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**Review Article**

# CRITICAL APPROACH TO THE ALTERNATIVE TREATMENT OF CHRONIC KIDNEY DISEASE IN DOGS AND CATS

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**Abstract:** Chronic kidney disease (CKD) is common in dogs and cats and can occur at any age, especially in geriatric animals. The various presentations of the disease and their different hemodynamic and metabolic alterations are issues of profound research. Currently clinicians improvements of the comprehensive management of chronic kidney disease focuses on the delay of the progression of clinical signs of the disease and there now are numerous novel methods that also were proposed to slow the progression of the disease, with the possibility of use in non-referral centers. The aim of this critical approach is to provide an overview of the comprehensive treatment of chronic kidney disease, expose new treatments that could improve the intervention of dogs and cats with chronic kidney disease and reevaluate the usefulness of some existing drugs.

**Key words:** chronic kidney disease; cardiorenal syndrome; glomerulonephritis; dog; cat

## Introduction

Chronic kidney disease (CKD) is a common disease in dogs and cats with greater prevalence in geriatric animals, although it can occur at any age and its incidence in the general dogs and cats population is approximately 0.5 and 4.5%, respectively (1-3). CKD is defined as an structural and/or functional disability in one or both kidneys present for more than 3 months (2, 4) and their main features are deteriorated renal excretion and decreased glomerular filtration rate (GFR) (5). In addition, endocrine and biosynthetic functions are progressively altered (3). Dialysis and kidney transplantation are still only performed in reference centers and sometimes are not feasible procedures for the owner. Despite medical treatment continues to be invaluable to slow the progression of the disease, nutritional modification is one of the most important factors that influence the metabolic imbalances and is a determining factor in the health-related quality of life of affected patients (6). Thus, in human and veterinary medicine, poor body condition has been associated with decreased health-related quality of life and survival time (7, 8).

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The clinical presentation of the disease, the early diagnosis and the comprehensive treatment are a medical challenge that needs individual strategies due to the great variability between different patients and diverse clinical presentation. The goals of medical treatment of CKD are to slow down the progression of the disease, prevent complications caused by decreased renal function and control the clinical signs of uremia. It is also critical to stabilize the biosynthetic process and correct non-renal diseases that may decompensate patients with CKD such as diarrhea, vomiting and dehydration. Sometimes secondary endocrine disruption of CKD is neglected because of purely renal approaches that usually take place (2, 3). The aim of this critical approach is to present the progress in recent years in the comprehensive treatment of CKD. In addition, it aims to provide a different perspective, in terms of treatments that have existed during the past decade and those medical and / or pharmacological implications that might have changed.

## Nutritional Intervention

### The Critical Role of Nutrition

One of the main signs that present dogs and especially cats with kidney dysfunction is the loss of appetite. Thus, nutritional intervention is always required, considering that decreasing the presentation of many complications related to functional deficiency of the kidney (p.e uremic syndrome, hyperparathyroidism and anemia), improve coming through in health-related quality of life and survival time (8). The specific targets of the nutritional modification are to prevent uremic syndrome, maintain acid-base control, correct electrolyte imbalances and slow down the progression of CKD. In addition, this diets provide water-soluble vitamins and minerals supplement for maintain a balance between nutritional requirements and the necessary dietary restrictions (2, 3, 9). Nevertheless, the primary goal of nutritional therapy is to maintain stable body condition and muscle mass. These therapeutic strategies are more effective combined with focused therapies that directly correct the progression of specified etiology of CKD (such as nephrotic syndrome, hypercalcemia, renal disease, urinary tract infection, chronic urinary tract obstruction, glomerulonephropathies and immune-mediated disease, etc.)(9, 10).

To initiate the nutritional modification, experts have recommended correcting first the clinical signs of uremia (11). The evidence-based medicine is the most important factor in the management of the CKD (12), many studies have demonstrated the implications of nutritional therapy and renal diets typically have low levels of protein, sodium, and phosphorus. But also, high levels of antioxidants, polyunsaturated fatty acids (Omega 3 and 6) and water soluble vitamins, fiber and more energy density (13-16). Renal diets statistically decrease 72% of the relative risk of uremic crisis in cats (9). In the same way, renal diets in canines allows to remain 2.5 times longer without showing signs of uremia in this species (7), demonstrating that only with renal diet, disease progression is slower (6, 13). Although there are few research about this topic, the health-related quality of life and life expectancy significantly improves with the nutritional management (16).

