Scholar Publishing Group
International Journal of Public Health and Preventive Medicine
https://doi.org/10.38007/IJPHPM.2022.030402
ISSN 2789-8377 Vol. 3, Issue 4: 9-18

Research Progress of Experimental Animal Model of Chronic Renal Failure in Combination of Disease and Syndrome

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Keywords: Chronic Renal Failure, Combination of Disease and Syndrome, Animal Model, Review

Abstract: Chronic renal failure (CRF) has become one of the chronic diseases that seriously damage human health worldwide. For the prevention and treatment of this disease, Chinese medicine has certain advantages due to its uniqueness. The diagnosis and treatment of chronic renal failure from the perspective of the combination of western medicine diseases and TCM syndrome types reflects the characteristics of TCM syndrome differentiation. The combination of disease and syndrome in animal models is widely needed in the connection between TCM clinical and basic experiments. Therefore, the successful construction of an animal model under the combination of disease and syndrome that conforms to the clinical characteristics of the disease has certain advantages for people to further understand the etiology and pathogenesis of the disease. This article reviews the research progress of CRF experimental animal models under the mode of combination of disease and syndrome, in order to provide a basis for the preparation of an animal models for TCM experimental research.

Chronic renal failure (CRF) is a clinical syndrome in the late stage of chronic kidney disease, which can be manifested as water electrolytes, acid-base balance disorders and kidney endocrine dysfunction. In severe cases, the body will retain a large number of metabolic end products and toxic substances, which has become one of the common chronic diseases that seriously harm people's health worldwide [1-2]. At present, the principle of diagnosis and treatment of CRF in

western medicine is to actively treat the primary disease, avoid and correct the risk factors of CRF progress, and prevent and treat complications [3]. Traditional Chinese medicine has no name of "chronic renal failure". According to the clinical symptoms of chronic renal failure, it belongs to the categories of "Guan Ge", "edema" and "urosis" in traditional Chinese medicine [4]. Based on syndrome differentiation, traditional Chinese medicine has increasingly prominent advantages in the clinical treatment of CRF [5].

In the process of medical experimental research, animal models are an important carrier of each experiment. Guided by the basic theory of Chinese medicine and the theory of combination of disease and syndrome, the successful construction of a standardized animal model of combination of disease and syndrome that not only conforms to the characteristics of Western medicine but also has the characteristics of traditional Chinese medicine is one of the important contents of the research on the modernization of traditional Chinese medicine [6-10]. At present, many scholars have used a variety of methods to construct CRF animal models.

1. Establishment of Animal Model of Chronic Renal Failure and Related Evaluation Indexes

1.1. Establishment of CRF Animal Model

Most CRF animal models are SD rats, followed by Wistar rats, mice, guinea pigs, and rabbits. The molding time is generally about one month. The complex pathogenesis of CRF has always been a hot and difficult topic in the research of kidney specialty and other related fields. After long-term exploration and practice, the types of CRF animal models are numerous and diverse, such as drug-induced (nephrotoxicity) CRF model, surgical-induced (nephrectomy) CRF model, gene knockout model, natural degeneration model, diet-induced model. (see Figure 1). At present, most experimental animal models used in modern medicine mainly use the first two methods [11].

