blood flow results in decreased kidney function. When this happens, the kidneys are not able to remove all wastes and extra fluids from your body, further worsening CKD (*High Blood Pressure and Chronic Kidney Disease | National Kidney Foundation*, n.d.). Thus, hypertension is also an important risk factor for CKD progression in humans.

Hypertension manifests differently in each of the species. While hypertension in humans occurs more spontaneously, dogs and cats usually develop hypertension due to CKD itself (Acierno & Labato, 2005). About 19.4%-61% of feline and 50-93% of canine patients with CKD are affected by elevations in blood pressure (Acierno & Labato, 2005). Hypertension develops due to CKD because renal dysfunction leads to the inability of the kidneys to regulate water homeostasis in the body (Hamrahian & Falkner, 2016). Chronic hypertension can lead to the damage of multiple organs because the increased pressure can cause the lining of your blood vessels to thicken, causing the blood flow to the organs to decrease (van der Veen et al., 2015). Decreased blood flow to critical organs such as the heart, brain, and eyes can lead to disease. In dogs, renal disease is characterized by glomerular lesions and proteinuria with hypertension being a less prominent component of the disease (Harley & Langston, 2012). Diagnosis and treatment of CKD dogs that do have hypertension may prevent the development of retinal lesions or may limit or slow the progression of renal and cardiac lesions (Acierno et al., 2018). Hypertension is also less prevalent in canine CKD than in feline CKD but is treated when present (J. Elliott et al., 2001). In cats, decreased kidney function is associated with activation of the renin-angiotensin-aldosterone system, which may contribute to disease progression (Kobayashi et al., 1990). In cats, hypertension during CKD is extremely common and often monitored using tail blood pressure (Bartges, 2012). There is some debate amongst the veterinary community if dry cat food contributes to the high prevalence of the disease (Buffington, 2008). Dental disease is another known risk factor for CKD in cats (Finch et al., 2016). Untreated hypertension will speed CKD progression and often leads to blindness due to increased ocular pressures (Kobayashi et al., 1990). Cats are often prescribed antihypertensives, such as amlodipine, to control blood pressure (Kobayashi et al., 1990). In canines, hypertension is more common in acute kidney disease rather than CKD. In cats and dogs with CKD, individuals are often placed on a prescription diet to help improve symptoms and slow disease progression.

In all species, hypertension is very important to monitor because unregulated hypertension can lead to the rapid worsening of kidney function. hypertension can also lead to significant damage to other important organs, such as the heart, brain, and eyes (Cohuet & Struijker-Boudier, 2006; Novellas et al., 2010). In humans, hypertension usually develops before CKD, and in dogs and cats, it usually develops after kidney function has declined. Kidney function in humans, dogs, and cats are all affected by hypertension because the function of the kidney in the body is very similar, and when it is not functioning properly the same problems occur. Therefore, blood pressure should be monitored and treated in individuals of all species that have been diagnosed with CKD (Acierno & Labato, 2005)

Section 2: Dialysis

When kidney dysfunction is bad enough in all species, additional treatments like dialysis are recommended for CKD patients to maintain their quality of life. Dialysis is when an internal or external filter mimics kidney function through the removal of toxic wastes and extra water from the blood (Lee, 2017). Individuals from any species with CKD can be treated with dialysis to prolong their life (Romagnani et al., 2017). Hemodialysis and peritoneal dialysis are the two forms of dialysis. Hemodialysis is when blood is filtered by a machine, called a dialyzer, instead of a kidney (*What Is Peritoneal Dialysis? | National Kidney Foundation*, n.d.). Because of their function, dialyzers are also known as artificial kidneys. Peritoneal dialysis uses the inside lining of your belly to act as a natural filter (*What Is Peritoneal*

Dialysis? | *National Kidney Foundation*, n.d.). In all three species, hemodialysis is the most commonly used to aid in treating CKD. Patients with acute kidney injury are more likely to receive peritoneal dialysis (*Hemodialysis vs. Peritoneal Dialysis in Veterinary Practice of Thailand - WSAVA 2015 Congress - VIN*, n.d.). Hemodialysis can be used to treat AKI, CKD, and certain toxicities in all species. CKD is by far the most common reason to perform hemodialysis in veterinary patients (Langston, 2002). In humans, hemodialysis is often performed while patients wait for a kidney transplant.

One of the main similarities between hemodialysis treatments in humans and pets is the dialyzer machines used to perform the procedure. Although, humans tend to respond to dialysis better than dogs (40%) and cats (56%) (D. A. Elliott, 2000; Fischer et al., 2004). The dialyser takes the blood, filters it by diffusion to the dialysate across a semipermeable membrane, and returns the cleaned blood to the body. The current standard is hollow-fiber dialyzers with fibers constructed chiefly of cellulosynthetic or synthetic noncellulosic materials (Fischer et al., 2004). Excess water, select solutes, and toxins pass through the small pores in the membrane, but larger solutes, such as proteins and cells, are retained in the patient (Langston, 2002). Dialysate is an electrolyte fluid similar to plasma water, but without the main blood plasma proteins, and is created by mixing an electrolyte solution with highly purified water (Langston, 2002). It has approximately the same concentrations of sodium, chloride, calcium, magnesium, potassium, and bicarbonate ions that are found in normal blood (Langston, 2002). The hemodialysis process may take about 3-5 hours and can take place in a hospital or a dialysis center three times a week. For humans, there are also at-home hemodialysis treatments (*Dialysis: Types, How It Works, Procedure & Side Effects*, n.d.). Another option is continuous renal replacement therapy (CRRT), which is needed less frequently (Tandukar & Palevsky, 2019). Hemodialysis is usually a several hour long procedure performed several times per week, while CRRT is a 24-48hr long procedure performed every few months (Tandukar & Palevsky, 2019). One common similarity in all three species is that dialysis needs to be done frequently to help support kidney function.

