PATHOGENESIS AND METHODS OF DIAGNOSIS OF CHRONIC KIDNEY DISEASE IN CATS: RETROSPECTIVE ANALYSIS (1981–2007)

Dmytro Morozenko, Roman Dotsenko, Yevheniia Vashchyk, Andriy Zakhariev, Seliukova Nataliia, Andrii Zemlianskyi, Ekaterina Dotsenko

The aim: to conduct a retrospective analysis of literature sources on the pathogenesis and methods of diagnosis of chronic kidney disease in cats.

Materials and methods. The research was conducted by the method of scientific literature open-source analysis: PubMed, Elsevier, electronic resources of the National Library named after V.I. Vernadsky (1981–2007).

Results. Chronic kidney disease is a common reason for cat owners to go to veterinary clinics. The term “chronic kidney disease” has a broader meaning than the more limited and not very specific name – chronic renal failure; it is also used to indicate the preazotemic stage of the disease. Chronic kidney disease is characterized by a gradual deterioration of the clinical condition of animals due to progressive decline in renal function. An idea of the pathogenesis and methods of diagnosis of chronic kidney disease in the period from 1981 to 2007 is presented.

Conclusions. According to the results of retrospective analysis of literature sources for the period from 1981 to 2007, the basis was identified aspects of the pathogenesis of chronic kidney disease in domestic cats, which have not lost relevance today. The main link during chronic kidney disease in cats is the development of hyperazotemia and, as a consequence, endogenous intoxication of the body, which develops gradually and leads to the death of the animal. The morphological basis of chronic kidney disease in cats is the development of diffuse nephrosclerosis, which is reflected in the results of clinical, biochemical and instrumental studies. According to biochemical analysis of blood, in cats recorded an increase in urea and creatinine, the results of clinical studies of urine showed a decrease in its relative density, as well as the development of proteinuria, the appearance of erythrocytes and cylinders. According to the results of hematological research, anemic syndrome develops due to decreased erythropoietin synthesis. With age in cats, ultrasound examination of the kidneys reveals a decrease in their volume due to uniform sclerosis of the parenchyma; it is determined by its thinning and increased echogenicity due to the accumulation of connective tissue components, which is a sign of nephrosclerosis. Although kidney biopsy is the most informative method of diagnosing chronic kidney disease, it has many contraindications, which does not allow its use in the routine diagnosis of nephropathy in domestic cats. Its thinning and increase in echogenicity due to the accumulation of connective tissue components, which is a sign of nephrosclerosis, is determined.

Keywords: chronic kidney disease, age, cats, pathogenesis, diagnosis, azotemia, endogenous intoxication

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1. Introduction

Chronic kidney disease is a common reason for cat owners to go to veterinary clinics. The concept of chronic kidney disease (CKD) has a broader meaning than the more limited and not very specific name – chronic renal failure (CRF); it is also used to indicate the preazotemic stage of the disease. CKD is characterized by a gradual deterioration of the clinical condition of animals due to progressive decline in renal function. Although the disease can affect animals of any age, its prev-
alence increases markedly during aging, resulting in the diagnosis of approximately 8% of cats over 10 years of age and 15% of cats over 15 years of age [1, 2]. According to S.A. Brown (2005), the incidence of kidney disease in cats is 0.5–2% of the total population of this species. However, the provision of therapeutic care is sought mainly by owners of aging animals [3]. According to materials collected at Purdue University, in 1980 renal failure was diagnosed in 4 cats per 1,000, and by 1990 this figure had risen to 16 animals per 1,000 [4]. In the age group of cats older than 15 years, CRF is found in every third animal [5]. A study of 13 clinically healthy cats over 7 years of age showed that all animals had creatinine levels above normal, with some cats having elevated blood urea levels. According to some authors, CRF is often one of the leading causes of death in older cats [3, 6]. According to the results of studies of the age predisposition of cats to the development of CRF, it was found that males with CRF were younger than females (average age 12 and 14 years, respectively), and the breed is not important in the development of this pathology [7].

