

## Effectiveness of complex treatment of cats for chronic kidney disease

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### Abstract

Treatment of cats with chronic kidney disease should be aimed at slowing the progression of the disease, which contributes to the preservation of residual kidney function, the elimination of clinical signs of CKD, and the quality of life of sick animals. During the II stages of chronic kidney disease in cats, hyporexia (60 %), polyuria and polydipsia (50 %), anemia of mucous membranes (60 %), impaired coordination of movements (30 %), vomiting and ulcerative stomatitis (40 %), an increase in serum levels of creatinine and urea ( $P > 0.001$ ), the level of symmetric dimethylarginine ( $P < 0.001$ ), the concentration of cystatin C ( $P > 0.001$ ), a decrease in the rate of glomerular filtration, the level of total calcium ( $P < 0.001$ ), an increase in the level of inorganic Phosphorus and Potassium. Arterial hypertension was established in 8 cats; the risk was moderate ( $148 \pm 4.7 / 98 \pm 3.8$  mmHg). Changes in the physical properties and chemical composition of urine have been established. The application of complex treatment of cats with II stages of chronic kidney disease for 14 days contributed to the restoration of appetite, increased motor activity, the absence of anemia of visible mucous membranes and vomiting, and a decrease in the level of polyuria and polydipsia was established. Hematological indicators improved, the content of symmetric dimethylarginine in blood serum ( $P < 0.001$ ), Cystatin C ( $P < 0.001$ ), the level of total calcium ( $P < 0.001$ ) normalized, azotemia decreased ( $P < 0.001$ ), the rate of glomerular filtration increased ( $P < 0.001$ ), the level of inorganic Phosphorus and Potassium ( $P < 0.001$ ). An increase ( $P < 0.001$ ) in the relative density of urine and a decrease in the content of protein and creatinine were noted in the urine. For arterial hypertension in cats with chronic kidney disease, life-long therapy is indicated, which is adjusted according to the needs and condition of the animal.

**Keywords:** cats; treatment; II stage of chronic kidney disease; diagnostic markers; hematological indicators; biochemical indicators; arterial hypertension; urine.

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### 1. Introduction

Kidney diseases in cats occupy a significant place in the structure of internal pathology, among which chronic kidney disease (CKD) is the most frequently diagnosed. Chronic kidney disease is a set of pathological processes accompanied by damage to kidney tissue, leading to the appearance of azotemia, combined with a violation of the concentration ability of the kidneys, with a partial or complete violation of the formation and excretion of urine due to a decrease in the rate of glomerular filtration (McLeland et al., 2015; Vaden & Elliott, 2016; Yu et al., 2022).

The peculiarity of this pathology is that its symptoms are manifested only when 65–80 % of the functional tissue is affected, which requires early diagnosis and treatment (Roudebush et al., 2009; Yatsyna & Suprovych, 2021).

Since renal replacement therapy (dialysis and transplantation) is not widely available in veterinary medicine, the treatment of cats with chronic kidney disease focuses on

early detection of pathology, maintenance of the animal's welfare, renoprotective treatment, which is designed to slow down the progressive loss of nephrons, elimination of general symptoms (hypertension, loss weight, dehydration) and permanent tubular damage (Bartges, 2012; De Santis et al., 2022).

The main goal of therapy for cats with chronic kidney disease is to identify and eliminate the cause of kidney damage. Suppose it is impossible to establish the cause of the disease. In that case, treatment should be aimed at eliminating the complications of CKD and improving the quality of life of the sick animal (Morozenko et al., 2023).

An equally important problem is the treatment of cats suffering from CKD with pronounced arterial hypertension (AH), which should be based on the results of complex diagnostics, including tonometry and clinical signs characteristic of hypertension. Adverse effects of antihypertensive therapy may include decreased renal function and weakness

and short-term loss of consciousness due to hypotension (Sent et al., 2015; Geddes & Aguiar, 2022).

The research aims to determine the therapeutic effectiveness of the developed treatment scheme for cats with the second stage of chronic kidney disease.

## 2. Materials and methods

The research was conducted in the small animal clinic of the Department of Animal Internal Diseases and Clinical Diagnostics of the Stepan Gzhytskyi National University of Veterinary Medicine and Biotechnologies Lviv.