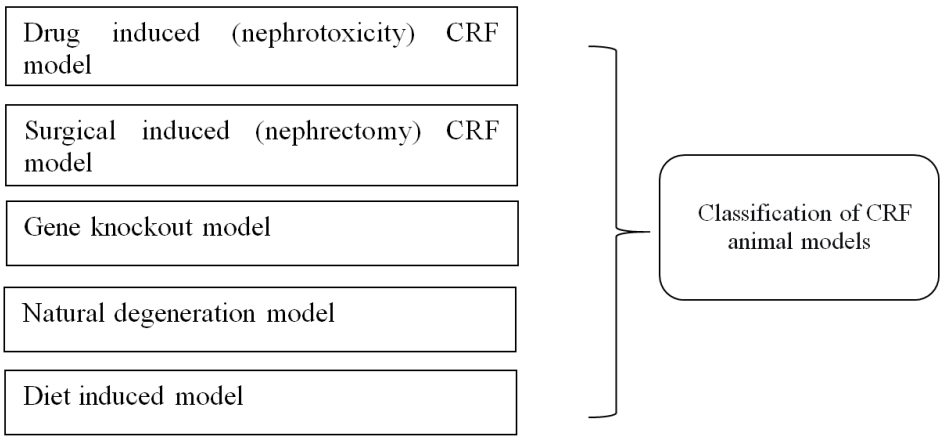

Figure 1. Classification of CRF animal models

Establishment of drug-induced (nephrotoxic) CRF model: For example, [12] selected Wistar rats and injected PAN (40mg/kg body weight) through jugular vein intubation to establish the model. [13] successfully used the same method to inject PAN (15 mg kg) into the tail vein of rats to establish the model. Zhang Yuanyuan [14] used BALB/C mice injected 10mg/kg ADR intravenously for the first time, and then injected the same dose of ADR two weeks later to make an adriamycin nephropathy model, successfully obtaining a typical FSGS performance. [15-16] induced CRF model by feeding rats with 0.75% adenine diet, and showed biochemical and pathological changes in the renal tubulointerstitium of CRF, thus affecting calcium and phosphorus metabolism. [17] also concluded that intragastric administration of 250 mg/(kg d) adenine for 5

weeks can successfully establish a rat model of chronic renal failure. [18] made the model of chronic renal failure in the decompensation period by intragastric administration of adenine. Stockelman MG [19] successfully prepared a mouse model of chronic renal failure by adding allopurinol to drinking water.

Establishment of surgery-induced (nephrectomy) CRF model: For example, [20] used 5/6 nephrectomy to prepare chronic renal failure models and observed renal function and pathological changes 3 and 8 weeks after surgery. Results success rate of modeling was above 83%. [21] successfully established a 5/6 nephrectomy chronic renal failure model in rats, and the blood biochemical indicators and morphology conform to the pathophysiological characteristics of renal failure. [22] established 5/6 nephrectomy chronic renal failure rat model. [23] successfully established a miniature pig CRF model by laparoscopy and 5/6 nephrectomy. [24] also successfully prepared the rat model of chronic renal failure by 5/6 nephrectomy. [25] observed the renal function, renal pathological changes, and renal tissue in the rat model of 5/6 nephrectomy α- Smooth muscle actin(α- The change of SMA) expression proving that 5/6 nephrectomy can make an ideal animal model of chronic renal failure and renal interstitial fibrosis. [26] studied CRF induced by 3/4 nephrectomy. [27] compared 5/6 nephrectomy and adenine gavage and concluded that both methods can be used to make the rat model of chronic renal failure with renal anemia.

After sorting out and listing the animal model literature, the authors found that although there are many single factor modeling methods for CRF, most of them still lack corresponding evaluation criteria, which is difficult to meet the requirements of preclinical pharmacological experiments or efficacy evaluation. At present, composite modeling methods are gradually increasing, and this model pays more attention to simulating the pathogenic effects of various possible factors in the human body. For example. [28] established the rat model of chronic renal failure by "single kidney resection plus adenine intragastric perfusion". [29] successfully established an animal model by one-step 5/6 nephrectomy and high phosphorus diet in rats. In the same way, [30] successfully prepared the rat model of chronic renal failure with vascular calcification by intragastric administration of adenine combined with a high phosphorus diet.