### Modulation of inflammation and Oxidative stress

A variety of benefits have been attributed to supplementation with polyunsaturated fatty acids (PUFA's), including its tendency to decrease cholesterol, modulation of inflammation and control of blood pressure (17, 18). In human patients with renal disease, improvement in glomerular renal circulation and decreased calcification has also been recognized with this supplementation (19). One review published by Roudebush and colleagues (9) found that injuries such as glomerulosclerosis, tubulointerstitial fibrosis and infiltration of pro-inflammatory cells decreased significantly in dogs diets supplemented with PUFA's.

Oxidative stress caused by free radicals generation and reactive oxygen species can cause kidney damage accelerate the progression of CKD (20). Yu et al (21) found that antioxidant supplementation significantly reduced oxidative stress and plasma creatinine levels compared with dogs receiving a diet without antioxidants. Other research in dogs with induced CKD showed that the nutritional supplementation with omega-3 and antioxidants (p.e vitamin E,

carotenoids and lutein) were independently reno-protective and its effect was additive when used together (22). However, at the time meta-analysis or cohort studies were not published to determine if PUFA´s have clinical value in representative populations of dogs or cats and further investigations are expected.

## Chronic Kidney Disease-mineral Bone Disorder

The mechanism of excretion and control of phosphorus is normally composed of glomerular filtration and tubular reabsorption (23, 24). During CKD glomerular filtration rate decreases and phosphorus is retained, then tubular reabsorption of Phosphorus increases as a countervailing mechanism of "false" decreasing in the amount of phosphorus reaching the tubule lumen, which ends with the development of hyperphosphatemia and all its related aberrations, especially hormonal imbalance responsible of mineral equilibrium (see figure 1) (25). Hyperphosphatemia plays an important role in the development of secondary hyperparathyroidism in CKD. There is now appropriated evidence to recommend diets with restriction of phosphorus in kidney-affected patients (10, 26, 27).

In patients with advanced stages of renal dysfunction (IRIS III-IV), the restriction of phosphorus in the diet alone does not prevent hyperphosphatemia (28). Using phosphorus binders (p.e hydroxide aluminum) would be of help at least in dogs. It should be said that some patients cannot tolerate the intake of hydroxide aluminum and no serious investigations were published with a good level of evidence that allow its recommendation in clinical practice. A new oral phosphate binder SBR759 (Lenziaren®) was developed and evaluated by King (28) with favorable results in acceptability, clinical improves, tolerability and safety in cats. However, further evidence is needed to prove the real clinical benefit.

Calcitriol is the hormone responsible of renal calcium metabolism (23). Kidney converts the 25-hydroxycholecalciferol by the enzyme hydroxylase 1 alpha, to the active metabolite 1, 25-Dihidroxicolecalficerol (Calcitriol). Thus, in turn has a relationship with the modulation of parathyroid hormone. Because the CKD may be associated with decreased production of 1, 25-dihydroxycholecalciferol, this deficiency can promote hyperplasia of the parathyroid gland, alteration known as secondary hyperparathyroidism to CKD (27). Calcitriol supplementation may decrease a variety of complications attributed to the excess parathyroid hormone (PTH) levels in kidney-affected patients (26) and research suggests that calcitriol therapy prolongs survival time in dogs (26, 27, 29). The authors recommend caution in this topic and waited for further research to define a possible overall conclusion.

## Hyperkalemia in CKD

The electrolytes disturbance, especially alteration of potassium (Hyperkalemia) is common in dogs with CKD. Although they are of common incidence in acute complications it has a critical role in the final stages of the disease (30). In addition, there is the possibility that the amount of potassium in the diet exceeds renal excretion resulting in hyperkalemia in some patients. In humans with primary renal disease, the use of angiotensin converting enzyme inhibitors (ACEI's) can have complications such as hyperkalemia (31). Although disagreement exist and little evidence in canine and feline patients, there may be also a moderate or similar risk to present hyperkalemia.