In general, CRF in cats is a progressive disease, it is necessary to determine its stages for adequate therapy. In veterinary medicine, the International Renal Society (IRIS) has developed a system for classifying CRF stages to standardize the diagnosis and treatment of diseases in dogs and cats. According to it, based on the results of determining the amount of creatinine in the serum of all patients divided into 4 groups by stages of the disease: Stage I (non-azotemic) – blood creatinine less than 140.0 mmol/l in the presence of symptoms of kidney disease; Stage II (mild renal azotemia) – 141.0–250.0 mmol/l; Stage III (moderate renal azotemia) – 251.0–440.0 mmol/l; Stage IV (severe renal azotemia) – more than 440.0 mmol/l [8].

Thus, CRF is common in cats older than 8 years and is the leading cause of death. The causes of kidney failure in most cases go unnoticed for many years. This is due to the great adaptive potential of the kidneys, their ability to compensate for the damage caused by intact nephrons. However, over time, such adaptation leads to increasing destruction of the glomeruli and tubular apparatus of the kidneys, resulting in the development of CRF [9].

According to D. A. Eliot, CRF in cats is a clinical syndrome that occurs due to the irreversible loss of metabolic, endocrine and excretory functions by the kidneys [10]. It is very important to be able to differentiate CRF from acute renal failure. Despite the importance of such differentiation, there is no “gold standard” that distinguishes between chronic and acute renal failure. There are some clinical signs, but it is very difficult to make such differentiation alone. These complications are exacerbated by the fact that animals may have an exacerbation of CRF [11]. Thus, CRF in cats is a progressive disease. However, the nature of the primary disease, the dynamics of its development and symptoms are unique to each patient and correspond to the stage of the pathological process. According to CRF in cats, it is important that diagnostic and therapeutic approaches are adequate stages of the disease [12].

The aim of the research to conduct a retrospective analysis of literature sources on the pathogenesis and methods of diagnosis of chronic kidney disease in cats (1981–2007).

2. Materials and methods
The research was conducted by the method of scientific literature open-source analysis: PubMed, Elsevier, electronic resources of the National Library named after V. I. Vernadsky (1981–2007).

3. Research results
3.1. Pathogenesis of chronic kidney disease in cats
According to CRF, cats have permanent irreversible damage to kidney tissue – normal tissue is gradually replaced by scarring (or mineralized), and the number of functioning nephrons decreases [13]. Histopathologically, CRF in cats is characterized by interstitial fibrosis, glomerulosclerosis on the background of chronic inflammatory process in the kidneys [11]. Thus, the morphological substrate of CRF is glomerulosclerosis. Regardless of primary renal pathology, it is characterized by glomerular depletion, mesangial sclerosis, and extracellular matrix expansion, the main components of which are laminin, fibronectin, proteoglycan heparansulfate, type IV collagen, and interstitial collagen, which is normally absent in glomeruli. Despite the variety of etiological factors, morphological changes in the kidneys during severe CRF are the same and are reduced to the predominance of fibroblastic processes with the replacement of functioning nephrons by connective tissue, hypertrophy of the remaining nephrons [14].

CRF causes disorders of endocrine balance, electrolyte metabolism, acid-base balance, lipid peroxidation and antioxidant system activity, loss of antioxidant defense factors, impaired hemostasis, erythrocytosis and functional activity of platelets [15]. In animals, as a result of the growth of connective tissue, part of the glomerular apparatus is excluded from the general circulation, the capillaries of the affected areas cease to function. Impaired blood circulation in the kidneys increases the formation and release of renin and angiotensin into the blood, which in turn leads to hypertension and myocardial hypertrophy. As the process progresses, the glomeruli and tubules die. The result is polyuria and the development of uremia. Significant deterioration of the diseased animal contributes to metabolic acidosis due to incomplete excretion of acidic metabolic products [16]. Recently, the role of medium molecules in the pathogenesis of CRF – products of normal life of the organism – has been widely and well-argued studied, although their true role in this pathology remains unclear. As early as 1976, F. Furst et al. [17] proved that the content of these substances has no correlation with the level of serum creatinine and urea, and they are insufficiently removed by hemodialysis. Medium molecules include about 30 substances with certain biological activity – vasopressin, oxytocin, neurotensin, angiotensin, parathyroid hormone, adrenocorticotropic hormone, glucagon, calcitonin, vasoactive intestinal peptide, secretin, motilin, sleep factors, endocrine agents, whey proteins, the activity of intestinal bacteria. Of particular importance is parathyroid hormone, the classic target organs of which are myocardial cells, visceral and vascular smooth muscle, pancreas and thymus, liver vessels and brain neurons, which explains the damage to many organs in the progression of CRF [18, 19].