During the work, 86 cats were examined, of which 37 had chronic kidney disease, and 26 had arterial hypertension (AH). When developing a treatment regimen for cats with chronic kidney disease, we used only conservative methods. A group of 10 cats, including 8 with arterial hypertension, was selected for the experiments. The control group included ten clinically healthy animals. Chronic kidney disease was diagnosed in cats older than 6–7 years (70 %) and older than ten years (30 %) of various breeds (British, Persian, Scottish, Angora, and half-breeds). All animals were studied according to the following scheme: collection of anamnestic data (age, sex, breed, body weight), clinical examination, tonometry, and laboratory tests of blood and urine.

Blood sampling from cats was carried out from the subcutaneous vein of the forearm. Hematological studies were performed using a Mythic 18 analyzer, and biochemical tests were performed using an automatic biochemical analyzer, “Mindray BS-120” (China), using PZ Cormay S.A. reagents. (Poland). A general urinalysis was performed using a urological analyzer, “URYXXON Relax Vet”, and a test strip, “Medi-Test Combi 10 Vet”, and urine sediment was obtained on the collection day. Tonometry was performed with a “Pet MAP+II” tonometer.

Symmetric dimethylarginine (SDMA) in blood serum was determined by the immunofluorescence method, and cystatin C content was determined by the immunoturbidimetric method in the veterinary laboratory “Labovet” in Lviv.

Cats with chronic kidney disease were given pronefr (phosphate binder, a drug that binds phosphates in the intestines); the suspension was given orally two times a day with food or after feeding; ipaketin powder (phosphate binder) orally 1 measuring spoon two times a day with feeding for one month. Animals that had vomiting were administered the antiemetic drug maropitant citrate (Serenia, Nivomit) at a dose of 1 mg/kg of body weight once a day. With arterial hypertension – azomex (active substance – S-amlodipine – blocker of slow calcium channels), in a dose of 0.1 to 0.5 mg once a day. All animals received Hills k/d diet chow and had constant access to fresh water. With clinically pronounced dehydration, polyion solution (Sterofundin ISO) was administered intravenously in a dose of 20 to 50 ml per kg of body weight at a rate of 4 ml per kg of weight/hour.

Control of treatment effectiveness was carried out on the 5th, 10th, and 14th days based on the results of blood and urine tests. The effectiveness of antihypertensive therapy was monitored by measuring arterial blood pressure, increasing the interval between determination of control indicators up to 2 months after adjustment, and establishing an effective dose of the drug.

Research results are given following the International System of Units recommended for use in clinical laboratory practice. The research results were analyzed using the Statis-

tica 7.0 software package (StatSoft Inc., USA). Data are presented in the table as  $x \pm SD$  ( $x \pm$  standard deviation). We used Tukey's test to compare the difference in mean parameters between control and experimental groups, where differences were considered statistically significant at  $P < 0.05$  for all data.

The recommendations of the “European Convention for the Protection of Vertebrate Animals Used for Research and Other Scientific Purposes” (Strasbourg, March 18, 1986) were followed during the research.

## 3. Results and discussion

During the II stages of horseradish kidney disease in cats, hypoxia (60 %), polyuria and polydipsia (50 %), anemia of mucous membranes (60 %), impaired coordination of movements (30 %), vomiting and ulcerative stomatitis (40 %) were noted. A significant increase in azotemia was established, accompanied by an increase in creatinine and urea content ( $P > 0.001$ ) compared to clinically healthy animals and a tendency to a decrease in glomerular filtration rate –  $115.8 \pm 1.43$  ml/min/1.73. The level of symmetric dimethylarginine in the blood serum of cats was higher ( $P < 0.001$ ) compared to the control group and was, on average,  $21.30 \pm 0.64$   $\mu$ g/dL. The concentration of cystatin C in the blood serum of cats with impaired kidney function increased ( $P > 0.001$ ) by 13.9 %. A violation of mineral and bone metabolism was established, characterized by a decrease ( $P < 0.001$ ) in the level of total calcium and an increase in the level of inorganic Phosphorus and Potassium in the blood serum of cats. Arterial hypertension was established in 8 cats; the risk was moderate ( $148 \pm 4.7 / 98 \pm 3.8$  mmHg) (Ostrovskiy & Slivinska, 2023).