Drug induced (nephrotoxic) CRF model is easy to operate with high repeatability and controllability, but the required drug dose is large and the modeling period is long, so the drug concentration and dose need to be strictly and accurately controlled, otherwise it is easy to cause animal death. The surgery-induced (nephrectomy) CRF model can clearly show the characteristics of each target gland axis, but it requires good surgical skills. Once it fails, it will cause irreversible damage to the animal body, and the amount of anesthesia and nursing will also lead to animal death. Drug induced (nephrotoxicity) and surgical induced (nephrectomy) animal models are relatively close to the clinical manifestations of patients and are currently recognized as mature modeling methods at home and abroad. However, there are some limitations in the multifactorial, complex, and individual specialization of etiology and pathogenesis. There are many influencing factors of simple diet induction, and it is difficult to establish a model, so it is less used. Although the model of gene knockout type is stable and not interfered by external factors, the experimental conditions are required to be high and expensive.

1.2. Evaluation of CRF Animal Models

At present, animal experiments mostly judge whether the model is successful by observing the behavioral characteristics of animals and testing the biochemical indicators of animals. Behavioral characteristics include common symptoms of chronic renal failure: polyuria, excessive drinking, mental depression, reduced activity, less food intake, weight loss, pale ears, light red eyes, squinting and eyelid edema, wet and cold tail, dry and loose body hair. (See Figure 2).

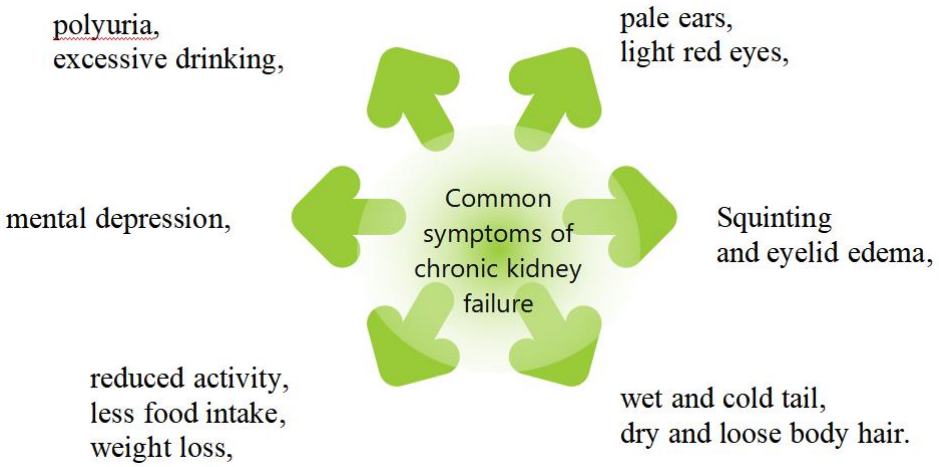

Figure 2. Behavioral characteristics include common symptoms of chronic renal failure

Biochemical criteria include significant increase of middle molecular substances (toxins), increase of serum creatinine and urea nitrogen, decrease of RBC, hemoglobin, HGB, hematocrit HCT and platelets, electrolyte metabolism disorders (high phosphorus, high potassium, low calcium, low sodium, etc.), amino acid metabolism disorder (decrease of essential amino acids) and anemia. The gross observation showed that the renal volume was significantly increased. Microscopic histopathological observation showed that most of the renal tubules in the renal tissue had been destroyed, and the epithelial cells of the tubules were edematous and necrotic. A large number of acicular or rectangular purine metabolite crystals were seen in the lumen and interstitium; Lymphocyte infiltration was found in the stroma, and local fibrous tissue hyperplasia was seen. Reading and sorting out a large number of documents, the records of behavioral characteristics mainly depend on the subjective evaluation of the experimenter, which inevitably leads to bias. Most experiments still use biochemical criteria to measure the success of animal models. It is worth thinking about the application of disease symptom combination of models.

2. Establishment of Animal Model of TCM Combination of Disease and Syndrome of Chronic Renal Failure and Related Evaluation Indexes

2.1. Establishment of CRF Animal Model Combining TCM Disease and Syndrome

With the in-depth research in recent years, the method of constructing CRF disease syndrome combination model is mainly based on the western medicine CRF model, combined with the preparation of relevant pathogenic factors. According to the etiology and pathogenesis of TCM, chemical drugs, physical methods and other methods are adopted to make experimental animals gradually show symptoms and signs consistent with the target syndrome type, so as to build a model with both disease and syndrome type.Disease of chronic renal failure is widespread, often involving the kidney, spleen and stomach, liver, lung, heart, the sanjiao (triple energizer), etc. (see Figure 3).

