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A Review on Animal Models of Chronic Kidney Disease- An Update

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Chronic kidney disease is a global health burden and is an independent risk factor for morbidity and mortality for many diseases. The estimated prevalence of CKD worldwide is 9.1% (697.5 million cases) in all the age groups and about 1·2 million people died from CKD in 2017. Proteinuria and decreased glomerular filtration rate are the major indicators of the kidney damage.The need for reliable models for increasing prevalence is apparent. Animal models allow analysis of complex disease pathophysiology, for introducing new drugs and interventions in CKD. Studying various models will help in selection of appropriate model suitable for the cause of CKD.

Keywords: Alport Syndrome; CKD; Calcification; GFR; Nephrectomy; Polycystic Kidney.

Chronic kidney disease is defined as abnormalities of kidney structure or function, present for greater than 3 months. This is defined as a GFR less than 60 mL/min/1.73 m2 or one or more markers of kidney dysfunction including albuminuria.The pathophysiological mechanism underlying CKD includes initial trigger mediated through inflammation or immunological response or a toxicant. Hyper filtration and hypertrophy occurs later that contributes to progression of kidney damage[1]. All these eventslead to secondary complications like diabetes, cardiac diseases, stroke, etc[2]. The increase in number of CKD cases is linked with the aging, increased prevalence of diabetes mellitus and hypertension,diabetesmellitus being the leading cause[3,4]. CKD is believed to affect 10% to 15% of the population and is estimated to contribute to 5 to 10 million deaths annually[5]. It is also observed that CKD imparts cardiovascular burden in the patients that may be because of intimal, medial and valvular calcification of arteries[5,6]. The abnormal toxins accumulation in CKD patients can cause imbalances in renin angiotensin aldosterone system causing increased blood pressure, increased coagulation that in turn may pose a threat of myocardial infarction culminating in heart failure. This pathway is known as Cardio-renal syndrome[7]. The findings from several studies also prove the linkage between CKD, small blood vessel diseases of cerebrum and impairment of cognition but the pathological mechanisms remain unclear[8]. The non-specific interventions in established CKD result in reduction of the disease progression. Also, Early investigations through imaging and biopsy techniques and Targeting Specific underlying cause is also crucial for delivering proper care in

the patients with CKD. Renoprotective agents-Angiotensin-converting enzyme II inhibitors and angiotensin II receptor blockers are considered as first line drugs in CKD irrespective of the underlying causes(both diabetic and non-diabetic). Drugs targeting renal fibrosis are still under investigations that can be promising agents for CKD treatment. Dietary sodium restriction and diuretic therapy reduce the fluid overload. Oral alkali therapy with sodium bicarbonate (1.5 to 3.0 g/day) slows the rate of progression[9]. Impairment of immune response in CKD either leads to increased risk of infections where as exaggeration leads toinflammation along with its after effects. Targeting these immune abnormalities can also be an effective strategy in advanced CKD[10].

Understanding the underlying mechanisms for the development and progression of kidney diseases is important for finding the new treatments in this context. For achieving these goals both rodent and non rodent models are proven to be valuable investigating tools. Rodents, especially Rats are able to replicate the human histological manifestations of kidney diseases to larger extent making them as useful options[11]. The present review focuses on animal models of CKD.

Hypertension model of CKD

Hypertension is considered to be a cause and outcome of CKD, characterized by proteins in urine and sclerosis of glomeruli. This leads to reduced glomerular filtration. The histology of hypertensive CKD ischaracterized by renal inflammation and interstitial fibrosis[12].

Spontaneously hypertensive rat model

8-week-old male spontaneously hypertensive rats(SHR) can serve as better tool for understanding hypertension induced kidney injury[13]. The uninephrectemised SHR rats are observed over a period of 40 weeks in presence or absence of drug treatments and at the end of 40th week, the urine samples are collected.The animals are then sacrificed; blood samples are collected followed by dissection of kidneys. Biochemical, histological and immunohistochemistry studies are performed. It is believed that in these models microinflammation is the cause of renal injury[14]. Proteinuria, glomerulosclerosis, and interstitial fibrosis are observed. The pathology can be exaggerated by introducing high salt diet especially in male SHR rats[15]. Oxidative stress appears in the beginning followed by inflammation[16].

