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# Animal models of chronic kidney disease – the missing piece of the puzzle for the development of new therapeutic options

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## Abstract

Chronic kidney disease (CKD) is considered one of the most important public health problems today. CKD is characterized by changes in kidney structure and impaired kidney function (reduced estimated glomerular filtration rate). Data show that more than 13% of the population suffers from CKD and that it will be the fifth leading cause of death by 2040. To date, numerous animal models for CKD have been developed. They are used to unravel the pathophysiological mechanisms of CKD development and represent a very important platform for the development of new therapeutic strategies. All animal models for CKD can be systematized in different ways, such as surgical/non-surgical models, subdivisions based on pathological changes in kidney structure or as subdivisions based on the pathophysiological mechanisms leading to the development of CKD. In surgical models, part of the kidney tissue is usually removed, while in non-surgical models, certain substances with nephrotoxic effects are used. The choice of model depends on the experimental design and the aim of the specific study. This paper provides an overview of all currently known animal models for CKD.

**Key words:** chronic kidney disease, animal models, nephrotoxicity, pathophysiology, rodents

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## Introduction

Chronic kidney disease (CKD) is one of the biggest public health problems (1), mainly due to early mortality and reduced quality of life (2). It is defined by abnormalities in kidney structure or function, present for a minimum of three months, with implications for health (3). Markers of kidney damage are pathological albuminuria, urine sediment abnormalities, persistent hematuria, electrolyte abnormalities, abnormalities detected by imaging or histology, as well as a history of kidney transplantation (3). Impaired kidney function is based on estimated glomerular filtration rate (eGFR) values (3). CKD is classified based on cause, GFR category (G1 – G5), and albuminuria category (A1 – A3) (CGA) (3). A low eGFR of less than 60 ml/min/1.73 $m^2$ indicates CKD and reflects a loss of about 50% of renal function (4).

High blood pressure and diabetes mellitus play the biggest role in the development of CKD, as it is estimated that one in three patients with diabetes mellitus and one in five patients with high blood pressure will develop CKD at some point (5). The main mechanism of the development of CKD can be described as microvascular dysfunction, since hypertension, smoking and dyslipidemia damage the glomerular endothelium (6).

It is estimated that more than 13% of the world's population suffers from CKD (7). The World Health Organization (WHO) estimates that between 5 and 10 million deaths can be directly attributed to the presence of CKD in patients (8). It has been shown that women suffer from CKD more frequently than men (9). One of the biggest challenges is the early diagnosis of CKD, as more than 90% of patients with moderate to mild renal impairment remain undiagnosed due to a lack of symptoms and signs of the disease (10).

Patients with CKD suffer from many comorbidities, but comorbidities from the cardiovascular disease group are the most common cause of death in these patients (11). CKD is expected to be the fifth leading cause of death by 2040 (12).

Patients with CKD have a significantly higher risk of developing cognitive impairment than the general population (13). According to the literature, the prevalence of cognitive impairment in patients with CKD is between 10% and 40% (13).

Animal models of kidney disease are useful for a better understanding of the pathophysiological mechanisms involved in the development of this disease and they are also a useful platform for testing new therapeutic options (14). Since most human diseases are very complex in terms of their mechanisms of development, it is difficult to find an ideal model that should fulfill the conditions for mimicking this human disease in the genetic and physiological sense (15). One of the most important stages on the way to clinical trials is pre-clinical testing, which in most cases involves an *in vitro* model which has to be validated in suitable animal models (16). Over the last 20 years, rodent animal models have provided a very valuable platform for research in the field of experimental nephrology (16). Rodent models, particularly mice, are widely used because they have very significant advantages, such as rapid reproduction, genetic characteristics as well as their size, and in recent years, numerous genetically modified strains that provide

important data for research have been developed (16). However, other animal species, such as the zebrafish, can also be used for these models (17).

All animal models can be subdivided or systematized in different ways. The first classification we will consider is the classification that categorizes all models into one of two broad groups: surgical and non-surgical models (11).