One Research done by Segev and colleagues (32) showed that hyperkalemia is a potential complication of CKD in dogs that consumed a commercial therapeutic diet. Nevertheless, this investigation apparently found no relationship between the administration of ACEI's and serum potassium levels in the study population. In addition, canines that require hemodialysis are prone to develop severe hyperkalemia and the point-of-care testing of electrolytes should be applied during the procedure (33). Finally, it is important to take into account that depending on the stage of the disease, each patient should receive an individual treatment and nutritional therapy corresponding to renal function, considering that one diet for a patient with stage IRIS II-III, cannot necessarily be identical to an IRIS patient IV (see table 1)(6).

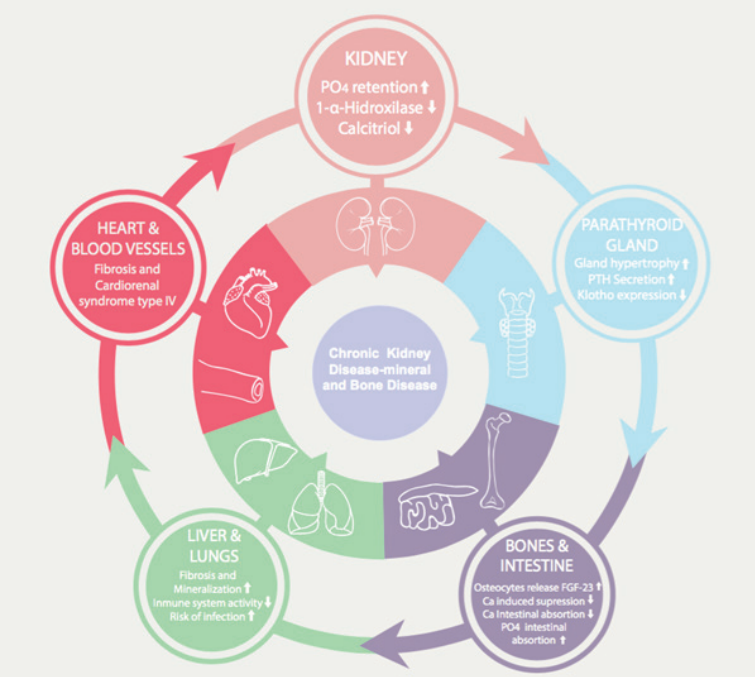


**Figure 1:** Chronic kidney disease-mineral and bone disorder is charactericed by PO4 retention as a consequence of declining GFR. FGF-23 increases in response to PO4 accumulation, but inhibits renal 1-α-hydroxilase and then decreases calcitriol levels. Hight calcitriol levels inhibit PTH synthesis and without this feedback inhibition, PTH increases. Other consequences of lower calcitriol levels are the increase of skeletal resistance to PTH action and the limitation of the Ca-induced suppression of PTH secretion. PTH secretion continue due to the fact that coreceptors klotho are diminished in the parathyroid gland. Impaired gastro-intestinal absorption of Ca due to low levels of calcitriol is another negative consequence. The liver, lung, heart and blood vessels are prone to the development of calcinosis and loss of function. The cardiorenal syndrome type IV is known as the impact of CKD on heart and vessels function and is recently reviewed in small animals. (Figure credit: Chiara Alessi)

**Table 1:** The CKD stratification system has been proposed by the International Renal Interest Society (IRIS) to help provide guidelines for clinical management of CKD. Staging is based on serum creatinine values, with substages identified for blood pressure and proteinuria. Taken and modified from (Foster JD. Canine chronic kidney disease current diagnostic and long-term management. Today's Veterinary Practice, September/October 2013)

| **CKD IRIS Staging System** | | |
|---|---|---|
| **Serum Creatinine mg/dl** | **Dogs** | **Cats** |
| Stage I | < 1.4 | < 1.6 |
| Stage II | 1.4 – 2 | 1.6 – 2.8 |
| Stage III | 2.1 – 5 | 2 - 5 |
| Stage IV | > 5 | > 5 |

