ADVANCE VETERINARY DIETS

Research reports

A RESEARCH UPDATE FOR THE VETERINARIAN FROM AFFINITY PETCARE

CHRONIC KIDNEY DISEASE (CKD) IN DOGS AND CATS

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How can nutrition help?

1 INTRODUCTION

Chronic kidney disease (CKD), also called chronic renal disease (CRD) and, at its final stage, chronic kidney failure (CKF) - is a process in which there is a progressive loss of functional renal tissue. It is a frequent and common problem in dogs and cats.

2 EPIDEMIOLOGY

- The prevalence of kidney diseases has been reported to range from 0.5 to 7% in dogs and from 1.6 to 20% in cats
- CKD commonly increases with age: the structural and functional changes of the kidney affect approximately **15% of dogs 10 years of age or older and 33% of cats 15 years of age or older** (Polzin et al., 1989) (Figure 1 and 1a)).
- Approximately 5% of all deaths in dogs and 3% of all deaths in cats are attributable to renal failure (Burkholder, 2000).
- Laboratory samples tested for chronic kedney disease show evidence of presence in approximately 50% of dogs with Leishmaniasis (Cortadellas et al, 2008).

FIGURE 1. IIncidence of chronic kidney disease in cats according to age *(adapted from Polzin et al, 1989)*

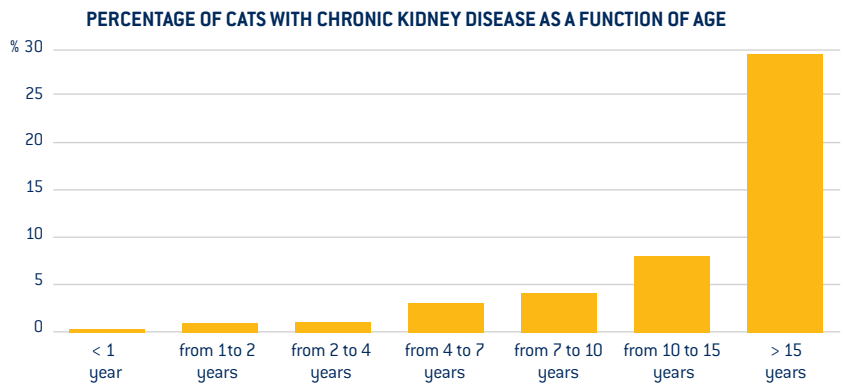


FIGURE 1A. Incidence of chronic kidney disease in dogs according to age *(adapted from Polzin et al., 1989)*

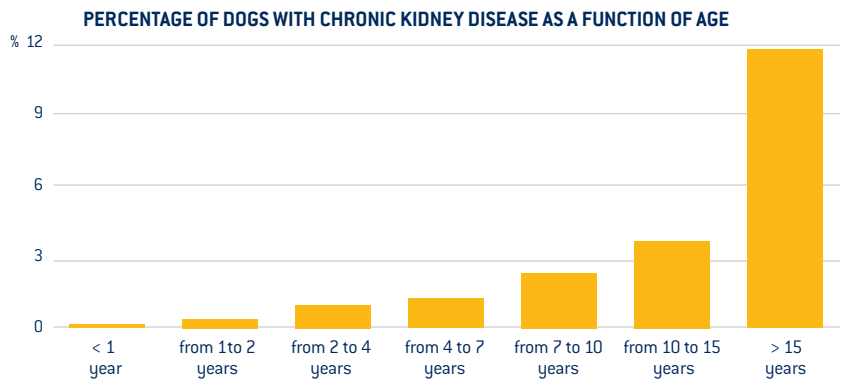


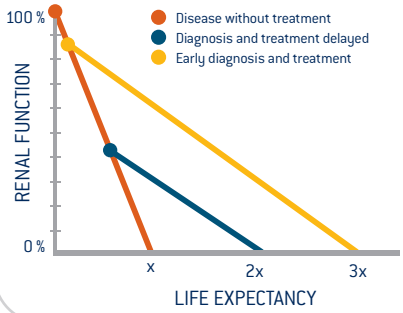
TABLE 1. Health benefits of a renal diet for dogs and cats with chronic kidney disease (CKD)

			WITHOUT RENAL DIET	WITH RENAL DIET	
Cat	2 years	Uremic crisis	26%	0	Ross et al., 2006
		Renal-related death	22%	0	
Cat		Median life expectancy	264 days	633 days (x 2.4)	Elliott et al., 2000
Cat		Median survival	210 days	480 days (+ 9 months)	Platinga et al., 2005
Dog	2 years	% of dogs with uremic crisis	65%	33% (72% risk reduction)	Jacob et al., 2002
		Period free from uremic crisis	252 days	615 days	
		% death (all causes)	94%	52%	
		% deaths from renal causes	65%	33% (69% risk reduction)	
		Median survival	188 days	594 days (x3.2)	

- 96% of veterinarians recommend a dietary change in cases of CKD (veterinarian interviews done by Affinity).