In addition, the models can be subdivided into models that primarily cause glomerulonephritis, glomerulosclerosis, interstitial fibrosis or vascular changes in the kidneys based on the pathological changes they cause in the kidneys (18). Finally, we can systematize these models based on pathophysiological mechanisms involved in the development of CKD into hypertension models of CKD, diabetic nephropathy models of CKD, drug-induced CKD models, CKD in aging rodents, autoimmune chronic kidney disease, and hereditary or genetic models of CKD (19).

## Surgical models of CKD

The most commonly used surgical models for CKD include partial nephrectomy and unilateral ureteral obstruction (UUO) models, as well as the ischemia-reperfusion injury model (11). Although it is primarily described as an acute kidney injury (AKI) model, the ischemia-reperfusion injury model can also be used as a CKD model (20).

### 1. Partial nephrectomy CKD models

These models imply the removal of a part of kidney tissue, such as ⅔, ¾, ⅚ or ⅞ of the kidney (11). Afterwards, the development of adaptive mechanisms in the remaining kidney tissue, such as hypertrophy, is noticed (21). The rat remnant kidney model of CKD is very often used, mainly because it mimics many of the features of CKD in humans (22). One of the most commonly used partial nephrectomy models is the ⅚ nephrectomy model (23), and it can be used in both mice and rats (24).

The essence of this model is to reduce the mass of kidney tissue by completely removing one kidney and leaving only one third of the tissue of the other kidney (24). Some research groups have established and validated a protocol which encompasses the removal of the right kidney (25), while other groups have implemented a protocol in which the left kidney is removed from the experimental animal (26). The authors describe various methods by which ⅔ of the tissue of the remaining kidney is excluded from its function. These methods may include: 1. the ligation of the upper and lower poles of the kidney with a surgical silk suture and afterwards, the development of tissue ischemia and subsequent necrosis is to be expected (27); 2. using a cauterizer (23) or 3. the surgical removal of ⅔ of the kidney mass (25). It is also possible to remove ⅔ of the tissue of one of the kidneys by ligating suitable branches of the renal artery that vascularize the upper and lower poles of the kidney (the inferior and superior segmental arteries), which is particularly pronounced and possible in rats due to the anatomy of the branches of the renal arteries (21).

This model can be performed as a single-stage ⅚ nephrectomy – where the left/right kidney and ⅔ of the kidney on the opposite side are removed in one operation (25) – or it can be performed in two stages, whereby ⅔ of one kidney is removed in the first operation and the kidney on the opposite side is removed after a certain time in the second operation (28). If this model is performed as a two-stage operation, the period between two operations can differ, but is usually 7 days (29). Having in mind that this is a surgical model, it is important to comply with asepsis and antisepsis methods to reduce mortality and morbidity (30). Various types of anesthetics are used for this operation, but ketamine/xylasine combinations (intraperitoneally) or inhalation anesthetics (e.g. isoflurane) (31) are most commonly used. It is also very important to administer analgesics before and a few days after the operation. Analgesics from the opioid group (e.g. buprenorphine) (32) are most commonly used, but analgesics from the non-steroidal anti-inflammatory drug (NSAID) group (e.g. meloxicam) (33) are also frequently used.

This model requires the use of sham-operated animals in order to eliminate the effect of anesthesia as a stress factor (11). In sham-operated animals, only the abdominal cavity is opened, the kidney is isolated without any intervention being performed on it, and then it is reinserted (30).

The disadvantages of this model are that certain strains of mice (C57BL/6 mice) do not develop a sufficient degree of fibrosis (34), the mortality rate is often high (30–40% of mice die from kidney hemorrhages) (24) and reduced residual tissue remains after the operation for further analysis. However, the great advantage of this model is that it has no direct effect on the CNS although the effects of anesthesia on brain function should be taken into account (35).

**2. The unilateral ureteral obstruction (UUO) model of CKD**

This model is one of the most commonly used models for renal fibrosis (36). It is very suitable because similar pathological changes in the rodent kidney are induced as in human CKD, including the occurrence of tubular atrophy and interstitial fibrosis (37). If this model were translated to changes in humans, it would be most similar to obstructive nephropathy (38).

Application of this surgical model requires the use of analgesics and anesthesia (36). The procedure is performed by placing the animal on its right side, making an incision through all the structures of the abdominal wall, locating the left ureter and ligating it with a double ligature (36).