It is known that the development of nephrosclerosis is based on chronic inflammatory processes of the kidneys, which in the conditions of their long-term development lead
to changes in most nephrons with the replacement of glomeruli by connective tissue. In chronic glomerulonephritis, the inflammatory process in the glomeruli is characterized by increased hyperplasia of mesangial cells, proliferation of the glomerular capillary network and capsule endothelium, collagenization of capillary membranes and the appearance of lymphoid cell infiltrates. At the same time, acid glycosaminoglycans and glycoproteins accumulate in the kidney tissue [20].

Thus, in the pathogenesis of CRF the leading role belongs to the connective tissue, quantitative changes, and qualitative restructuring of which lead to disruption of the structure and distortion of renal function.

### 3.2. Diagnosis of chronic kidney disease in cats

In the early stages of CKD, clinical symptoms are nonspecific or absent. Blood and urine tests are needed to make an accurate diagnosis. Glomerular function can be assessed by glomerular filtration rate and urinary protein excretion. Also, to examine the condition of the renal tubules determine the relative density and osmolarity of urine, fractional clearance of electrolytes, conduct a test with water deprivation [9, 21]. According to CRF in cats, the relative density of urine is usually lower than 1.015. But some cats with compensated CRF may excrete urine with a relative density of about 1.030 [22].

The traditional method of assessing renal function is to determine the concentration of substances in the blood plasma that are normally excreted in the urine. The content of urea and creatinine in blood serum is most often determined [23]. These parameters are indicators of renal function and glomerular filtration rate. The determination of urea in blood serum is used more often, although the creatinine content is the best indicator, not affected by diet and the level of protein breakdown [22]. Creatinine is constantly formed in the muscles as a result of creatine metabolism. It is excreted only in the urine, passing completely through the glomeruli in the kidneys and only slightly exposed to the renal tubules [24]. According to K. Sasaki et al. (2003), in cats one of the serum markers of inflammation is amyloid A, the content of which increases rapidly with the development of renal failure [25]. Measurement of glomerular filtration by insulin clearance is even more accurate, but this analysis is rarely used in practice [22, 23].

Proteinuria can develop at any stage of CRF, but its intensity is determined by the etiology of the disease, which is based on damage to the glomerular filter [24, 26]. Plasma urea concentration is also important for the diagnosis of CRF. Some researchers believe that this indicator correlates better with the clinical signs of the latter than the concentration of creatinine.

Electrolyte disorders (hyperphosphatemia, hypokalemia, hypocalcemia) are noted in the period of significant renal dysfunction, but they are absent in the early subclinical stages. However, it is known that the study of electrolyte balance to determine the level of decreased renal function is uninformative. The same can be said about the degree of anemia [15].

Biochemical examination of urine is also important in the diagnosis of renal dysfunction. In chronic glomerulonephritis and chronic pyelonephritis, the metabolism of renal connective tissue changes in the early stages, which is manifested by increased excretion of oxypoline and glycosaminoglycans in the urine, and is important for early diagnosis of nephrosclerosis and, of course, CRF [27]. It is known that in cats with secondary renal hyperparathyroidism, which develops on the background of CRF, the content of calcium and phosphorus in the urine is reduced [22]. With the development and progression of CRF, the concentration capacity of the kidneys decreases [27]. This reduces the level of excretion of urea, creatinine, calcium and phosphorus [13]. According to S. Arata et al. (2005), transforming growth factor (TGF-beta1), an inflammatory cytokine found in the urine of cats and used as a marker of renal tissue fibrosis, plays a role in the development of glomerular and tubulo-interstitial fibrosis [28].