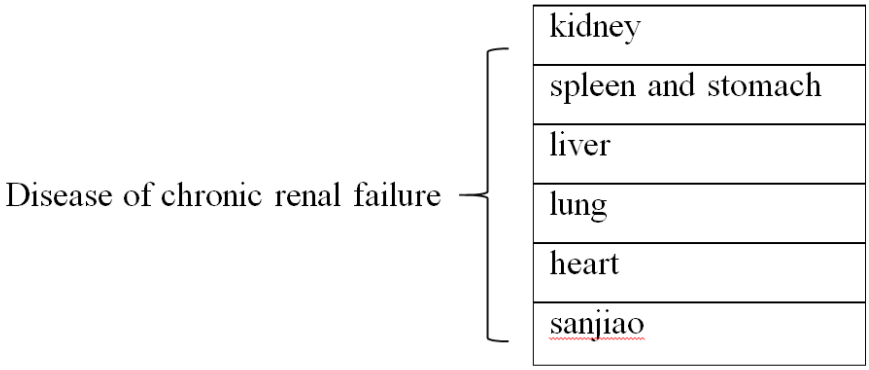

Figure 3. Disease of chronic renal failure

Etiology and pathogenesis is complicated, with qi is the basic pathogenesis, this deficiency syndrome type has a license to qi deficiency, blood deficiency syndrome, Yin deficiency, and Yang deficiency syndrome with a total of 4, the empirical model with dampness syndrome, damp heat syndrome, blood stasis syndrome, drowned poison, 4 kinds of composite syndrome types of chronic renal failure, made up of two or more basic syndromes, It includes Qi and blood Yin and Yang deficiency syndrome, blood stasis and water dampness syndrome, damp-heat drowning syndrome [31]. (see Figure 4).

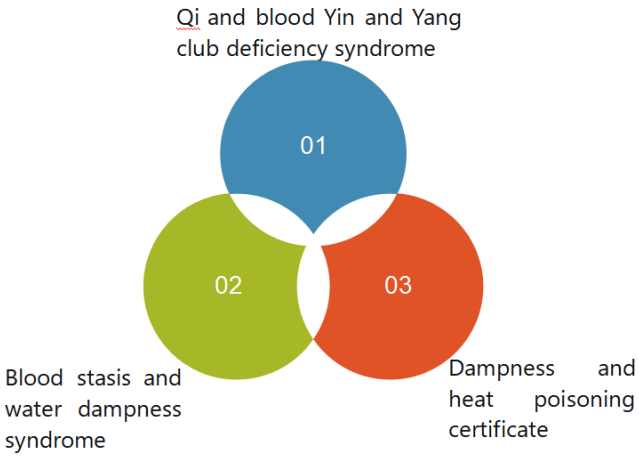

Figure 4. Complex syndrome of chronic renal failure

At present, some scholars have successfully prepared CRF animal models of kidney Yang deficiency syndrome and blood stasis syndrome in chronic renal failure [32-35]. Successfully induced the establishment of a rat model of kidney Yang deficiency syndrome of chronic kidney disease by tail vein injection of doxorubicin 3 mg kg-1 for four consecutive weeks. [36] also successfully induced CRF animal model with kidney Yang deficiency syndrome by intraperitoneal injection of 3.75 mg/kg hydrocortisone solution. [37] used male SD rats to prepare the kidney Yang deficiency model by gavaging adenine (100 mg kg-1) for 8 weeks. After 21 days of administration of adenine, [38] observed that the weight of rats decreased, the grip was weakened, the anal temperature decreased, the drinking water and urine volume of rats significantly increased, and the urine 17-OHCS, serum ACTH and CORT contents significantly decreased, suggesting that the kidney Yang deficiency model was successfully established. [39] used adenine gavage to replicate

the mouse model of kidney Yang deficiency. [40] used 5/6 renal cortical resection plus propyl thiouracil (PTU) intragastric administration to create the kidney Yang deficiency model of chronic renal failure in rats. [41] established a model of chronic renal failure of kidney Yang deficiency in SD rats by administrating adenine 200mg/kg d.