A peculiarity of cats is the ability to secrete a small amount of concentrated urine from an acidic reaction. Changes in the physical properties and chemical composition of urine have been established. In particular, the urine of cats is light yellow, transparent, and has a weak smell, which indicates its low concentration. The average specific gravity of urine was  $1.016 \pm 0.11$ . 80 % of the animals were diagnosed with proteinuria and microalbuminuria, increased protein to creatinine (UP/C) ratio, and hematuria – in 20 %. Microscopy of the urine sediment revealed the presence of erythrocytes, leukocytes, hyaline and granular cylinders, epithelial cells, bacteria, and crystals.

Chronic kidney disease is an irreversible process, and the treatment of cats should be individualized for each patient depending on the stage of the disease, which is based on the concentration of symmetrical dimethylarginine (SDMA) and creatinine in the blood serum of animals, according to the classification (IRIS) (Carney et al., 2016).

Treatment of sick cats with CKD and severe arterial hypertension should be based on the results of complex diagnostics, including tonometry and clinical signs characteristic of hypertension. Systemic measurement of arterial blood pressure indicates the degree of risk of chronic kidney disease. It is an essential factor in establishing the diagnosis and avoiding the unjustified use of antihypertensive drugs. Adverse effects of antihypertensive therapy may include decreased renal function weakness and short-term loss of consciousness due to hypotension (Lawson & Jepson, 2021).

Dietary modification is an essential and proven aspect of treating cats with chronic kidney disease. Therapeutic diets limited in protein, Phosphorus, and sodium and high in wa-

ter-soluble vitamins, fiber, and antioxidant concentrations can prolong and improve the quality of life of cats with chronic kidney disease (Markovich et al., 2014).

After the treatment of cats for 14 days, according to the results of a clinical study, it was established that the appetite was restored, motor activity increased, there was no anemia of visible mucous membranes and vomiting, and the level of polyuria and polydipsia decreased.

It was established not only the improvement of the clinical condition of cats but also an increase in the number of erythrocytes, hemoglobin content, hematocrit, red blood indices, a decrease in the number of leukocytes, normalization of the content of symmetric dimethylarginine, cystatin C in the blood serum, a decrease in azotemia, the level of inorganic Phosphorus and Potassium, an increase in the speed of glomerular filtration, level of total calcium. An increase ( $P <$

0.001) in the relative density of urine and a decrease in the content of protein and creatinine were noted in the urine.

In cats in the II stage of CKD, almost all hematological indicators were at the lower limit of physiological fluctuations. Although the number of erythrocytes increased ( $P < 0.001$ ) during treatment by 24 % and averaged  $7.3 \pm 0.38$  T/L. 100 % of cats were diagnosed with a decreased hematocrit decrease ( $P < 0.001$ ) compared to clinically healthy animals. After the treatment on the 5th, 10th, and 14th day, this indicator increased by 10.1 %, 24.8 %, and 45 %, respectively. The increase in hematocrit in cats was due to an increase in the number of erythrocytes since their average volume remained unchanged.