## Getting to the extremes

Both anorexia and malnutrition are the most critical clinical complications in CKD of dogs and cats if it takes take into account their contribution on morbidity and mortality (6, 7). Sometimes assisted feeding should be provided in order to minimize the risk of uremic crisis or death because it allows the feeding and prevents long periods without nutrition or liquid consumption (34, 35). The first step is to ensure that lost of appetite is due to syndromes that increase metabolic complications such as dehydration states, gastrointestinal bleeding, metabolic acidosis, hypokalemia or urinary tract infection. When these possible causes have been excluded or corrected and no improvement is seen in appetite, it is recommended to intervene. For example gastrointestinal complications are routinely treated with the administration of H2 antagonists (p.e famotidine 0.5 mg/kg q12h PO), antiemetics (Maropitant citrate 1 mg/kg q24h S.C) and gastric mucous protectors (sucralfate 40 – 250 mg/kg q12h P.O). Isolated reports suggest that the placement of a feeding tube can reduce weight loss associated with CKD (34). However, their implications for health-related quality of life and long-term outcomes are still undefined.

## Endocrine disturbances and conservative advanced therapies

### Hormone replacement and Anemia

The decrease in red blood cells count, percentage of hematocrit and hemoglobin is common in dogs and cats with CKD in stage IRIS III-IV (2). In kidney-affected patients the main cause of anemia is hypoplasia of erythroid elements secondary to inadequate production of erythropoietin (EPO) in the renal marrow and is exacerbated by the short life of the erythrocytes due to azotemia, acid-base disorders, the premature apoptosis, gastrointestinal bleeding, nutritional disorders, iron deficiency and bone marrow fibrosis (36-38). Erythropoietin hormone replacement usually leads to develop with recombinant human alpha EPO in dogs (rHuEPO; Epogen® Amgen, Thousand Oaks, CA, USA). This is highly effective but with short-live in bloodstream (39). Recent research has revealed that dogs with CKD and anemia treated with rHuEPO stabilize the hematocrit levels, the augmentation in appetite was also evidenced and health-related quality of life then improving (9). Unfortunately, the development of antibodies against rHuEPO in dogs and cats has limited its use to a minor amount of the population and therefore, the use of rHuEPO should be limited to patients with less than 22 or 20% hematocrit and signs of anemia like hypoxemia, exercise intolerance, cyanosis or heart murmurs.

Although little research has been done in veterinary medicine, darbepoetin alpha it may be less immunogenic compared with rHuEPO (40). Lu and colleagues (41) evaluated the efficacy and safety of recombinant canine erythropoietin (rCaEPO) in dogs with non-regenerative anemia secondary to CKD. They found that in dogs receiving rCaEPO, a slightly increased erythrocyte production was evident. In addition, there was hyperplasia in bone marrow, reticulocytosis, normal levels of hematocrit and direct improving of health-related quality of life. In contrast, complications related to the creation of anti-rCaEPO antibodies were very low. Furthermore, it should be known that hypertension is a complication in some human patients that are treated with rCaEPO, but there is still no evidence that support this in animals. Thus, there is disagreement on whether it is preferable to improve anemia partially or completely to avoid adverse effects like cardiovascular events, coagulation abnormalities and metabolic complications related to the use of these drugs, their dose and increased erythrocyte production and hemoglobin as a direct consequence (39). Respected to animal patients it is not clear whereas the complete correction of anemia represents a negative effect on CKD.

Other methods have shown interesting results in correcting anemia caused by CKD. Erythropoietin gene therapy has proven to be able to correct anemia in mice with induced anemia (42, 43). The peginesatide is a synthetic peptide that is not homologous to human erythropoietin, representing an absence of cross-reaction and production of anti-EPO (39). However, this drug has not been demonstrated superiority in the control of anemia, compared with the other drugs discussed above (44).

### Based therapy in Mesenchymal Stem Cells

Based therapy in mesenchymal stem cells (MSC) offered protection in different forms of acute kidney injury in humans (45) and there is good evidence of the positive effects of MSCs in reducing the loss of function of kidney in the early stages of CKD (46). Therapy with MSC has particular functions related to the release of growths factors and cytokines with a paracrine action (47, 48). Bi et al (49) demonstrated in a murine model of acute kidney injury that administration of conditioned medium derived from bone marrow mesenchymal stem cells (CM-MSC) increased the survival time and decreases progression of renal injury. The protective effect of CM-MSC apparently are related to the action of pro-angiogenic factors such as vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF) and insulin growth factor (IGF) (50). Exosomes and microvesicles may have a similar effect (51, 52).