After UUO is performed, the stagnation of urine leads to an increase in hydrostatic pressure, which in turn leads to the activation of the renin-angiotensin system, and angiotensin II activates NADPH oxidase and the production of reactive oxygen species (ROS) (39). This increased production of ROS activates transforming growth factor beta-1 (TGF-β1), one of the main factors for the further development of fibrosis (39).

One of the advantages of this model is that certain processes can be predicted over time, i.e. it is known that significant fibrosis and a reduction in the number of nephrons occur in a relatively short period of time (7 – 14 days) (40).

Limitations of this model often include a low survival rate after surgery, aggressive disease progression, the compensatory mechanisms of the contralateral kidney and the smaller amount of urine that could be used for further analysis (40).

### 3. Ischemia-reperfusion injury (IRI) model of CKD

Another surgical animal model is the ischemia-reperfusion injury (IRI) model. Although primarily an acute kidney injury (AKI) model, this model is very important for studying the transition from AKI to CKD (20). IRI is described as one of the most important causes of AKI, as it can occur in daily clinical practice due to the occlusion of blood vessels during surgery and as a result of postoperative hypoperfusion (20). The most commonly used rodent IRI models for AKI-CKD transition research are bilateral IRI (bIRI) (41), unilateral IRI (uIRI) (42) and unilateral IRI with contralateral nephrectomy (uIRIx) (20).

After IRI, the kidneys in rodents can develop CKD after a few weeks to a few months (20). This model is based on the occlusion of one or both renal pedicles for a certain period of time, followed by a period of reperfusion (43).

## Non-surgical models of CKD

Most non-surgical CKD models rely on the use of nephrotoxic substances and, on the other hand, on the use of genetically modified animals (11).

### 1. Crystal-induced nephropathy models

The two main substances that can be added to the diet of rodents to cause CKD are adenine and oxalate, both of which are excreted via the kidneys where they form crystals and subsequently develop inflammation and fibrosis as well as all the other features of CKD (44, 45). However, it should be considered that they also lead to extrarenal crystal deposition and could impair the function of other organ systems (46).

#### *1.1. Adenine-induced preclinical model of CKD*

Adenine is a purine base with several essential functions in the human body, including nucleic acid synthesis, the production of energy-rich compounds and cell signaling, and also serves as a cofactor for many important enzymes (46). It is found in various foods used in the daily diet, e.g. in different types of meat and fish, and it is also present in beer and legumes (47).

In the gastrointestinal tract, adenine is absorbed and then metabolized by adenine phosphoribosyl transferase (APRT) into AMP, which is a precursor of various compounds, including xanthine (46). Xanthine is then converted into uric acid and finally excreted via the kidneys (46).

Although it has many important physiological functions in the body, high doses of adenine can cause kidney damage (46).

The rat adenine model of CKD was first described by Yokozawa in 1986 (48). The now widely used model of CKD, the diet with 0.75% adenine was developed by experimenting with different adenine concentrations in the diet – from 0.075% to 0.25% and from 0.5% to the current 0.75% (49). Compared to mice, rats are generally more tolerant to adenine (46). In addition to being added to food, adenine can also be administered intraperitoneally (50). The 4-week administration of 0.75% adenine in food to rats has become a widely accepted model for the study of kidney injury (51), as this model mimics the structural and functional changes in the human kidney very well (46). The mechanism of kidney damage is based on the conversion of adenine into 2,8-dihydroxyadenine, which then leads to the formation of crystals in the kidneys (52).

### *1.2. Oxalate-induced preclinical model of CKD*

Like adenine, oxalate is also excreted via the kidneys (53). As it is an ionized conjugated base (54), it forms compounds with calcium in the kidneys, i.e. calcium oxalate crystals are formed, which in turn leads to the congestion of the tubules that ultimately leads to the development of CKD (55). Foods that contain significant amounts of oxalate, as well as substances from which it can be formed (e.g. vitamin C), are used in the daily diet (55). These include certain types of tea, juices and nuts (55). It is estimated that around 15% of the oxalate ingested with food is absorbed in the gastrointestinal tract (56). An increased concentration of oxalates in the bloodstream leads to an accumulation of oxalates in a variety of tissues and organs of the body, including bones, parts of the cardiovascular system, kidneys and retina (55).