Most dogs and cats die within 2 to 3 years after a diagnosis of kidney disease is made, although there is considerable variation in the duration of the survival period (Burkholder, 2000). Both the cause, and the length of time that the disease remains undiagnosed and untreated, influence the duration of the survival period of the animal after kidney disease is recognized (Figure 2), highlighting the importance of finding markers that allow early and site-specific detection of kidney dysfunction (Grauer 2005).

FIGURE 2. Potential benefit of early diagnosis and treatment of Chronic Kidney Disease *(adapted from Grauer, 2005)*



It has been demonstrated that appropriate dietary management can significantly improve the quality of life (uremic crisis) and life expectancy of affected dogs and cats. (Table 1)

3 DIAGNOSIS OF CKD

The best way to diagnose kidney disease is by assessing the glomerular filtration rate (GFR). In general, routine examination of kidney function evaluates blood and urine biochemistry, giving an indirect analysis of endogenous markers (Table 2).

Recently, the IRIS [International Research Interest Society] staging system has been proposed for evaluating severity and evolution of the disease (Figure 3). According to IRIS, chronic kidney disease is classified into stages based on stable serum creatinine concentration and into sub-stages based on level of proteinuria and hypertension (Tables 3, 4 & 5); all these factors are associated with disease severity and survival.

A consensus for each condition has been proposed which offers the best medical management according to stage and sub-stage (Lees et al, 2005; Brown et al, 2007). In the early stages, the main goal is to treat the etiology and prevent development. Once the disease has developed, clinical signs have to be treated.

4 PHYSIOPATHOLOGY

Numerous causes of CKD have been identified in dogs and cats (Table 6). These disorders induce pathophysiological changes in the nephron (within glomeruli, tubules, interstitial tissue or blood vessels) and finally render the entire nephron non-functional (Figure 4). Renal histopathology preparations usually show some combination of a loss of tubules (replaced by fibrosis and mineralization), glomerulosclerosis and glomerular atrophy, and foci of mononuclear cells (small lymphocytes, plasma cells, and macrophages) within the interstitium.

The theory of hyperfiltration supports the progression from renal injury to renal insufficiency. When nephrons become non-functional, homeostasis is maintained by the remaining nephrons, which undergo compensatory changes (increases in size and length of glomerular and tubular segments, increases in perfusion and fractional clearance of blood through the kidneys). These compensatory mechanisms are beneficial in the short term but ultimately are damaging to the kidneys, eventually causing more nephrons to be destroyed. At this point, in the majority of cases an improvement of renal function is not possible, and management of the CKD patient is aimed at reducing "renal workload," with a consequent reduction of the clinical signs associated with the decreased renal function (Finco et al, 1999; Burkholder 2000).

TABLE 2. Some parameters for estimating renal function

BIOCHEMICAL PARAMETERS	**Glomerular function** Blood urea nitrogen (BUN) Creatinine Proteinuria (mainly albumin & low molecular weight protein)
	Tubular function Urinary density Low molecular weight proteinuria Blood/urine Na, K, P, pH
DYNAMIC PARAMETERS	GFR determination (by creatinine, inulin, ...)
PHYSIOLOGICAL CHANGES	Intra-glomerular capillary tension
HISTOLOGICAL CHANGES	Glomerular hypertrophy, sclerosis or atrophy. Loss of tubules (replaced by fibrosis and mineralization), with presence of lymphocytes, plasma cells and macrophages in the interstitium

TABLE 3. CKD stages using the IRIS system as a function of serum creatinine concentration