2.2. Evaluation of CRF Disease Syndrome Combined With Animal Model

The diagnostic criteria of western medicine are evaluated through experimental indicators, relevant physical and chemical indicators, etc. (see Table 1).

Table 1. Western medicine diagnostic criteria

1	Decline in autonomous activity
2	Decline in absorption function
3	Indicators of specific pathological changes of kidney-yang deficiency syndrome

For example, weight-bearing swimming test and open field test can reflect the decline of autonomic activity of rats with spleen and kidney yang deficiency. Physical and chemical indexes such as urinary D-xylose excretion rate or serum D-xylose content can measure the absorption function of rats, thus objectively reflecting the physiological function of the spleen; the contents of cyclic adenosine monophosphate, guanosine monophosphate in plasma and 17 hydroxysteroid in 24h urine are recognized as indicators reflecting the specific pathological changes of kidney yang deficiency syndrome [42-45].

Although many animal models have been successfully prepared for CRF research, there are few research models with TCM characteristics and guided by traditional theories on the combination of disease and syndrome, which is one of the factors restricting the development of integrated traditional Chinese and western medicine. It has become an important part of traditional Chinese medicine research to study the pathogenesis and intervention measures of diseases by using animal models of combination of disease and syndrome, which is an important link in the research of modernization of traditional Chinese medicine.

3. Conclusions

According to the Guidelines for the Diagnosis and Treatment of Chronic Renal Failure with Integrated Traditional Chinese and Western Medicine, it is determined that CRF includes qi deficiency syndrome, blood deficiency syndrome, yin deficiency syndrome, and yang deficiency syndrome in the original deficiency syndrome , dampness turbidity syndrome, damp heat syndrome, blood stasis syndrome, and poisoning syndrome in the standard empirical type, and the complex syndrome type includes qi blood yin yang deficiency syndrome, blood stasis water dampness syndrome, and dampness heat poisoning syndrome. If we study this disease from the aspect of traditional Chinese medicine, it is clearly not enough to reproduce some symptoms and specific pathological changes. We should combine the pathological basis of western medicine with the theory of traditional Chinese medicine, to discuss the different syndrome differentiation types. The following lists the experimental models based on TCM theory, such as

The model of qi deficiency and blood stasis was made by swimming fatigue method, and the syndrome of spleen deficiency and damp excess was simulated by feeding a lot of honey and oil food, and the syndrome of yin deficiency was simulated by feeding thyroxine. However, the CRF animal model with combination of disease and syndrome was not added. In the known CRF animal experiments, many scholars realized that there was a weak correlation between disease and syndrome when preparing animal models under the combination of disease and syndrome. In terms

of model evaluation, currently, for behavioral characteristics such as tongue coating, pulse condition, conscious perspiration, fatigue, etc., these information are abstract and need to rely on the subjective judgment of the experimenter. How to standardize and establish a systematic evaluation process is the direction of future animal model research. It should be combined with metabonomics technology to enrich the content of model feature evaluation from different angles and levels such as DNA, RNA, protein, metabolites, etc., and provide a reliable experimental basis for the research and development of new TCM anti-CRf drugs.

In conclusion, the application of disease-syndrome combination method is an important link in the development direction of CRF animal models, which needs continuous revision, exploration, and improvement. It is worthy of further practice and exploration to develop a disease-syndrome combination animal model scheme that conforms to clinical characteristics and is supported by rigorous physical and chemical criteria.

Funding

No funds.

Data Availability

No new data is used or generated.

Conflict of Interest

No conflict of interest.

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