The major disadvantage of this model is the formation of crystals in other organs and not only in kidneys, which may be of significance when the connection with other organ systems is examined (55).

## 2. Genetic models of CKD

Various genetic models mimicking CKD have been established, such as the Buffalo/Mna rat, which involves spontaneous focal segmental glomerulosclerosis (57), Col4a3, Col4a4, and Col4a5 knockout mice that are used as a model of Alport syndrome (58), etc. Patients suffering from polycystic kidney disease (PKD) have a large number of fluid-filled cysts in their kidneys, and this disease can manifest as autosomal dominant polycystic kidney disease or autosomal recessive polycystic kidney disease (59). Rodent models for PKD include Pkd1 knockout mice (60), the Han:SPRD-Cy rat as one of the spontaneous hereditary models for PKD, the pcy (polycystic) mouse and the Crj:CD/SD model (19). One of the HIV-associated nephropathy (HIVAN) transgenic mouse models is the transgenic 26 (Tg26) mouse in which proteinuria already occurs after 24 days of life (18). MRL/lpr mice are a strain that exhibits the clinical features of systemic lupus erythematosus, including glomerulonephritis (61).

## Preclinical models from a different perspective – pathological changes in the kidneys

As already mentioned, CKD models can be systematized on the basis of the pathological changes they cause in the kidneys into models that primarily cause glomerulonephritis, glomerulosclerosis, interstitial fibrosis or vascular changes in the kidneys (18). The UUO model mentioned earlier, for example, is a surgical model, but if we look at it in terms of the changes it causes in the kidney, we include it among the models that cause fibrosis (62).

### 1. CKD models associated with glomerular sclerosis

Models that mainly cause glomerular sclerosis include: the radiation nephropathy model, aging, Adriamycin-induced nephropathy and others (18). The aforementioned Buffalo/mna rat and HIVAN genetic models, which are considered as non-surgical models of CKD, now show that they develop glomerulosclerosis as a primary pathological change in the kidneys (18). According to this classification, the ⅚ nephrectomy model described above also belongs to the group of models whose primary pathological substrate is glomerulosclerosis (63).

#### *1.1. Aging*

It has long been known that aging has been described as one of the most important risk factors for the development of end-stage renal disease (64). In Sprague-Dawley rats, the incidence of chronic progressive nephropathy after 2 years of age is significantly higher than the incidence after the first year of life (65). One of the pronounced changes that occur in the kidneys during the aging process is the thickening of the basement membrane of the proximal tubule (65). Research focusing on the aging of mice has shown that they also have age-related kidney dysfunction (66).

#### *1.2. Radiation nephropathy*

Studies show that the primary phase of radiation nephropathy is characterized by changes in the glomeruli, but that tubular changes also occur (67). Just a few weeks after irradiation, there is a loss of glomerular endothelial cells and numerous changes in the glomerulus, which ultimately lead to the development of glomerulosclerosis (67). A study was conducted in C57BL/6 mice in which focal bilateral X-ray irradiation was applied, and changes in renal function were recorded 10 weeks after the irradiation (68).

#### *1.3. Adriamycin-induced nephropathy*

This is the most important model for the study of primary focal segmental glomerulosclerosis, which progressively leads to a decline in glomerular function and ultimately to the development of CKD (69). The use of Adriamycin leads to numerous changes in the kidneys, such as fibrosis, damage to the glomeruli and increased protein content in the urine. In rodents, all of the above changes occur 6 weeks after the intravenous administration of this drug (19). A limitation of this model is that one of the

most commonly used mouse strains – C57BL/6 – is known to be an Adriamycin-resistant strain (69).

**2. CKD models associated with glomerulonephritis**

Prolonged glomerulonephritis can lead to the development of CKD (70). Models that mainly cause glomerulonephritis as a pathoanatomical substrate are: Alport syndrome, Thy-1 nephritis model, anti-GBM nephritis model and MRL/lpr mice (18). The Alport syndrome model, already mentioned in the genetic models of CKD, primarily causes glomerulonephritis, just like the MRL/lpr mouse strain (18).