The research developed by Van Koppen and colleagues (53) found a significant decrease in systolic blood pressure in rats with induced CKD treated with CM-MSC compared to the group of rats that not receiving CM-MSC (146 ± 17 vs 163 ± 21 mmHg; $p < 0.05$). They also found a decrease in proteinuria in rats with CKD receiving CM-MSC ($p = 0.007$). However, they found no difference in renal clearance of creatinine and urea. In contrast, plasma creatinine in rats that did not receive

CM-MSC was always higher compared with the group receiving treatment with CM-MSC ($p < 0.05$). The most important result of their research was that the higher percentage of glomerular endothelial cells present in rats receiving CM-MSC and rats that did not receive CM-MSC, presented a percentage of 31 and 26% of not sclerotic glomeruli respectively. Interstitial fibrosis and tubular atrophy was lower due to decreased deposition of collagen type I and III in rats receiving CM-MSC demonstrating that repeated administration of CM-MSC as rescue intervention of kidney function is probably due to an increase in long-term endothelial regeneration and recovery.

In summary, this novel treatment could slow down the loss of glomeruli, decrease fibrosis and alterations in glomerular function. As well as help in adjusting changes in vascular pressure, considering this latter like one important factors for life expectancy of patients with CKD and impacting the velocity of degeneration and the associated clinical signs. Furthermore, it should be necessary to review more investigation in the future to assess the impact on pets with diseases of natural progression and the evaluation of large cohorts of patients could be of help to determine the impact on life expectancy and clinical usefulness in reducing the progression of CKD and recognize the real effect of CM-MSC.

## Based therapy in Electroporation of Plasmid Growth Hormone

CKD in humans can affect growth hormone-release hormone; growth hormone; insulin-like growth factor I axis (GHRH/GH/IGF-I) (54, 55), which may affect disease progression and cell metabolism. Although little research exist in veterinary medicine about the axis (GHRH/GH/IGF-I) in CKD of natural progression; gene therapy based in plasmids growth hormone is a possible treatment in canine and cats, mainly for its influence on bone metabolism, proteins and glucose (56). GH and their mediator, IGF-I are growth regulators and maintain homeostasis in body weight and renal function. Some changes seen in patients with CKD are caused by the imbalance of the (GHRH/GH/IGF-I) axis (57, 58).

Therapy with GH produces a positive anabolic effect and helps maintain a physiological balance of renal function in people with CKD (59, 60). Electroporation (EP) is a very important technique in gene therapy because it allows a single dose with a long duration. This is a key factor to commensurate the impact of this type of drugs on the commodity of patients and owners that have complications receiving the medication or when owners cannot administer medication at intervals or schedules required by the clinician. The study published by Brown and colleagues (61) developed a multicenter control group study using gene therapy with GH and EP in dogs and cats with CKD as an animal model for CKD on humans. Acording to the results, they found out an increase in survival time and increased body weight and muscle mass. In addition, health-related quality of life was improved in the group of patients treated with GHEP. Particularly dogs treated with GHEP increased physical activity and appetite, compared with the control group ($p = 0.001$).

At the biological level increased blood-levels of IGF-I in patients treated with GHEP slightly improved hematologic parameters were found. The main reason for using these therapeutic options is to increase synthesis and bioavailability of IGF-I. This study suggests that clinical intervention with GHEP can preserve kidney function and reduce the negative effects of CKD in the health-related quality of life, especially decreasing the amount of times that the drug must be administered and the need for recurrent hospitalization. Furthermore, research are needed for recognize the long-term impact in the disease.

## Tanshinone IIA as an alternative therapeutic option in CKD

Red sage (*Salvia miltiorrhiza*) is a perennial plant, valued as one of the most important ancient medicines, describe in the Shen-Nung's Pen-Ts'ao book of herbal medicine and agriculture of traditional Chinese medicine (62). Their chemical component (salvianolic acid, Dihidrotanshinone, Tanshinone I and Tanshinone IIA) has been also studied for years, especially for its effects against cancer and degenerative inflammatory diseases. Tanshinone IIA is the most abundant chemical component of the rhizome of the plant and its particularly evaluated for the treatment of arthritis, hepatitis, acute coronary syndrome, neuropathic pain, bone tumors and Alzheimer's

disease (63-67). This molecule has antioxidant properties and protects against oxidative stress. But also, chemical component alows vasodilation by stimulating the release of Nitrous Oxide (NO) on consequent decrease in blood pressure in animal models of hypertension and with the same protective effects in people with diabetic nephropathy (68, 69).