5/6thNephrectomy model

Often called as sub total nephrectomy, is the best model for studying progressive renal failure with loss of renal mass[17]. Tissue ablation or ligation of renal tissue induces renal failure[18]. 12- weeks after establishing the model, drastic increase in blood urea nitrogen and proteinuria can be observed[19]. This method requires expertise in surgical procedures.Nephrectomy-induces systolic arterial hypertension and thereby cause changes in remnant kidney tissue both structurally and functionally. Structural changes include glomerular hypertrophy, mesangial expansion, glomerular sclerosis, interstitial fibrosis and tubule-interstitial atrophy[20]. This model is considered as an established model for glomerulonephritis and renal fibrosis especially in female wistar rats[21].

Deoxycorticosterone acetate salt hypertension induced model of CKD

Deoxycorticosterone acetate salt induces hypertension by increasing expression of TNF alpha there by increasing inflammation in renal tissue[22]. This is a model of primary aldosteronism that also induces oxidative stress and renal fibrosis[23]. Uninephrectomy performed 8 weeks old Sprague Dawley rats are given access to NaCl; and DOCA salt is administered subcutaneously that develop hypertension and fibrosis[24]. This model lasts only for 8-12 weeks.so not a popular choice for modelling CKD.

Diabetic Nephropathy model of CKD

Diabetic nephropathy is the leading cause of CKD worldwide. It is characterized by renal inflammation and fibrosis, tissue remodeling along with oxidative stress[25,26]. Glomerulosclerosis is also a characteristic feature of diabetic nephropathy, reflecting the accumulation of á-smooth muscle actin and the epithelialmesenchymal transition. Diabetes can be induced by single intraperitoneal injection of 45mg/kg of Streptozotocin in 8-week old SD rats. Increased weight of kidneys, blood glucose, alanine transaminase, aspartate transaminase, catalase, superoxide dismutase and glutathione are the parameters to be assessed[27]. Transforming Growth Factor-â1 is deemed to take a vital part in the deposition of Extracellular matrix, serum creatinine and blood urea nitrogen

(BUN) levels in Diabetes[28]. Addition of high fat diet to Steptozotocin can mimic human type 2 diabetes(insulin resistance). SD rats are fed with high fat diet containing 50 % fat in food for 9 weeks. Streptozotocin (35mg/kg) is injected i.p. at 4th and 6th week then plasma and renal parameters can beevaluated[29].

The Akita^{Ins2+} mice that has spontaneous point mutation in preproinsulin gene produces Type 1 Diabetes by direct pancreatic beta cell toxicity is a model for studying progressive events of kidney disease including mesangial expansion and albuminuria. Non obese diabetic mice is characterized by autoimmune destruction of beta cells of pancreas thus produces renal injury in 40days due to mesangial expansion and podocyte loss. New Zealand Obese mouse (Type 2 diabetes along with obesityrelated to leptin resistance),*Ob/ ob, db/db* and Zucker fatty rat models can be useful for studying Diabetic Nephropathy[30].

Drug induced Chronic Kidney disease

As surgical methods possess risk of mortality among the animals in the study, the use of inducing agents to produce chronic nephrotoxicity is considered as desired and beneficial option.

Adriamycin induced CKD

Adriamycin induces nephropathy similar to renal injury in humans. Glomerular damage, increased proteins in urine, segmental sclerosis and tubular interstitial fibrosis are the sequeale of renal events associated with adriamycin. All these events occur 6weeks after a single intravenous injection of Adriamycin (5mg/kg) in male albino rats[31,32] or 20mg/kg i.p. in wistar rats[33]. Adriamycin causes podocyte injury followed by expression of transforming growth factor beta-1 associated with glomerulosclerosis, depletion of podocytes and decreased renal function[34].

Adenine-induced model of CKD

This model is first explained in 1986 by Yokozawa et al. and is very much adopted in recent studies. Adenine when given either with diet or vehicle causes occlusion of renal tubules, ischemia and finally fibrosis leading to CKD progression and retardation of growth which is more relevant to CKD in human[35]. In initial models, 0.75%w/w of adenine was given with diet, this is later modified to 0.5 or 0.25% w/w. Diet containing 0.25% adenine when fed for 35days in 9-10 weeks old Sprague Dawley rats, produces progressive CKD. Adenine increased plasma concentrations of inflammatory cytokines and decreased antioxidant levels[36,37] serum blood urea nitrogen, creatinine and uric acid are found to be increased with adenine diet[38]. Adenine model is more advantageous over surgical model of CKD as it reduces mortality and inter-species difference during experimentation[39].