STAGE	CREATININE (MG/DL)	COMMENTS	CHARACTERISATION	TREATMENT
I	<1.4 in dogs <1.6 in cats	Non-azotemic Confirmed renal disease present	• Renal disease (etiology) • Change in renal function	• Disease-specific therapy
II	1.4-2.0 in dogs 1.6-2.8 in cats	Mild renal azotemia (lower end of the range overlaps within reference) Clinical signs usually mild or absent	• Renal disease • Change in renal function • Individual patient specific problems	• Disease-specific therapy • Reno-protective therapy
III	2.1-5.0 in dogs 2.9-5.0 in cats	Moderate renal azotemia, many extra-renal clinical signs may be present	• Renal disease • Change in renal function • Individual patient specific problems • Try to characterize	• Reno-protective therapy • Disease-specific therapy • Symptomatic
IV	>5.0 in dogs and cats	Severe renal azotemia Many extra-renal clinical signs	• Patient specific problems	• Symptomatic (reno-protective therapy)

TABLE 4. IRIS system sub-stages as a function of protein/urinary creatinine ratio [UP/C]

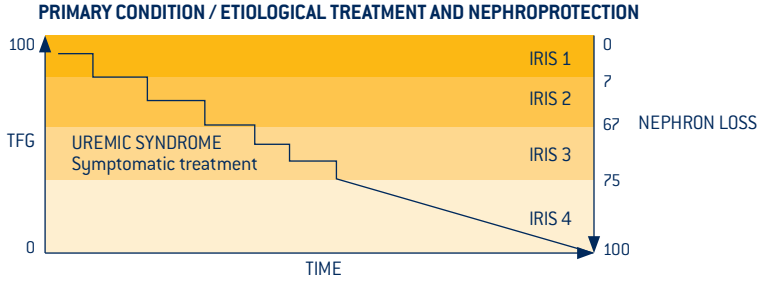
UP/C VALUE	INTERPRETATION
<0.2 in dogs and cats	Non-proteinuria
0.2–0.4 in cats 0.2–0.5 in dogs	Borderline proteinuria
>0.4 in cats >0.5in dogs	With proteinuria

TABLE 5. IRIS Sub-stages as a function of arterial blood pressure

RISK*	SYSTOLIC (mm Hg)	DIASTOLIC (mm Hg)
Minimal	<150	<95
Low	150–159	95–99
Moderate	160–179	100–119
High	≥180	≥120

*Risk = likelihood that high pressure will further damage the kidney and other affected organs

FIGURE 3. Evolution of glomerular filtration rate (GFR) and % nephron loss according to IRIS stage



5 THE ROLE OF DIET IN THE MANAGEMENT OF CKD

To understand how nutrition can help patients with CKD, it is important to remember the physiological function of the kidneys and clinical signs of CKD [Table 7]. The dietary treatment functions at three levels in order to improve clinical signs, encourage macro and micro-nutrition (energy, amino acids, vitamins, minerals...) and delay the progression of the disease [Figure 6].

» WATER

Water intake is very important to compensate water loss due to urine dilution and to avoid dehydration. To increase water intake, feeding wet food or spraying water on dry food can be done.

» PALATABILITY

In dogs and cats, the so called "uremic syndrome" may be responsible for anorexia, nausea, vomiting, stomatitis, gastrointestinal tract ulceration and an altered sense of taste and smell. These changes often contribute to reduced appetite and malnutrition. Cachexia may contribute to the uremic syndrome, including increased susceptibility to infection, delayed wound healing, and decreased strength and vigour. Therefore, prevention of protein-calorie malnutrition by (ensuring adequate nutrient intake) is crucial.

A gradual transition to the renal diet over 2 to 4 weeks is recommended. An appetite stimulant can be given if needed.

» ENERGY

Consuming sufficient energy prevents protein-calorie malnutrition. It is recommended to administer a diet with a high energy density that allows animals with a low appetite to eat a smaller amount of food but to still cover their food needs (also reducing gastric bloat and likelihood of nausea and vomiting). However, excessive energy should be avoided since in cats, diets higher in calories have been associated with an increased number of non-glomerular lesions (Finco et al., 1998).

» FAT

Increased dietary fat is generally recommended as fat contains twice the energy of carbohydrates, it is palatable, and is a source of fat soluble vitamins. It has been shown that fat supplementation rich in omega-3 fatty acids is beneficial for CKD patients.

- In cats, high EPA (eicosapentaenoic acid) content seems to be a key factor for longer survival : in a recent study of renal diets the longest survival was in the group whose diet had the highest EPA level and 53 g protein/kcal (Plantinga et al, 2005) (Figure 7).