The investigation published by Ahn et al (70) evaluated the influence of Tanshinone IIA in renal function, proteinuria and expression of angiotensin II (Ang II), transforming growth factor beta I (TGF-B1) and type IV collagen in an experimental murine model. Taking as a hypothesis the harmful relationship of the Ang II, TGF-B1 and collagen type IV in the pathogenesis of CKD and the development of glomerulosclerosis (GC), the results found that prolonged use of Tanshinone IIA (8 to 12 weeks), the proteinuria significantly decreased. Moreover, glomerulosclerosis evaluated histologically was more widespread in the group that cannot receive Tanshinone IIA (3.2 ± 0.2 vs 2.1 ± 0.1; $p < 0.05$). The protein expression analysis showed that the use of Tanshinone IIA prevents expression of (TGF-B1) (33.8 ± 4.8 vs 20.2 ± 2.9; $p < 0.05$). In contrast, the expression of type IV collagen in patients receiving Tanshinone IIA was significantly decreased (0.45 ± 0.04ng/ml, $p < 0.05$).

In conclusion these results could be demonstrate that Tanshinone IIA decreases the progression of CKD, attenuating the pathological structural manifestation of chronic kidney disease and the progressive characteristic fibrosis. Furthermore, these results must be interpreted with caution and more investigations are expected with other animal models to deeply assess their true benefit in CKD of natural progression. Nevertheless, the reason for exposing here this plant is mainly the approach of a possible integration between modern medicine and traditional medicine, due the potential beneficial impact of combined treatment with standard therapy. Taking into account, that actually different efforts exist to create the critical approach that aims to integrate alternative therapies for CKD, but with evidence-base medicine and long-term results.

## Thinking outside the box "ACE inhibitor"

In addition to the nutritional intervention and its benefits in renal protection and improvement of the health-related quality of life in dogs and cats with CKD, of all drugs studied in the last decade, angiotensin converting enzyme inhibitors (ACEI`s) have shown to be statistically the most effective. An early research with these molecules in humans was done by Lewis and colleagues (71), which evaluated the efficacy of ACEI's in treating diabetic nephropathy and initially, they efficacy was attributed to the antihypertensive effects "hemodynamic effects". However, at the time, it is well-know that their effects are not restricted to pressure. The ACEI´s are frequently used in veterinary medicine for the treatment of heart failure in dogs and cats (72, 73). These molecules are also key drugs in CKD in dogs, cats and humans.

The Renin-angiotensin-aldosterone system (RAAS), partially blocked by these ACEI's drugs, is traditionally known as an endocrine axis of control of water and salt reabsorption, commonly characterized by initial activation of renin in the kidney. Nevertheless, the production of all components of the RAAS can be synthesized in the absence of this release of renin by the kidney and could be synthesized in any organ, especially the heart, lung, brain, placenta, pancreas, adipose tissue and vascular bed (74). The difference between systemic RAAS and renal RAAS activation has a clinical importance related to ACEI's drugs use, specifically in the inhibition of tissue and plasmatic ACE. In the latter, inhibition is much lower and was confirmed by investigations of Lavoie et al (74). Moreover, the activity and concentrations of ACE, Angiotensin II and its receptor (AT-1) in the kidney are different from other organs. The renin is synthesized by cells of the juxtaglomerular cortex; angiotensinogen is secreted in the proximal tubule cells, ACE is found in large quantities in the brush border of the cell membranes of the proximal tubule and this promotes rapid conversion and levels of Angiotensin II (Ang II) rise about 1000 times more than in the general circulation (74, 75).