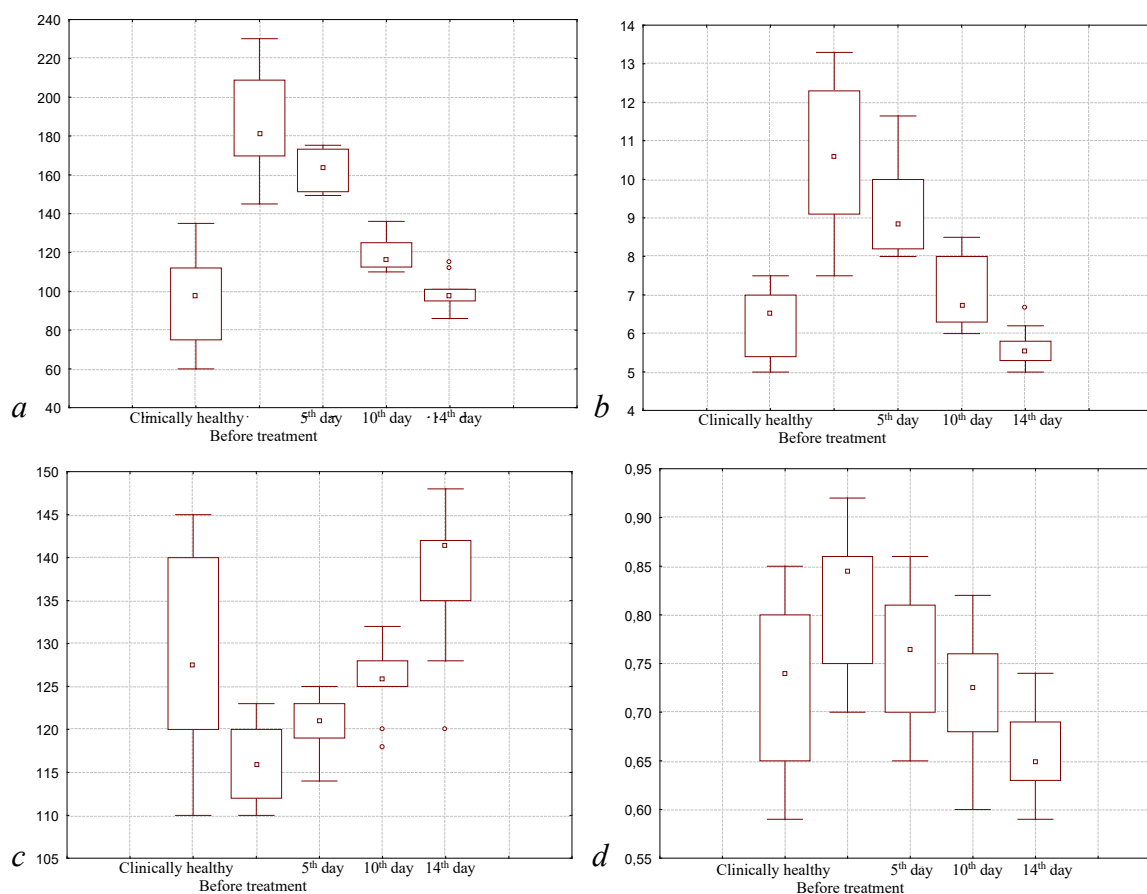
Regarding indicators of the functional state of the liver, we found that in cats, these indicators were at the upper limit of physiological fluctuations at the beginning of treatment and gradually decreased during treatment (Table 1).

**Table 1**

Effect of treatment on some biochemical indicators of blood of cats for the II stage of chronic kidney disease

Indicators	Clinically healthy, n = 10	Before treatment n = 10	5 <sup>th</sup> day n = 10	10 <sup>th</sup> day n = 10	14 <sup>th</sup> day n = 10
Total protein, g/L	55.6–75.0 $65.5 \pm 2.09$	62.8–75.8 $68.8 \pm 1.38$	63.3–68.0 $65.4 \pm 1.37$	59.0–64.7 $62.5 \pm 0.94^*$	55.6–70.0 $63.4 \pm 1.56$
Albumin, g/L	27.5–38.0 $31.9 \pm 1.04$	24.7–38.5 $33.4 \pm 1.26$	27.3–34.5 $32.4 \pm 0.86$	30.4–35.6 $32.6 \pm 0.90$	27.5–35.0 $31.3 \pm 0.80$
ALT, UN/L	15.0–40.4 $32.6 \pm 1.04$	48.5–67.9 $56.8 \pm 2.06^{***}$	46.2–58.0 $51.4 \pm 0.96^*$	43.5–49.4 $46.8 \pm 1.31^{***}$	35.0–45.0 $38.2 \pm 1.39^{***}$
AST, UN/L	18.0–42.0 $31.5 \pm 2.65$	44.0–59.6 $50.8 \pm 1.62^{***}$	41.3–49.3 $44.8 \pm 1.18^*$	36.0–45.0 $40.7 \pm 1.48^{***}$	25.0–42.0 $35.4 \pm 1.57^{***}$

Note:  $P < 0.05^*$ ;  $P < 0.01^{**}$ ;  $P < 0.001^{***}$  – compared to the beginning of treatment and clinically healthy subjects