In all species, hemodialysis has to be done frequently to have a positive effect on the body. The most common dialysis symptoms in humans are fatigue, pain, muscle cramps, nausea, vomiting, constipation, diarrhea, itching, dryness of the skin, sleep disorders, and emotional problems (Karadeniz Teknik Universitesi Saglik Bilimleri Fakultesi, Hemsirelik Bolumu, Trabzon, Turkiye et al., 2018). Not only do patients take a toll on their bodies, but it also affects their emotional health (*A "New Normal": Life on Dialysis-The First 90 Days*, n.d.). In dogs and cats, they become dependent on dialysis for survival. Unfortunately, most dialysis-dependent animals cannot live for more than 3-5 days off dialysis (Fischer et al., 2004). Symptoms in cats and dogs could be cramps, lightheadedness, nausea, etc. (Steuer et al., 1996). Dialysis in animals is generally rare since it is very expensive and only performed at tertiary referral hospitals. Many pet owners will have their regular clinic perform fluid diuresis instead. Diuresis is a condition when the kidney produces too many bodily fluids (Langston, 2017). In all species, when dialysis can no longer uphold the function of the kidney, it is time to consider kidney transplantation. A kidney transplant is a surgery to place a healthy kidney from a living or deceased donor into another, whose kidneys no longer function properly (*Kidney Transplant - Mayo Clinic*, n.d.). Hemodialysis is also known for specifically preparing cats for possible kidney transplantation (Cowgill & Langston, 1996). In pets, it is known in CKD cases like these, to use active euthanasia. Active euthanasia is when they are voluntarily giving the patient a lethal dose of a drug. For CKD, this is used so they aren't in pain, and they don't suffer too much before they die (Brock, 1992).

Section 3: Kidney Transplantation

Kidney Transplantation, also known as renal transplantation, can provide improved quality of life for individuals with CKD. Kidney transplantation has been more successful in the management of human and feline patients when compared with canine patients, which have higher morbidity and mortality rates (Hopper et al., 2012). Kidney transplants in humans are evaluated by age and comorbidities. The United Network for Organ Sharing (UNOS) manages the list of all the people across the US waiting for an organ transplant. UNOS ensures that deceased donor organs are distributed fairly using a transparent system (*The Kidney Transplant Waitlist – What You Need to Know* | *National Kidney*

Foundation, n.d.). People who have received a kidney transplant have a 5-year survival rate of 86% (Romagnani et al., 2017). Kidney transplantation and organ donors in humans are more common than in dogs and cats. Kidney donors in humans could be from a deceased patient or even a living one, although less common. A living-donor kidney transplant is associated with improved outcomes (*Living-Donor Kidney Transplant - Type - Mayo Clinic*, n.d.). Most cats that undergo a kidney transplant are most likely to be stage 3 and 4 of CKD (Aronson, 2016). But in all the species, there are lots of differences in regards to kidney transplantation.

In terms of a kidney transplant, all three species have many differences. We know a lot more information about kidney transplants when it comes to humans, while we know almost nothing about canine kidney transplants. Feline kidney transplants are more common than canine kidney transplants because felines are the most predominant species to undergo renal transplantation in veterinary therapeutics (Aronson, 2016). Although we don't know much about canine kidney transplants, dogs are commonly used as a preclinical model for organ transplantation. Dogs have long been used for medical studies because of their size, temperament, and immune system. Since canines have been used as a preclinical model for organ transplantation, there was a need to obtain knowledge of its immunogenetics equivalent to the knowledge gathered for humans. Because of these studies, drugs found to have immunosuppressive effects in small laboratory animals are tested extensively in dogs before their clinical use in humans. The dog has been almost the sole experimental animal for research on kidney preservation (Bijnen & Obertop, n.d.). In humans, you may get a kidney transplant if you have end-stage renal disease, which is essentially kidney failure. You can also treat end stage renal disease with dialysis (*Kidney Transplant | Johns Hopkins Medicine*, n.d.). The human kidney transplantation success rate for living donors is 98.11%, and transplants from deceased donors have a slightly diminished success rate (*Find and Compare Transplant Programs*, n.d.). In a study of feline transplant recipients between 1987 and 1996, there was a 29% mortality rate, which is much higher than that of humans (Hopper et al., 2012). This may at least be partially due to fewer known transplantation markers available for type matching (Hopper et al., 2012). The median survival in cats that survived transplantation was one year (Mathews & Gregory, 1997). In a canine kidney transplant case series, the median survival was only 24 days, with a 100-day survival probability of only 36% (Hopper et al., 2012). The cause of death for canines after transplantation surgery was primarily attributed to thromboembolic disease and infection (Hopper et al., 2012). In all species, the left kidney is preferred for kidney donors because of a longer renal vein (Bernsteen et al., 2000; Khalil et al., 2016).