Angiotensin converting enzyme (ACE), not only converts Ang I to Ang II, also degrades bradykinin, with important effects on natriuresis and control of the balance between vasoconstriction and vasodilatation (76). Furthermore, Ang II is also converted by specific tissue enzymes (chymase, cathepsin G and chymostatin) (77). Angiotensin II is the most powerful end effector systems, which control blood pressure through the reabsorption

of sodium and water, stimulating receptors (AT-1 and AT-2) in the kidney or indirectly stimulating the production of aldosterone by the adrenal glands. Although ACEI's inhibit the conversion of Ang I to Ang II, these do not inhibit conversion mechanisms not ACE (chymase, cathepsin G and chymostatin) and then, Ang II levels cannot completely be suppressed. This are defined as "angiotensin breakthrough". Lantis and colleagues (77) found that aldosterone levels do not appear to decrease in patients treated with ACEI's, this also known as aldosterone breakthrough. The implications of both “breakthroughs" in the pathophysiology of cardiovascular and kidney disease as we knew are enormous and perhaps revolutionary.

Exposures to high and prolonged concentrations of aldosterone result in sodium retention, expansion of extracellular volume and fibrosis contributing to endothelial damage (75). Possible options to avoid this breakthrough are the use of drugs as Ang II receptor blockers “ARBs”, aldosterone receptor blockers or direct renin inhibitors (77). Regardless of the etiology of CKD, glomerulosclerosis and interstitial fibrosis are characteristic pathologic findings in the final stages of CKD (IRIS III-IV) (78). The RAAS activation has proven to be the cause of progressive hypertension, fibrosis, tubulointerstitial injury and increased pro-inflammatory cells in the kidney in different species including dogs and cats (74). Specifically Ang II increases the formation of Tissue Growth Factor type B1 (TGF-B1) a fibrogenic cytokine responsible not only for the increase in the synthesis but also the decreased degradation of extracellular matrix (ECM) by the expression of fibronectin, laminin, collagen, proteoglycans and entactines that develop interstitial fibrosis.

The (TGF-B1) also stimulates contraction of vascular smooth muscle and mesangial cells, the latter involved in the development of glomerulosclerosis (11). Serpin E1 (inhibitor of plasminogen activator type 1 or PAI-1) are directly related to the pathophysiology of thromboembolic events and arterial fibrotic; it’s a protein responsible for preventing fibrinolysis, by inhibiting urokinase and tissue plasminogen activator (uPA and tPA). The production of this protein increases due to the Ang II (79) causing inhibition of proteases that regulate the formation of ECM, increasing progression of glomerulosclerosis, tubulointerstitial fibrosis and increased inflammatory cells in kidney, especially macrophages (80). Another mechanism that increases the formation of ECM is the inability to self-regulate glomerular pressure. In physiological situations, variations in systemic blood pressure have little influence on glomerular arteriolar pressure, as CKD progresses this ability is lost, leaving the glomeruli exposed to very marked changes in systemic pressure and then distend the glomerular capillaries with subsequent stimulation of mesangial cell and production of TGF-B1. Thus, CKD progresses to chronic renal failure (CRF), but the authors recommend that indiscriminately both terms have been used to refer to the same concept. There may be chronic kidney disease without renal failure. However, renal failure cannot exist without chronic or acute kidney disease.

The ACEI's lower blood pressure experimentally when inhibit Ang II production and help decreasing the formation of ECM (production of TGF-B1) and these effects have been study in rodent models. One research develop by Brown and colleagues (81) started administrating Benazepril (0.25mg / kg V.O SID) for 6.5 months to cats with induced CKD, showing a decrease in glomerular pressure (< 12-14 mmHg). The relation between afferent arteriolar and efferent arteriolar resistance decreased in the cats receiving Benazepril. Other studies also confirmed these results (82). In dogs with induced CKD treated with ACEI’s, experimentally a decrease of 30% in efferent arteriolar resistance was evident, while the afferent remained unchanged (83).

Hypertension is associated with kidney damage and progressive loss of kidney filtration in people (44). Although not widely investigated in dogs and cats, there are enough reasons to extrapolate this from humans to pets with CKD. Considering the above, the use of ACEI’s as hypotensive and antisclerotic drug can benefit patients with CKD. However, the decrease in blood pressure is not evident in a percentage of the population by the breakthrough of angiotensin, the decreased plasma renin activity in some patients and high circulating levels of sodium (78). The decrease in blood pressure is dose dependent especially in cats. Using ACEI’s as Enalapril to 0.25 mg/ kg once a day, the blood pressure decrease 23%, whereas if the same dose is administered twice a day, blood pressure decreases near 41% (84). The calcium channel blockers such as amlodipine, belonging to the dihydropyridine drugs, is the first

choice in the treatment of high blood pressure in cats and can be used in a joint with ACEI's therapy to treat patients with uncontrolled hypertension and CKD (85).