TABLE 6. Causes of CKD in dogs and cats

CONGENITAL RENAL DISEASES (BREED SPECIFIC)	ACQUIRED RENAL DISEASES
Amyloidosis	**Idiopathic and autoimmune**
Glomerulopathy	Chronic interstitial nephritis (54% of cats)
Glomerulonephropathy	Glomerulopathy
Polycystic disease	Glomerulonephritis
Renal dysplasia	Immune complex
Protein losing nephropathy	Amyloidosis
Fanconi syndrome	**Infections**
Autosomal nephropathy	Pyelonephritis (10% cats)
Basal membrane dystrophy	Leptospirosis
Renal agenesis	Piroplasmosis
Congenital malformations	Leishmaniasis
	Cancer
	Anaphylactic shock
	Metabolic diseases
	Cushing's syndrome
	Hypercalcemia
	Metabolic urolithiasis
	Toxic and iatrogenic
	Vascular diseases
	Trauma and obstruction/ Hydronephrosis (neoplasms, stones, ...)

FIGURE 4. Schematic representation of the kidney and the nephron

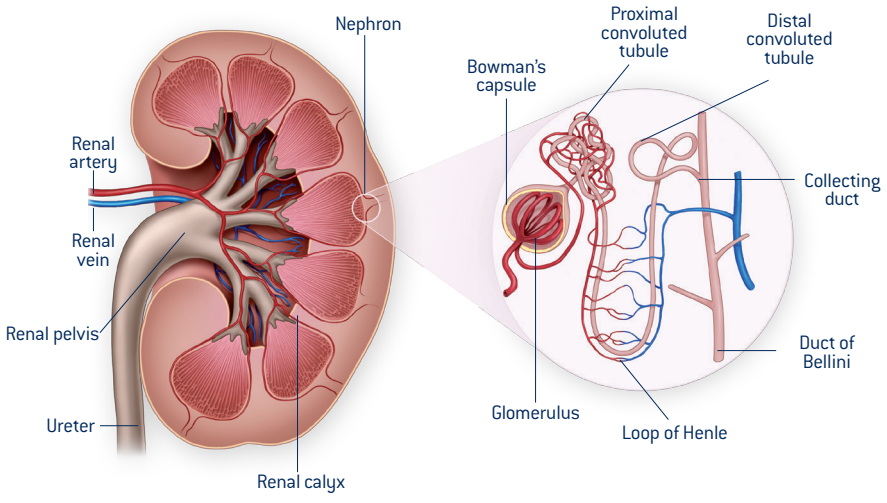


FIGURE 5. Pathophysiology of renal failure: hyperfiltration theory

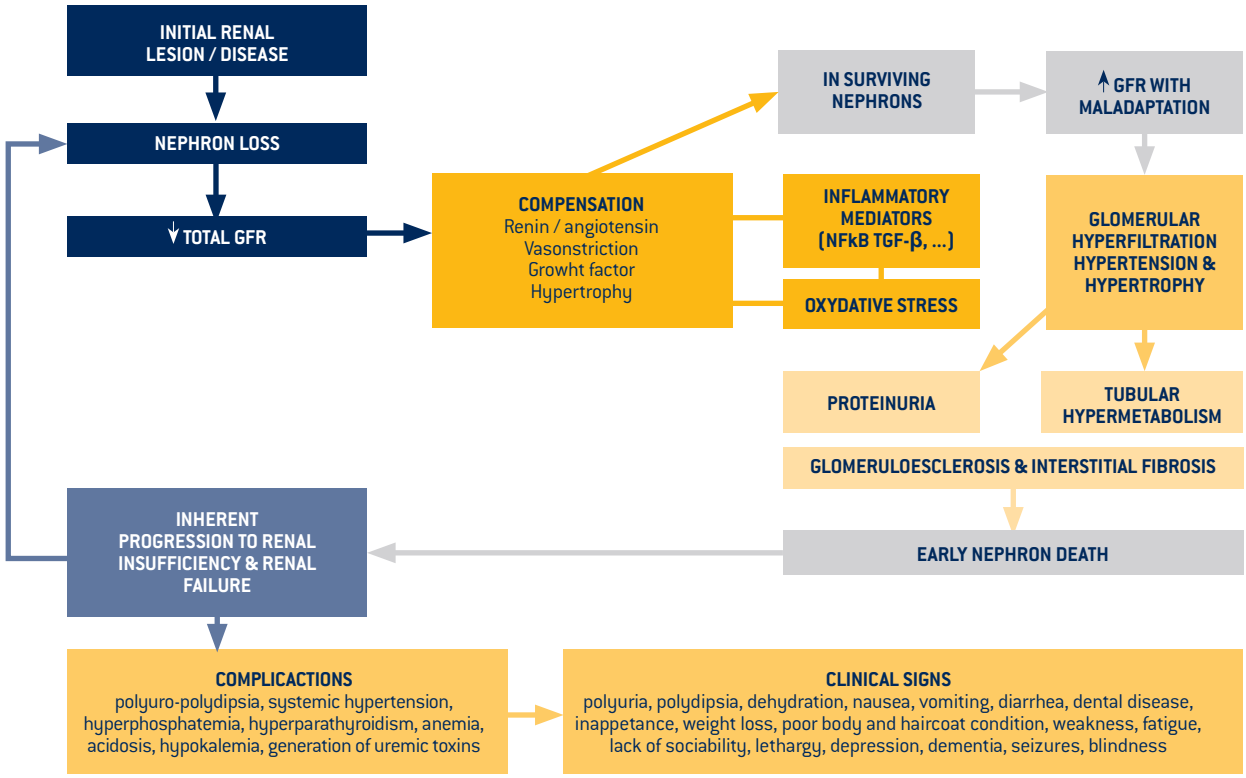


TABLE 7. Normal kidney functions, their alteration in case of chronic kidney diseases, laboratory modifications in blood and urine, clinical signs and possible dietary support

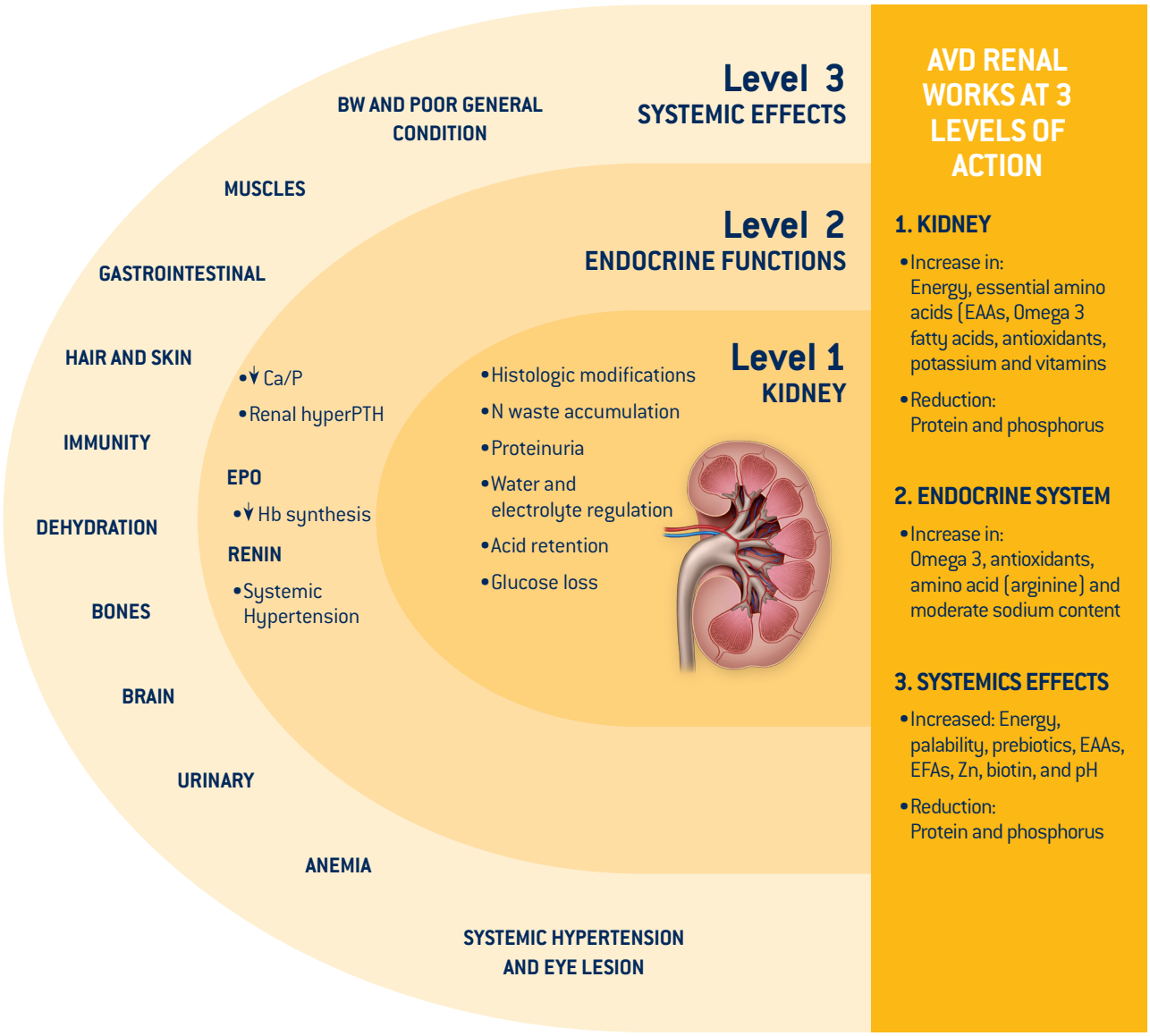
KIDNEY FUNCTIONS	CKD ALTERATIONS			DIETARY SUPPORT
Glomerular and tubular functions	**Glomerular and tubular functions**	**Laboratory result modifications**	**Clinical signs**	