Kidney transplantation improves the quality and even length of life for individuals with CKD that receive one. Not only can it benefit patients, but it also leads to improvement in research, laboratory animal medicine, pathology, and drug monitoring (O'Connell et al., 2020). Several studies indicate that kidney transplantation is associated with lower mortality rates, and improved quality of life compared with dialysis treatment (Port, 1993; Schnuelle et al., 1998; Tonelli et al., 2011). Cats receiving kidney transplants have been known to survive as long as 6 years or more after surgery (*Feline Kidney Transplantation - General Information*, n.d.). The implanted kidney functions normally and should provide a much-improved quality of life for the recipient. Feline donors are usually healthy, young adult cats without any disease. The cats also have to have a blood match with the recipients (*Penn Vet | Renal Transplantation*, n.d.). Not much is known about the benefits of canine kidney transplants since only a handful of operations have been done (Bijnen & Obertop, n.d.). On the other hand, there are some known downsides to kidney transplantations in all species. Treatments and supportive care for CKD are eliminated, but therapy for maintaining the transplanted kidney is added. Transplant patients require daily lifelong immunosuppressive medication to prevent rejection of the new organ for all species. There are lots of different immunosuppressants to consider depending on the species as well as individual patient circumstances (*Feline Kidney Transplantation - General Information*, n.d.; *Medications After Kidney Transplant | Transplant Center | UC Davis Health*, n.d.). Because of the immunosuppressives, all individuals will be immunocompromised, which means the patient will be more prone to other diseases and infections. Infection of the new kidney is the most concerning (Hopper et al., 2012; Schmiedt et al., 2008; Tonelli et al., 2011). In cats and dogs, after medication and other treatments aren't enough to keep them stable, pet parents and veterinarians have to consider euthanasia to prevent prolonged suffering (Brock, 1992).

Section 4: Diet and Nutrition

The diets of all the species change drastically with treatment. All species need a well-balanced diet according to their health circumstances. All three species must stick to the prescribed diet as much as possible to prevent further harm to the kidney. In humans, they must stick to a low-fat diet to reduce high cholesterol levels (*A "New Normal": Life on Dialysis-The First 90 Days*, n.d.). Reducing high cholesterol levels helps maintain cardiovascular function and aids in keeping strong blood flow to the kidneys. Changing the diet to be more kidney-friendly can also reduce the amount of work your kidney has to do (Kistler et al., 2021). A common change in diet could be low sodium or a low-protein diet for blood pressure (Kistler et al., 2021). In cats and dogs, it is generally recommended to eat a low fat, moderate protein, and low phosphorus diet (Parker, 2021). Maintaining energy intake is very important in all CKD patients. In all species, CKD is known to result in nausea, loss of appetite, and subsequent weight loss so good nutrition is key to staying healthy for as long as possible (Bartges, 2012; Chazot, 2009).

Humans and pets have different dietary requirements and should consult a relevant nutritionist for their situation. This is especially true in pets fed a home-cooked diet. . Humans can make their food, but dogs and cats cannot. Humans can cook food according to their diet plan, or have food sent to them through renal-friendly food delivery service (example and/or reference here). Human diets can vary a lot, but they all talk to a dietitian and/or nutritionist for recommended foods and a diet plan (*A "New Normal": Life on Dialysis-The First 90 Days*, n.d.). Cats and dogs are typically fed commercial dry kibble diets or canned foods. These renal-friendly diets in pets tend to have moderate protein restriction, restricted phosphate levels, and increased levels of water-soluble vitamins. In feline renal diets, it is known to be supplemented with potassium (McGrotty, 2008). After being diagnosed with CKD, they typically go on commercial prescription kibble or canned diets. It is typically recommended that feline patients, who are known to drink less water, eat more canned food than kibble because of the higher moisture content. Pets can also have a home-cooked diet, prepared by their human caretakers (Parker, 2021).

Conclusions

There are a lot of different factors that contribute to the development, treatment, and support of humans, canines, and felines with CKD. Four key treatments center around a reduction in hypertension, hemodialysis, kidney transplantation, and supportive nutrition. Hypertension is known to exacerbate CKD in all three species, so blood pressure should be monitored closely. Hemodialysis helps support the patient by performing the same filtration of the blood that the kidney would. In humans, hemodialysis is relatively common but it is rare in dogs and cats. After dialysis can no longer support the patient, renal transplantation is necessary. Transplantation is a long-term treatment for CKD, which can improve the quality and survival of the recipient. Diet and nutrition can make a huge impact on kidney function and patient quality of life. All three species must stick to the right individual diet to help support kidney function and prevent any further kidney harm. In conclusion, there are both similarities and differences in how each of the species deal with CKD.

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