Proteinuria is caused by alterations in the permeability and selectivity of the glomerular membrane, such as mechanical factors (excessive pressure), incomplete coverage of the glomerular podocytes caused by hypertrophy through toxins or immune complexes in the surface. The ACEI's are protective for future increases of proteinuria, despite the molecular and cellular mechanisms under its antiproteinuric effect at the time cannot yet fully elucidated. Several hypotheses exist and one is the molecular modulation of podocytes. Podocytes are visceral glomerular cells, lining the outside of the glomerular basement membrane; this being the final barrier to the loss of protein (86, 87). The author Asanuma and colleagues (86) recently reviewed the importance of podocytes in the progression of damage, glomerulosclerosis and progression of renal disease. The first decrease in proteinuria appears to be development by decreasing blood pressure (78, 88).

Enalapril and benazepril has been the most ACEI drugs documented to decrease proteinuria. Urinary Protein creatinine ratio (UP/C) decreases approximately 4.2 times in patients treated with Enalapril vs 1.9 times in feline patients treated with placebo (83, 88). In summary, the use of ACEI's in patients with CKD modulate blood pressure, renal excretion of protein and slows the rise on blood creatinine levels. Moreover, reduction of the incidence of decompensation in the final stages of the disease is one of the critical benefit (78, 88, 89). The effectiveness is dependent when ACEI treatment starts (90). Overall, it has been admitted that the administration of ACEI's early in the course of CKD improve the antihypertensive, anti-proteinuric and antiesclerotic effects (11, 75, 90).

The ACEI's has been shown to increase survival time by 36% in patients with CKD (88). Moreover, changes in diet and simultaneously medication with ACEI's produces an increase of 53% life expectancy (73). CKD has the consequences that decrease the concentration of plasma proteins due to their loss through the affected glomeruli (90) and the use of ACEI's showed that in cats with CKD also contributes to maintaining stable levels of protein in plasma. However, further research is recommended to interpret some missing issues of the mechanism of action of these drugs. Finally, it is unquestionable that the ACEI's remain the critical drugs of choice in CKD for dogs and cats.

## Conclusions

After discussing about different treatment options, it is clear that further research is needed to develop better treatments and optimize the use of current therapy. Furthermore, the integrated management of proteinuria, clinical symptoms and the changes in biosynthesis, are unquestionably, factors influencing the health-related quality of life, survival time and disease progression. Recommended here, treatments are part of that integrated management, although individually reported each effects on the CKD, the joint use of these therapies and drugs may have superior effects. Nevertheless, it is important to recommend that every patient is different, their status, initial condition, the variability of disease and its approach are factors to be necessarily taken into account and the need to treat several patients in a specific way not will necessarily be the same in another.

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## KRITIČEN PRISTOP K ALTERNATIVNI OBRAVNAVI KRONIČNE ODPOVEDI LEDVIC PSOV IN MAČK

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**Povzetek:** Kronična odpoved ledvic (CKD – iz angl. chronic kidney disease) se pogosto pojavlja pri psih in mačkah katerekoli starosti, pogostejša je pri starih pacientih. Z različnimi oblikami bolezni in njihovimi raznolikimi hemodinamskimi in presnovnimi različicami se ukvarja veliko raziskav. Trenutno izboljšanje celostnega zdravljenja kronične odpovedi ledvic se osredotoča na upočasnitev napredovanja kliničnih simptomov bolezni, obstaja pa vedno več novih metod za ta način zdravljenja v nereferenčnih centrih. Cilj predlaganega kritičnega pristopa je zagotoviti celovito obravnavo kronične odpovedi ledvic ter izpostaviti nove načine zdravljenja, ki bi lahko izboljšali poseganje v zdravje psov in mačk s kronično odpovedjo ledvic in ponovno oceno uporabnosti nekaterih obstoječih zdravil.

**Ključne besede:** kronična odpoved ledvic; kardiorenalni sindrom; glomerulonefritis; pes; mačka