Excretion of toxins and metabolic waste	Uremia and azotemia	Azotemia	Weight loss, polyuria,polydipsia,	Protein restriction
Filtration, secretion and reabsorption (aa, glucose, P, Ca, Na, K, H,...)	Nutrient loss (glucose, protein, ions,...)	Decreased urinary density	Dehydratation, Gastrointestinal	Energy
Water and electrolyte regulation	Water and electrolytes disequilibrium	Proteinuria	Anorexia, nausea, vomiting	Protein quality
Acid base status	Metabolic acidosis	Hypokalemia (20-30% cats)	Gastroenteritis, stomatitis, gingivitis, halitosis	Nutrient balance
Endocrine functions	Renal hyperparathyroidism	Metabolic acidosis	Oral ulceration	Palatability
P and Ca metabolism (calcitrol)	Anemia	Hyperphosphatemia	Gastric ulceration	Vitamins
Hemoglobin synthesis (EPO)	Hypertension	Hypocalcemia	Ptyalism	Water
Arterial tension regulation		Non-regenerative anemia	Constipation (cats)	K
(ie renin-angiotensin-aldosterone, atrial system, ...)		↓Platelet function	Lethargy , weakness, apathy	pH control
		Bacterial urinary infection	Behaviour changes	P restriction
		Small kidney on palpation	Uremic encephalopathy	Arginine
			Hyperparathyroidism	Antioxidants
			Hyperlipidemia	Moderate Na restriction
			Anemia	ω3 FAs
			Systemic arterial hypertension and ocular injury	