CKD in Aging rats

Aging is characterized by proteinuria, lesions in tubularinterstitium and cell damage. Thus is an important factor for development of end stage renal disease[40]. Endoplasmic Reticulum stress and apoptosis are considered as the contributing factor for tubular cell injury. Rodents older than 20 to 24 months are considered to be aged and are suitable for the study[41]. Short term high fat diet fed aged Sprague Dawley rats for 15 days can produce renal inflammation and fibrosis[42].

Autoimmune Chronic Kidney disease

Kidney can be target of autoimmunity resulting in nephritis caused by systemic lupus erythematosus in 35-55% of patients because of abnormal glomerular inflammation[43]. Lupus Nephritis, that is one of the serious complication of Systemic Lupus Erythematosus causes activation of inflammatory cells and proliferation of local tissue that stimulate chemokine and cytokine release[44]. Nephritis induced by IgA causes hematuria and glomerulonephritis involving mesangial cells. IgG anti-IgA formation induces inflammation that causes kidney failure[45]. Heymann Nephritis is another form of immune mediated injury of glomerulus often termed as membraneousglomerulo-nephropathy. Its active model is produced by injection of isolated brush border components of rat's proximal tubules into Lewis or fisher rats. Within 3 to 4 weeks, IgG deposition occur in glomerulus and proteinuria develops in 8-weeks[46]. Whereas in passive model, antisera produced from antigen of another animal is injected to exhibit immune response[47]. Injection of rabbit or mouse thymocyte serum through tail vein induces membrano proliferative glomerulonephritis that causes proliferation of mesangial cells and proteinuria with in 1-week. This model repairs on its own after 3 weeks whereas repeated injections cause progressive chronic kidney disease[12]. Anti- Glomerular Basement Membrane model is another modelof glomerulonephritis induced by

Table 1. Animal models for chronic kidney diseases

	Model	Animal/Strain	Changes In Histology	Reference
1	Hypertension models of CKD			
A	Spontaneously hypertensive rat model:	7 to 8 weeks old male SHR rats	Glomerulosclerosis, and interstitial fibrosis	15,55,56
B	5/6 Nephrectomy model:	Male Sprague–Dawley rats, female wistar rats	Mesangial expansion, glomerular sclerosis, interstitial fibrosis and tubule-interstitial atrophy.	20,21,57
C	Deoxycorticosterone acetate salt hypertension-induced model	8- weeks old Sprague Dawley rats	renal fibrosis	23,24
2	Diabetic Nephropathy model of CKD			
		8-week old SD rats(STZ 45mg/kg I.P)	Glomerulosclerosis	27
		Zucker fatty rat	Renal interstitial fibrosis and glomerulosclerosis	58
		db/db	Glomerulosclerosis,	59
		Ob/ob	Podocyte apoptosis	60
		Non Obese mouse	Glomerular lesions	61
3	Drug-induced Chronic Kidney disease			
A	Adriamycin induced CKD	Adriamycin (5mg/kg) in male albino rats. 20mg/kg i.p. in wistar rats.	Podocyte injury, glomerulosclerosis	32,33
B	Adenine-induced model of CKD	9-10 weeks old Sprague Dawley rats	Renal fibrosis	34
4	CKD in Aging rats	24-months old male Sprague Dawley rats	Tubularinterstitial lesions,Glomerulosclerosis	40,55
5	Autoimmune Chronic Kidney disease			
A	Lupus Nephritis	MRL/*lpr* and NZB/W mice	Renal fibrosis	55
B	IgA induced Nephritis		Mesangioproliferative glomerulonephritis	55
C	Heymann Nephritis	Lewis or fisher rats	Membranous nephropathy	62
D	Anti GBM Nephritis	Wistar Kyoto Rats	Membranous nephropathy	49
6	Hereditary or genetic models of CKD			
A	Alport syndrome	Alport mice	Tubularinterstitial lesions,Glomerulosclerosis	55
B	Polycystic kidney disease	Han:SPRD-Cy rat	Intraglomerular injury	53,54
		PCK rats	Intraglomerular injury	53,54
		Pcy mouse	Intraglomerular injury	53,54
		bpk (BALB/c polycystic kidney) mice	Intraglomerular injury	53,54

active immunization with isolated or recombinant collagen IV or by injection of anti GBM antibodies passively in Wistar Kyoto Rats[48,49].