**Fig. 1.** The effect of treatment on the content of creatinine, urea, glomerular filtration rate, and cystatin C in the blood serum of cats with II stages of chronic kidney disease: a – creatinine content ( $\mu\text{mol/l}$ ); b – urea content ( $\text{mmol/l}$ ); c – glomerular filtration rate ( $\text{ml/min/1.73}$ ); d – cystatin C content ( $\text{mg/l}$ ). Different letters indicate that data sets are significantly ( $P < 0.05$ ) other according to Tukey's test with Bonferroni correction

As a result of biochemical studies of the blood of cats with the II stage of chronic kidney disease, it was established that the urea level was within the physiological range after the treatment. At the same time, the creatinine content decreased ( $P < 0.001$ ) almost two times on the 14th day of treatment compared to the beginning of the experiment (Fig. 1).

Such a decrease in creatinine may indicate hypertrophic changes in the glomerular apparatus of the kidneys, which improves their excretory function (Tymoshenko et al., 2019).

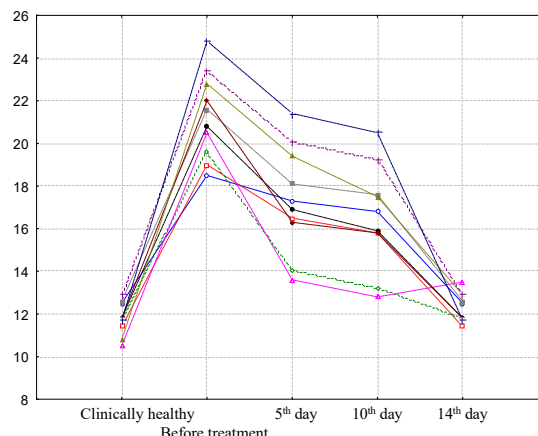
After treatment of cats with II stages of chronic kidney disease, the average glomerular filtration rate increased ( $P < 0.001$ ) by 16.3 % compared to the beginning of treatment, and the content of cystatin C decreased ( $P < 0.001$ ) by 19.5 %, respectively (Fig. 1).

Cystatin C in blood serum is negatively correlated with the value of glomerular filtration rate (GFR) and is a sensitive marker of impaired glomerular filtration rate, especially in the absence of an increase in creatinine content.

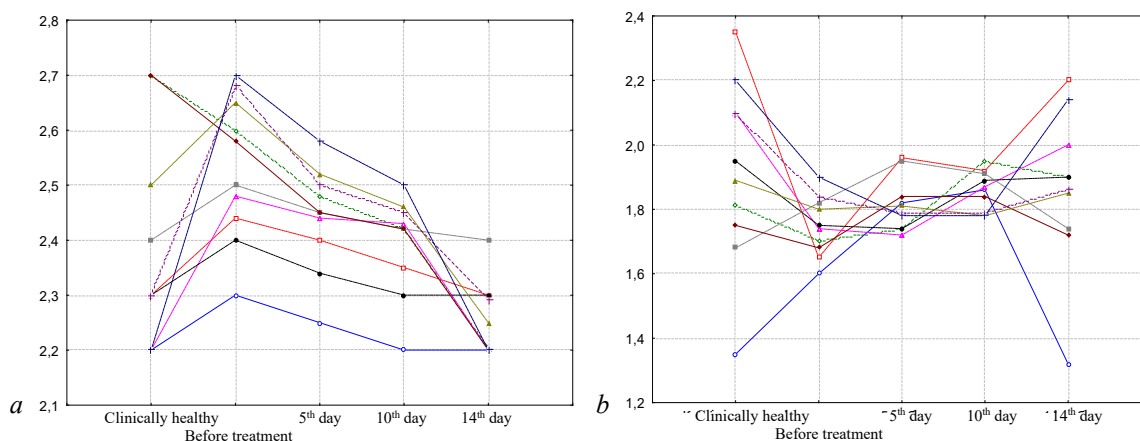
We found that the level of symmetrical dimethylarginine in the blood serum of cats after the 14th day of treatment decreased by 42.2 % compared to the beginning of the therapy (Fig. 2).

After 14 days, an increase ( $P < 0.001$ ) in the level of total calcium by 12.4 % compared to the beginning of treat-

ment was established. The increase in this indicator was facilitated by an increase in glomerular filtration and a weakening of tubular reabsorption (Ross et al., 2006; Quimby et al., 2015). The level of inorganic Phosphorus throughout the treatment was within the physiological range, although it tended to increase.