***2.1. Anti-GBM nephritis model***

Goodpasture syndrome, in which glomerulonephritis occurs as one of the clinical manifestations, is also characterized by the presence of circulating anti-GBM antibodies (71). This model can be induced in rodents in various ways, either by active immunization with substances containing collagen type IV or passively by the transfer of anti-GBM antibodies (71). It can also be applied to mice and rats. The most commonly used strain in this model is the Wystar-Kyoto rat, mainly because this rat model closely mimics the disease in humans, with the presence of circulating anti-GBM antibodies (72). After performing this model, the rodents develop proteinuria and azotemia of considerable severity after a few weeks (18). However, individual studies show varying degrees of success in the introduction of this model (73).

***2.2. Thy-1 nephritis model***

This mesangioproliferative glomerulonephritis model is obtained after intravenous administration of anti-Thy-1 antibodies in rats, with glomerular necrosis occurring as early as one hour after administration (74). However, it has been shown that the most damaged glomeruli return to their normal state 1 – 3 months after the administration of the antibody injection (75). It has been shown that anti-Thy-1 antibodies may be responsible for the fragmentation of DNA molecules in glomerular and mesangial cells (76).

**3. CKD models associated with interstitial renal fibrosis**

Renal fibrosis is caused by the increased synthesis and accumulation of extracellular matrix components, and depending on where these components are deposited, interstitial fibrosis or glomerulosclerosis can occur (77). Histological findings in CKD are glomerulosclerosis and tubular atrophy in addition to the aforementioned fibrosis (77). The models that lead to the occurrence of renal fibrosis as a pathohistological finding are: folic acid nephropathy, UUO and Cyclosporine A (CyA) nephropathy model (18). The UUO model was mentioned in the surgical models of CKD, and from the aspect of the pathohistological changes it causes in the kidneys, it is classified as a model that causes renal fibrosis.

### *3.1. CyA nephropathy model*

Cyclosporine is an immunosuppressant used after kidney transplantation, as well as in some glomerulonephritis treatments, but its long-term use has been described as nephrotoxic and can lead to the development of CKD (78). Cyclosporine damages tubule cells, impairs DNA synthesis and ultimately leads to apoptosis (79). Some studies show that TGF-β1 plays an important role in the pathogenesis of cyclosporine-induced chronic nephropathy (80). CyA nephropathy is characterized, among other things, by the presence of interstitial fibrosis (81). In rodents, reduced dietary salt has been shown to increase the sensitivity of rodents to the nephrotoxic effects of cyclosporine, and in this model, the first week is on a low-salt diet (81). After a week, cyclosporine is administered subcutaneously (81).

### *3.2. Folic acid nephropathy*

High doses of folic acid (250 mg/day) are often used for the development of CKD in animals (82). In both mice and rats, the injection of folic acid at a dose of 250 mg/kg intraperitoneally causes AKI, and if AKI is not treated, CKD develops after 4 weeks (83). When folic acid is administered, it forms crystals in the kidneys that lead to tubular necrosis, inflammation and fibrosis (82). Some of the advantages of this model are that folic acid is a vitamin and is available in most laboratories, it is quite safe to use (82), and it generally only affects the kidneys without damaging the chest organs (84).

### **4. CKD models associated with vascular changes in the kidneys**

The most important representative of this group of models is the spontaneously hypertensive rat. This strain has been used since 1963 and is very interesting for studying the development of chronic kidney disease in hypertension (85). Hypertensive kidney damage is observed after 30 weeks of life (85).

## Preclinical models from a different perspective – the underlying pathophysiological mechanism

It is interesting to systematize all the animal models of CKD mentioned so far from the point of view of the pathophysiological mechanisms involved in the development of CKD in hypertension models of CKD, diabetic nephropathy models of CKD, drug-induced CKD models, CKD in aging rodents, autoimmune chronic kidney disease, and hereditary or genetic models of CKD (19).