Clinical signs are not evident until more 70% of the nephrons stop functioning

- In dogs, fish oil supplementation is associated with fewer renal structural lesions, less hypertension and glomerular hypertrophy, less proteinuria, better preservation of GFR, and better lipid metabolism (Brown et al 1996, 1998, and 2000) (Figure 8).

It is recommended to maintain the ratio between Omega 6/Omega 3 fatty acids at around 5 to prevent a decrease in cell immunity, taking account of the high percentage of dogs infested with Leishmaniasis that suffer from CKD.

FIGURE 6.The 3 target levels of the nutritional management of renal diseases in dogs and cats



To improve food intake, it is necessary for the diet to be very tasty

» PROTEIN, PROTEIN SOURCE, AMINO ACIDS

The rationale of **protein restriction** is based on the following assumptions:

- There is general acceptance of the theory that decreased excretion of protein catabolites contribute significantly to uremic signs and to many laboratory sample abnormalities found in CKD patients.
- In rats with CKD, it has been shown that protein restriction decreases glomerular hypertension and hyperfiltration.
- In *in vitro* cell-tests, proteins have been shown to be toxic to tubular epithelial cells (inflammation or enzymatic degradation).
- Proteins are a rich source of phosphorus and generally their metabolism increases uric acid and promotes metabolic acidification, all these factors having a negative impact on renal function.

However, canine and feline studies using a remnant kidney model (which is not the same as the natural occurring disease) have failed to demonstrate an association between dietary protein *per se* and lesions in the renal tissue or effects on longevity (Finco et al, 1998, McCarthy et al, 2001). The observed positive effects of protein restricted diets may be due to protein or phosphorus restriction, a combination of both,

or additional confounding factors (such as omega 3 fatty acids, acid base balance, sodium, potassium,...).