**Fig. 2.** The effect of treatment on the level of symmetric dimethylarginine in the blood serum of cats with II stage CKD ( $\mu\text{g/dL}$ ).



**Fig. 3.** The treatment effect on total calcium and inorganic phosphorus content in the blood serum of cats with II stages of chronic kidney disease: *a* – content of total calcium (mmol/L); *b* – inorganic phosphorus Phosphorus (mmol/L).

The content of Potassium in the blood serum of cats on the 5th day of treatment increased by 15.3 % ( $P < 0.01$ ), by 10 – 18.4 % ( $P < 0.001$ ), and on the 14th day – by 23.6 % ( $P < 0.001$ ) compared to the beginning of the experiment.

Treatment of cats also had a positive effect on urine parameters. In particular, on the 14th day, the relative density of urine increased ( $P < 0.05$ ). Proteinuria disappeared, compared to the beginning of treatment, which indicates an improvement in the concentration function of the kidneys, and this is associated with hypertrophy of intact nephrons (Morozenko et al., 2023). It should be noted that the hydrogen indicator in the urine of cats was within the physiological range, which indicates the low informativeness of this indicator for chronic kidney disease. Indicators of protein content in urine and urinary protein index creatinine (UP/C) were also normalized. This indicates a slowing down of disease progression and the development of glomerular fibrosis (glomerulosclerosis).

Antihypertensive therapy in complex treatment reduced systolic blood pressure from 30 to 60 mm Hg. For arterial

hypertension in cats with chronic kidney disease, life-long treatment is indicated, which is adjusted according to the needs and condition of the animal.

Thus, the treatment scheme for cats with II-stage chronic kidney disease is quite effective. It has a positive effect not only on the clinical condition of animals but also normalizes indicators of erythrocytopoiesis, protein and macroelement exchanges, helps reduce azotemia, accelerates glomerular filtration, reduces the content of symmetrical dimethylarginine, cystatin C in the blood, normalizes the physical properties and chemical composition of urine, which allowed to continue duration and improve the quality of life and health of cats.

#### 4. Conclusions

1. At the II stages of chronic kidney disease in the blood serum of cats, an increase in the content of diagnostic markers symmetrical dimethylarginine by 44.6 % ( $P < 0.001$ ), cystatin C by 13.9 %, a decrease in GFR by

9.5 % ( $P < 0.001$ ) was established. The biochemical indicators of the blood of cats were characterized by an increase in the content of creatinine and urea by 1.9 and 1.7 times, total protein by 4.9 %, albumin by 4.5 %, AAT by 38.1 %, AAT by 42.6 %, and as well as total calcium by 5.9 %, a decrease in inorganic Phosphorus 8.9 % and Potassium by 27.1 % compared to clinically healthy animals. A decrease in specific gravity to  $1.016 \pm 0.11$ , proteinuria, and an increase in creatinine were found in the urine.

2. The use of complex treatment of cats with II stages of chronic kidney disease for 14 days contributed to the improvement of the clinical condition, hematological indicators, normalization of the level of symmetric dimethylarginine in blood serum ( $12.3 \pm 0.22 \mu\text{g/dL}$ ;  $P < 0.001$ ), cystatin C ( $0.66 \pm 0.02 \text{ mg/l}$ ;  $P < 0.001$ ), the level of total calcium ( $2.25 \pm 0.05 \text{ mmol/l}$ ;  $P < 0.001$ ), reduction of azotemia ( $P < 0.001$ ), increase in glomerular filtration rate (on 16.3 %;  $P < 0.001$ ), levels of inorganic Phosphorus (8.8%) and Potassium (by 23.6 %;  $P < 0.001$ ). An increase ( $P < 0.001$ ) in the relative density of urine and a decrease in the content of protein and creatinine were noted in the urine.

3. Lifelong therapy is indicated for arterial hypertension in cats with chronic kidney disease, which is adjusted according to the needs and conditions of the animal. Mandatory systematic tonometry makes it possible to determine the effectiveness of antihypertensive therapy and change the drug dose.

#### Conflict of interest

The authors declare that there is no conflict of interest.

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