Hypertension is described as a major cause of CKD, and so it is not surprising that we have a group of hypertension models for CKD that include: the 5/6 nephrectomy model, spontaneously hypertensive rat model and deoxycorticosterone-acetate-salt hypertension-induced model (19). Hypertensive nephropathy is considered to be one of the most important and highly prevalent consequences of chronic high blood pressure (86). The underlying molecular mechanisms and histological features of hypertensive kidney disease include renal fibrosis, inflammatory cell infiltration, tubular atrophy and glomerular sclerosis (87). Moreover, a plethora of evidence has confirmed

that angiotensin II (Ang II) is one of the key molecules implicated in the development and progression of hypertension and hypertensive nephropathy (88). To further elucidate the underlying pathomechanisms and tailor novel treatment approaches, a preclinical model of Ang II-induced kidney inflammatory injury and fibrosis has been established. This animal model encompasses a four-week long administration of an Ang II infusion in rats or mice via a subcutaneous osmotic minipump (88). Research has shown that Ang II exhibits dual deleterious effects on the kidneys: acting indirectly by increasing blood pressure, and directly by stimulating inflammatory and fibrotic processes in the blood vessel wall and renal tissue (89). Ruiz-Ortega et al. (90) have shown that Ang II infusion activates the nuclear factor kappa B (NF-κB) signaling pathway and thus enhances proinflammatory gene and protein expression that are under NF-κB control, such as tumor necrosis factor alpha (TNF-α), interleukin-6 (IL-6), monocyte chemoattractant protein-1 (MCP-1) and adhesion molecules (90).

Many drugs have a nephrotoxic effect and can be used to induce CKD in animals (19). Therefore, there is a group of drug-induced CKD models, which include the adriamycin-induced CKD model and the adenine-induced CKD model (19).

The link between diabetes mellitus (DM) and CKD has long been known, but it is now estimated that almost half of patients with diabetes are affected by CKD (91). It is precisely for this reason that numerous diabetic animal models have been developed today, such as the Zucker diabetic fatti (ZDF) rat, BB rats, LEV1AR1/-IDDM rats, streptozotocin (STZ) rats, Nonobese diabetic (NOD) mice and Akita mice (92). Following the parenteral administration of steptozotocin, the beta cells of the pancreas are damaged in rodents, resulting in hyperglycemia (93).

An autoimmune mechanism of kidney disease has also been described (94). Various structures of the kidney (tubules, glomeruli and vascular elements) can be the target of autoimmune processes (95). The aforementioned strain of MRL/lpr mice (which has been described as a model for lupus nephritis) and the Anti-GBM Nephritis model cause kidney damage through an autoimmune mechanism (19).

Finally, the use of hereditary or genetic models of CKD has to be mentioned, having in mind that many of these models have been modified, such as PCK rats (19).

## Confirmation of CKD

Following the implementation of any of the previously described CKD models, it is important to confirm that the animal has developed CKD. This requires the collection of samples of various tissues and organs as well as fluids (blood and urine). It is also important to check kidney function, especially by determining the GFR value. The GFR can be measured in different ways: by measuring the FITC inulin clearance, by using contrast medium, creatinine or EDTA (96). In recent years, however, more modern methods for measuring the GFR have been developed, such as the transcutaneous measurement of fluorescein sinistrin labeled with isothiocyanate (FITC sinistrin) (96). The advantage of this method is that it makes it possible to measure the GFR value at a

specific point in time (96). This method has other advantages: no biological material, i.e. blood and urine, has to be collected, which saves a considerable amount of time, because urine often has to be collected in metabolic cages for twenty-four hours for urine collection, and blood collection from the tail vein in rodents is often very difficult (96). Another advantage of this method is that the GFR values can be measured several times in the same animal (96).

The blood samples used for the analysis are usually taken terminally (25), i.e. after the sacrifice of the animal, although blood can also be taken from the tail vein at various time points. Blood for analysis can also be obtained from the retro-orbital plexus (97). The most commonly used blood tests to confirm the development of CKD are urea and creatinine, as CKD patients have been shown to have elevated serum urea, creatinine and phosphate levels (25). Using the example of mice after 5/6 nephrectomy, it was shown that after 10 weeks of surgery, they had increased levels of serum urea, creatinine and phosphate in comparison to sham-operated mice (25).

When the collection of urine as biological material is considered, it is also important to confirm the development of CKD by an increased excretion of albumin in the urine. For urine collection, metabolic cages are generally used in which urine is collected 24 hours a day (23), although overnight (18-hour) urine collections are also possible (25). It was shown that urinary protein levels were elevated in 5/6 nephrectomy animals compared to sham-operated animals (97).