Recently, the hypothesis of medium molecules is increasingly gaining the attention of nephrologists. This hypothesis helps to study the course of kidney disease, in particular CRF [29, 30]. Based on the results of the research, a relationship was found between the stages of CRF, determined by traditional methods (Reberg test) and the average molecules [31].

To assess the functional state of the kidneys, such calculated indicators as urea concentration factor, creatinine concentration index and renal tubular reabsorption coefficient are used [32–34]. Thus, a decrease in tubular reabsorption is observed in acute and chronic pyelonephritis, chronic glomerulonephritis, nephrosclerosis, and other diffuse kidney lesions [35].

During the progression of CRF, the symptoms of uremia increase due to the accumulation of nitrogenous toxins in the blood and changes in water-electrolyte metabolism. Hypoplastic anemia is observed in patients with CRF, which is expressed in a significant decrease in the amount of hemoglobin, erythrocytes and erythropoietin, neutrophilic leukocytosis with a shift of the nucleus to the left, in severe cases – an increase in erythrocyte sedimentation rate. Protein, erythrocytes and cylinders are found in urine. The level of creatinine and urea in the blood serum increases, the level of calcium, sodium decreases, the content of potassium, magnesium and phosphorus increases. The pH of the blood is reduced, which corresponds to the development of metabolic acidosis [35, 36]. According to studies by J. Elliot et al. (2003), a decrease in urine pH was observed in 52.6 % of cats with CRF at the stage of severe azotemia, with moderate azotemia – In 15 %, with a slight decrease in pH did not occur. This suggests the impossibility of using urine pH as a diagnostic test to detect CRF in the early stages [37].

According to the literature [38], in domestic cats to assess renal function can be used caucine, or carboxyesterase – a protein that is excreted in domestic cats, based on the proximal straight tubules of the kidneys. The level of this protein decreases in tubulo-interstitial nephritis when normal cells of the renal tubules are replaced by fibroblasts.

Thus, in the diagnosis of CRF a wide range of clinical, laboratory and biochemical studies plays an important role and allows to obtain quantitative objective criteria for the stages of CRF development, including early, which allows you to plan and conduct timely and effective treatment.

Among the instrumental methods of diagnosing kidney disease in cats most often use radiography, ul-
transude, a special place is occupied by renal biopsy. There is also evidence that the study of the fundus has a special place in the diagnosis of nephropathy in cats, in particular, CRF [39]. More sophisticated research methods, such as radiology, computed tomography, magnetic resonance imaging and renal arteriography, can potentially be important, but are not widely used in veterinary practice [40].

Radiography is not very important in the diagnosis of kidney disease. Simple pictures can only show the size and shape of the kidneys. If overt hyperparathyroidism is observed, X-rays show low bone density (especially of the upper jaw) and soft tissue calcification, although this is rare in cats. Radiography may be of diagnostic value in congenital kidney disease (polycystic kidney disease), but in most cases of renal failure, the contrast of the kidneys in the images does not increase, or they look small and uneven [22]. Also, radiography may confirm the assumption of kidney damage during injury [41].

According to Weiden (2005), ultrasound can provide more accurate information about the size and shape of the kidneys, as well as the renal parenchyma, than radiography. In CRF, there is a general increased echogenicity of the kidneys and blurred boundaries of the cortical and cerebral layers [11]. Due to its high resolution, nephrosonography provides ample opportunities in the diagnosis of morpho-functional changes in the kidneys and diffuse alternative processes. In addition, ultrasound is considered the most informative method for the initial detection of patients with renal disease [42]. Of particular interest are diffuse alternative processes in the renal parenchyma, as kidney damage is associated with similar morphosonographic characteristics, regardless of which disease they are [43–45].

When performing ultrasound diagnosis, a complete scan of both kidneys in cats is always performed in the transverse and longitudinal planes, which allows you to determine the size of the kidneys more accurately, otherwise focal spots will be detected [46].