The diet should meet protein needs of kidney patients to prevent the mobilization of endogenous proteins and any signs of protein deficiency such as: hypoalbuminemia, anemia, weight loss, muscle wasting, poor hair quality and cachexia. In practice, a **moderate protein restriction** is still recommended.

Protein quality (i.e. with high digestibility and high in essential amino acids) is important as well. The objective is to match essential amino-acids requirement, optimize protein and urea synthesis while maintaining minimum nitrogen waste and NH3 production.

Arginine (involved in urea cycle and hypertension) and branched chain amino acids (for muscular mass synthesis) are particularly important for this pathology.

L- Arginine (Arg) is synthesised from glutamine, glutamate and proline via the intestinal-renal axis; it is an essential amino acid for cats and dogs and it is conditionally essential in other species. Arg is involved in urea synthesis (urea cycle) and is required for the detoxification of ammonia. Arg degradation pathways also produce NO (Nitric oxide) which is a potent vasodilator and is required for normal endothelial function.

Arterial hypertension (due to Na retention, renin-angiotensin–aldosterone system, ...) is a common complication in CKD patients (20-69% of cats, 0-36% dogs, 80% if glomerulopathy is present), for which the preservation of endothelial function is required.

Studies of canines and felines performed with a model using residual kidney tissue have not demonstrated an association between dietary protein *per se* and renal tissue lesions or effects on longevity

When considering arginine supplementation in patients with renal disease it is important to maintain a ratio of Arginine/Lysine below 2.5 to avoid a Lysine deficiency as both amino acids compete for entry into cells.

» PHOSPHORUS [P] AND PHOSPHATE BINDERS

Secondary hyperparathyroidism is a common complication in CKD patients (figure 9).

The restriction of phosphorus is an important dietary modification to be made from the earliest stages of the disease:

- In cats, a high phosphorus content diet (1.4 vs 0.4% DM basis) causes mineralization and renal fibrosis (Ross et al., 1982).
- In dogs, high dietary P (1.5 vs 0.44%) is associated with a greater decrease in GFR and reduced survival (Finco et al, 1992).

If dietary restriction is insufficient to maintain phosphatemia (dog 26-62mg/l, cat 25-81mg/l), P binders must be administered.

A positive effect of protein restriction has sometimes been hypothesised as being due to P restriction (confounding factor).

» ACID-BASE STATUS

The acid/ base balance is determined by the following ions :

- bases: magnesium (Mg), calcium (Ca), sodium (Na), potassium (K)
- acids: phosphorus (P), chlorine (Cl), sulphur (S) (in addition to the sulphur amino acids, methionine and cysteine)

Metabolic acidosis is frequent in cats (53-88% cats in severe stages, 15% in moderate stage), due to decreased H+ elimination and decreased re-absorption of HCO3 (Elliott et al, 2003) (Figure 10). Because many commercial feline diets induce a slightly acid pH (to prevent urolithiasis), it is important to switch the cat to an adapted diet.

On the other hand, metabolic acidosis is also a common complication of CKD in dogs. The potential benefits of controlling metabolic acidosis may include (Dow et al, 1990; DiBartola et al, 1993; Mitch 1997; Elliott, 2006):

Avoid diets excessively rich in fats to limit side effects on the gastrointestinal tract

FIGURE 7. Median survival (months) of cats with CKD fed different foods *(adapted from Platinga et al., 2005)*

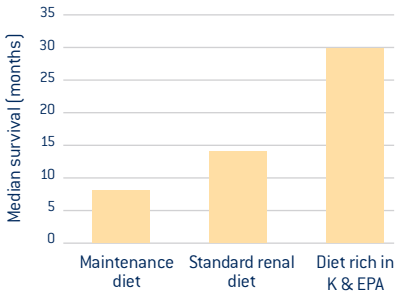
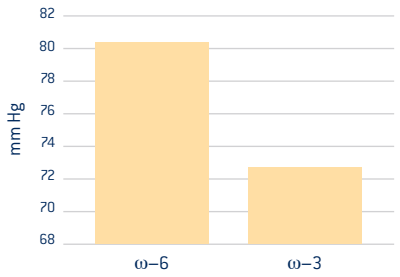


FIGURE 8. Glomerular capillary pressure in dogs fed diets rich in ↓3 or ↓6 polyunsaturated fatty acids *(adapted from Brown et al., 2000)*