Hereditary or genetic models of CKD

Alport syndrome is an inherited genetic disease that occurs due to mutation in genes encoding collagen IV á5 chain(*COL4A5*). Accumulation of these chains occurs in glomerular basement membrane and alters its function. The development of nephropathy is same in both sexes[50]. Initially it is manifested as hematuria. Further collagen signallings causes albuminuria that further contribute to renal fibrosis[51]. Polycystic kidney disease is hereditary disorder characterized by abnormal cell proliferation, fluid accumulation, inflammation and renal fibrosis. Two types of Poly cystic kidney diseases include, Autosomal dominant polycystic kidney diseases and Autosomal recessive polycystic kidney diseases[52]. Autosomal dominant polycystic kidney diseases is one of the common genetic cause of renal disease. It is associated with mutations in genes of polycystic kidney disease (PKD1 & PKD2). The Han:SPRD-Cy rat strain is one of the spontaneous hereditary model for PKD characterized by large number of cysts formed by missense mutations. Another rodent model includes, PCK rats that are discovered from Sprague Dawley rats outbreeding, Pkhd1 being the responsible gene. Pcy(polycystic) mouse derived from KK strain produces missense mutation in gene similar to human Nphp3 is also one of the hereditary model for PKD[53]. Crj:CD/SD is another homozygous mutant model for PKD that develop renal cysts within one week after birth where as*bpk* (BALB/c polycystic kidney) mice model, homozygous mutants develop renal cysts and die within 4 weeks after birth. Although many models of PKD share similar pathological features of end stage renal diseases, understanding molecular mechanisms and identifying novel drug targets still remain as a challenge.[54] Podocyte-specific genetic model for focal segmental glomerular sclerosis(Nep 25 mice) is produced by administration of immunotoxin specific to podocytes under nephrin promoter in mouse causing intraglomerular injury. Human immunodeficient virus associated Nephropathy, is produced in Tg26 mice (it has replication deficient HIV transgene) characterized by severe proteinuria, ascites, low levels of urinary albumin and mesangial hyperplasia especially on FVB/N, C57BL/6, 129/Sv strain backgrounds[55].

Recently role of Sirtuins in development of renal diseases has gained attention. Various body organs especially kidneys are vulnerable to age related damage and also injuries occurring due to toxic substances. Silent information regulators are NAD^+ dependent deacetylases(consisting of 7 isoforms-SIRT1 to SIRT7). SIRT1 gene is highly expressed in nucleus and cytoplasm of fetal and adult tissues like Liver, Kidney, Brain. High glucose concentrations can increase expression of p53 and cleaved caspase-3 in renal epithelium. This stimulates expression of SIRT1 by medullary mesenchymal cells that inturn reverses the p53 levels. Thus SIRT1 inhibits podocyte apoptosis. Thus SIRT1 has a significant role in Diabetic kidney disease. Additionally it regulates the TGFbeta/Smad pathway thereby inhibits kidney fibrosis. It also has role in regulation of renal inflammation in diabetic nephropathy through TNF alpha and COX-2 gene downregulation. Thus upregulation of SIRT1 activity can inhibit renal cell apoptosis.(63,64,65) Podocyte-specific Sirt1 knockout mice model is useful to study the role of sirtuins in Diabetic nephropathy where it inactivates p65 subunit of NF-kB and STAT3 and suppresses podocyte dysfunction.[66]

In addition, Klotho, an antiageing gene has been involved with cellular senescence. Deficiency of klotho gene induces oxidative stress, associated with multiple disorders like atherosclerosis, infertility, osteoporosis, cognitive decline etc. Klotho deficient mice can be a useful tool for studying premature ageing like syndrome-altered glucose, lipid and amyloid beta metabolism.[67] Low klotho expression is associated with raised Fibroblast growth factor(FGF23) that causes advanced CKD associated with cardiovascular complications such as vascular calcification, Left ventricular atrophy and cardiac fibrosis.[68]

CONCLUSION

Chronic kidney disease is becoming a common disease with greater prevalence associated various etiologies, majorly with Diabetes and Hypertension. Immune mediated responses also account for many cases of CKD worldwide. Hence there is an immediate need for modeling kidney diseases that approximate to human pathology.

Animal models, especially mice and rats are convenient for evaluating the novel drugs in chronic kidney diseases. Even after the discovery of various models for CKD, no single model exactly reflects human CKD. Strain, genetics and non-detectable effects of CKD can be limitations of animal studies, Thus progressive efforts are put forward in this direction to create new models or improve existing ones. Presence of co-morbidities, age, causative factors of kidney disease are to be taken into consideration while designing new models. Further advancement in molecular biology techniques are useful in understanding CKD molecular level pathogenesis and its complications which further aid in developing new transgenic models. The present review provides concise information on animal models of CKD along with their histological data for discovering new leads for CKD.

Conflict of Interest

There are no conflicts of Interest.

Funding Sources

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