It is known that ultrasound signs of diffuse kidney damage are not specific to a particular kidney disease. With the development of nephrosclerosis, renal tissue is difficult to differentiate from the surrounding tissue, because the parenchyma is condensed due to intimal hyperplasia, increased elastic fibers, hyalinosis, sclerosis of arterioles and glomerular capillaries. This causes increased echogenic properties. Due to the fact that the surface of the kidneys becomes uneven, large and small bumps, there is tissue destruction – nephron cirrhosis, which disrupts not only morphological but also ultrasound differentiation of the renal layers. Thus, in cats of different sex, age and breed in the norm and in nephrosclerosis established correlations of morphological and sonographic characteristics [47].

With age, sonography of the kidneys in cats shows a decrease in their volume due to uniform sclerosis of the parenchyma: it is determined by its thinning and increased echogenicity due to the accumulation of connective tissue components. The reason for this picture is vascular lesions of the parenchyma (angionephrosclerosis), often in combination with pyelonephritic changes [45]. It is known that in chronic pyelonephritis, depending on the stage of the disease, polymorphism of echo-}

6. Conclusions

According to the results of retrospective analysis of literature sources for the period from 1981 to 2007, the basis was identified aspects of the pathogenesis of chronic kidney disease in domestic cats, which have not lost relevance today. The main link in the course of CKD in cats is the development of hyperazotemia and, as a consequence, endogenous intoxication of the body, which develops gradually and leads to the death of the animal. The morphological basis of CKD in cats is the development of diffuse nephrosclerosis, which is reflected in the results of clinical, biochemical and instrumental studies. According to biochemical analysis of blood, in cats recorded an increase in urea and creatinine, the results of clinical studies of urine showed a decrease in its relative density, as well as the development of proteinuria, the appearance of erythrocytes and cylinders. According to the results of hematological research, anemic syndrome develops due to decreased erythropoietin synthesis. With age in cats, ultrasound examination of the kidneys reveals a decrease in their volume due to uniform sclerosis of the parenchyma: it is determined by its thinning and increased echogenicity due to the accumulation of connective tissue components, which is a sign of nephrosclerosis. Although kidney biopsy is the most informative method of diagnosing CRF, it has many contraindications, which does not allow its use in the routine diagnosis of nephropathy in domestic cats.

Conflict of interests

The authors declare that they have no conflict of interests.

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Dmytro Morozenko*, Doctor of Veterinary Sciences, Senior Researcher, Head of Department, Department of Veterinary Medicine and Pharmacy, National University of Pharmacy, Pushkinska str., 53, Kharkiv, Ukraine, 61002

Roman Dotsenko, PhD, Senior Researcher, Associate Professor, Department of Veterinary Medicine and Pharmacy, National University of Pharmacy, Pushkinska str., 53, Kharkiv, Ukraine, 61002

Yevheniia Vashchyk, Doctor of Veterinary Sciences, Associate Professor, Department of Veterinary Medicine and Pharmacy, National University of Pharmacy, Pushkinska str., 53, Kharkiv, Ukraine, 61002

Andrii Zakhariev, PhD, Associate Professor, Department of Veterinary Medicine and Pharmacy, National University of Pharmacy, Pushkinska str., 53, Kharkiv, Ukraine, 61002

Andrii Zemlianskyi, PhD, Assistant, Department of Veterinary Medicine and Pharmacy, National University of Pharmacy, Pushkinska str., 53, Kharkiv, Ukraine, 61002

Nataliia Selukova, Doctor of Biological Sciences, Associate Professor, Department of Veterinary Medicine and Pharmacy, National University of Pharmacy, Pushkinska str., 53, Kharkiv, Ukraine, 61002

Ekaterina Dotenko, PhD, Senior Researcher, Laboratory "Veterinary Sanitation and Parasitology", National scientific center «Institute of Experimental and Clinical Veterinary Medicine», Pushkinska str., 83, Kharkiv, Ukraine, 61023

*Corresponding author: Dmytro Morozenko, e-mail: d.moroz.vet@gmail.com