- clinical signs that are mostly caused by uremic acidosis; metabolic acidosis can induce K loss and may result in anorexia, vomiting, and general weakness.
- preventing the catabolic effects of metabolic acidosis on protein metabolism, a key issue for muscle protein catabolism.
- limiting skeletal losses resulting from bone buffering
- limiting progression of kidney disease

A gradual change of diet over 2 to 4 weeks is recommended

» POTASSIUM (K)

Hypokalemia is a frequent complication, mainly in cats (20-30% CKD cat); the cause is unknown but it could be explained in part by increased urinary and digestive hemorrhages. It can be responsible of polymiopathy, tubule-interstitial nephropathy, polyuria, intestinal atony and bradycardia. Before supplementing with potassium, it is important to check for hyperkalemia which is toxic, and in dogs with CKD consuming a therapeutic diet, hyperkalemia seems to be more frequent than hypokalemia (47% vs 14%) (Segev et al, 2010).

» SODIUM (NA)

Sodium intake has to be balanced. An excessive restriction can favour extracellular dehydration and acidosis but an excess can potentially induce hypertension and edema.

» B GROUP VITAMINS

Supplementation is recommended to compensate for greater losses through increased diuresis.

» FIBRES

For digestibility, crude fibre should be less than 4%, but soluble/fermentable fibres may be beneficial for several reasons:

- To improves digestive health (that can be affected in CKD patients) (Simpson, 1998)
- For a prebiotic effect (favouring growth of beneficial bacteria) (Younes et al, 2004, Verbrugghe et al, 2010).
- These beneficial bacteria utilise plasma urea ("natural enteral dialysis") which lowers BUN.
- Propionate produced by fermentation is gluconeogenic sparing amino acids for other functions. Therefore, replacing non fermentable fibres by fermentable fibres allows an increased N fecal excretion to the detriment of urinary excretion.

» ANTIOXIDANTS

In dogs and cats with CKD, some authors have shown an increased oxidant stress that contributes to renal interstitial fibrosis, glomerulosclerosis, glomerular hypertension, systemic and renal inflammation, and progressive decline in kidney function (Brown, 2008; Yu and Paeteau-Robinson, 2006; Keegan and Webb, 2010).

Important generators of reactive oxygen species (ROS) in the kidneys are glomerular cells, tubular cells, and activated macrophages. In chronic kidney disease (CKD), the surviving renal tissue becomes adaptively hyperfunctional, leading to a dramatic increase in cellular oxidative phosphorylation. This, in combination with decreased antioxidant defenses leads to oxidative damage (Figure 5).

Natural dietary antioxidant (vitamins A, C, and E; carotenoids; flavonoids; and polyphenols) and ω-3 fatty acids (that decrease the generation of pro-inflammatory eicosanoids) are recommended respectively to enhance oxidative defense and reduce ROS production. In dog models, both approaches are additive in reducing a decline in GFR, and antioxidant addition improves proteinuria, glomerulosclerosis and interstitial fibrosis (Brown, 2008). In cats with spontaneous renal insufficiency, dietary supplementation with vitamins E and C, and beta-carotene significantly reduced DNA damage (Yu and Paetau-Robinson, 2006).

Synergy effects from antioxidants (vitamins E, C, ...) will also help the immune response in the case of an infection by Leishmania in dogs.

FIGURE 9. Pathophysiology of secondary renal parathyroidism

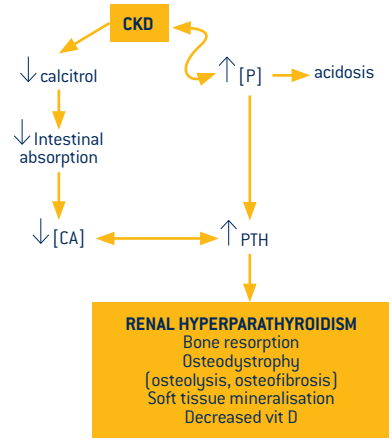
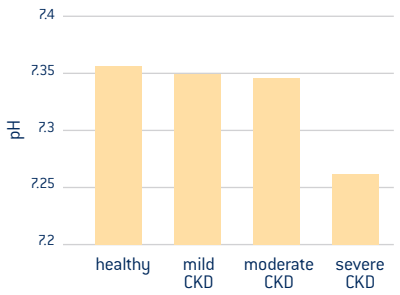


FIGURE 10. Mean venous pH healthy cats and in cats with to severe CKD
(adapted from Elliott et al, 2000b)



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