Histologic confirmation of CKD is also required. Histologic changes in CKD kidneys include interstitial fibrosis, tubular atrophy and glomerular sclerosis (99). The most commonly used histological stains for the detection of fibrosis are Sirius red (25) and Masson's trichrome (99). Glomerulosclerosis can be confirmed by PAS staining (100).

## Conclusion

This paper gives an overview of all known animal models for CKD. If a question of whether there is an ideal model for CKD were raised, the answer would be – no. Each of the abovementioned models has its advantages and disadvantages. No model has yet been developed that fully mimics CKD in humans. Therefore, when choosing a model, consideration should always be given to how well the results obtained in the model can be transferred to human medicine. The choice of model depends largely on the design of the experiment and what the aim of the study is, as well as the resources available. If the aim of the research is to study the relationship between CKD and another organ system, it would be better to choose a model that acts exclusively on the kidneys without affecting other organ systems, especially the system of interest. Surgical models are often very demanding and require great manual skills. The most important features of preclinical models for CKD include the translational value, robustness and predictive validity of the obtained findings. However, there is no ideal animal model that fully recapitulates human kidney disease: genetic landscape, complex pathomechanisms and brain-kidney crosstalk. Nevertheless, preclinical models of CKD provide a valuable insight and reveal

pathogenesis, offering potential novel molecular drug targets and biomarkers that can be tested and implemented in clinical practice. For instance, the 5/6 nephrectomy model may help explore the molecular mechanisms underlying development and disease progression resembling CKD following the loss of functional nephrons in the human population. The UUO model mimics chronic obstructive nephropathy observed in humans, while MRL/lpr strain spontaneously develops lupus nephritis, capturing the histopathological findings confirmed in patients suffering from this autoimmune disease. Taken together, all models represent a valuable platform for testing novel therapeutic options and when combined, they provide a comprehensive and in-depth insight into epigenetic and genetic factors, key molecular mediators and pathophysiological mechanisms that underlie kidney disease.

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## Declaration of Competing Interests

The authors declare that they have no conflicts of interest to disclose, including financial, personal or other relationships.

## Author contributions

MI: conceptualization, investigation, data curation, writing – original draft; DS: conceptualization, investigation, data curation, writing – editing; MK: investigation, data curation, writing – editing; JP: investigation, data curation; AI investigation, data curation; JN: investigation, data curation; GNS: investigation, data curation; VP: conceptualization, investigation, supervision, project administration, funding acquisition, writing – original draft & editing. All authors have read and approved the final version of the manuscript.

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# Životinjski modeli hronične bolesti bubrega – deo slagalice koji nedostaje za razvoj novih terapijskih mogućnosti

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## Kratak sadržaj

Hronična bolest bubrega (HBB) se smatra jednim od vodećih zdravstvenih problema današnjice. HBB se karakteriše oštećenjem strukture i funkcije bubrega što se procenjuje na osnovu promene intenziteta glomerularne filtracije. Podaci govore da više od 13% svetske populacije boluje od HBB, kao i da će HBB biti peti vodeći uzrok smrtnosti do 2040. godine. Do danas su razvijeni brojni životinjski modeli HBB. Ovi preklinički modeli su korisni za bolje razumevanje patofizioloških mehanizama nastanka HBB, a takođe predstavljaju i veoma važnu platformu za razvoj novih terapijskih mogućnosti. Svi životinjski modeli HBB se mogu sistematizovati na različite načine kao što su na primer: hirurški/nehirurški modeli, podela na osnovu patoloških promena do kojih dolazi u bubrežnom parenhimu ili podela na osnovu patofizioloških mehanizama uključenih u nastanak HBB. Kod hirurških modela obično se uklanja deo bubrežnog tkiva, dok se kod nehirurških modela koriste određene supstance sa nefrotoksičnim efektom. Izbor modela zavisi od eksperimentalnog dizajna i cilja same studije. U ovom revijskom radu su opisane karakteristike i osnovne prednosti i mane različitih prekliničkih modela HBB.

**Ključne reči:** hronična bolest bubrega, životinjski modeli, nefrotoksičnost, patofiziologija, glodari