JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue
JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)
An International Scholarly Open Access, Peer-reviewed, Refereed Journal

COMPARATIVE ANALYSIS OF VARIOUS RAT MODELS OF DIABETIC NEPHROPATHY: STRENGTHS, LIMITATIONS, AND TRANSLATIONAL RELEVANCE)

DEEPA CHAUHAN[1], QUMRE ALAM[2], DR. AMARJEET SINGH[3], AKASH JOHRI[4]

[1]M.pharm Scholar, Innovative College of Pharmacy, Greater Noida, U.P.
[2,4]Associate Professor, Innovative College of Pharmacy, Greater Noida, U.P.
[3]Professor& HOD, Innovative College of Pharmacy, Greater Noida, U.P.

Abstract:Diabetic nephropathy is a severe complication of diabetes mellitus and a leading cause of end-stage renal disease (ESRD) worldwide. Various rat models of diabetic nephropathy have been developed over the years, each with its strengths and limitations. Understanding these models and their translational relevance is critical for developing effective therapeutic strategies for this debilitating condition. In this review article, we provide a comparative analysis of various rat models of diabetic nephropathy, highlighting their strengths and limitations, and discussing their translational relevance. We examine the key pathological features of diabetic nephropathy recapitulated in these models, including mesangial expansion, glomerular hypertrophy, proteinuria, and tubulointerstitial fibrosis. Among the different rat models of diabetic nephropathy, the streptozotocin (STZ) model is the most commonly used model, but it has limitations in recapitulating the natural history of human diabetic nephropathy. Other models include the Akita model and the Zucker diabetic fatty (ZDF) model, each with their own strengths and limitations. Despite these limitations, rat models of diabetic nephropathy remain an essential tool for studying the pathophysiology of this condition and for developing new therapeutic strategies. Recent advances in genetic engineering and stem cell technologies have led to the development of more sophisticated rat models that closely mimic the pathophysiology of human diabetic nephropathy. These models hold great promise for improving our understanding of diabetic nephropathy and for developing new and effective therapies for patients with this condition.

Keywords: Diabetic nephropathy, rat models, streptozotocin, Akita, Zucker diabetic fatty, pathophysiology, therapeutic strategies, genetic engineering, stem cell technologies.

I. INTRODUCTION

Diabetic nephropathy is a serious complication of diabetes mellitus and a major contributor to end-stage renal disease (ESRD) globally. Several rat models of diabetic nephropathy have been developed over the years, each with its own strengths and limitations[31]. These models have been essential for understanding the pathogenesis of diabetic nephropathy and for developing therapeutic strategies. Therefore, understanding the strengths, limitations, and translational relevance of these rat models is crucial.

In this review article, we aim to provide a comparative analysis of various rat models of diabetic nephropathy, highlighting their strengths and limitations, and discussing their translational relevance[5]. We will also examine the key pathological features of diabetic nephropathy that are recapitulated in these models, including mesangial expansion, glomerular hypertrophy, proteinuria, and tubulointerstitial fibrosis.

Among the various rat models of diabetic nephropathy, the most commonly used model is the streptozotocin (STZ) model due to its simplicity and reproducibility[1]. However, this model has certain limitations in terms of recapitulating the natural history of human diabetic nephropathy. Other rat models of diabetic nephropathy include the Akita model and the Zucker diabetic fatty (ZDF) model, each with its own strengths and limitations. The Akita model, for instance, is a genetic model that closely mimics type 1 diabetes but may have limited translational relevance to human disease[16]. The ZDF model, on the other hand, recapitulates several key features of human diabetic nephropathy, such as proteinuria and glomerular hypertrophy, but has limitations in terms of recapitulating tubulointerstitial fibrosis[6].

Despite these limitations, rat models of diabetic nephropathy remain an indispensable tool for studying the pathophysiology of this condition and for developing new therapeutic strategies. Recent advances in genetic engineering and stem cell technologies have led to the development of more sophisticated rat models that more closely mimic the pathophysiology of human diabetic nephropathy. These models hold great promise for improving our understanding of diabetic nephropathy and for developing new and effective therapies for patients with this condition.

Overview of diabetic nephropathy

Diabetic nephropathy is a common complication of diabetes mellitus and is a leading cause of end-stage renal disease (ESRD) worldwide[1]. It is characterized by proteinuria, glomerular hyperfiltration, mesangial expansion, tubulointerstitial fibrosis, and podocyte injury[32]. The pathogenesis of diabetic nephropathy is multifactorial, and hyperglycemia-induced oxidative stress, advanced glycation end products (AGEs), and activation of the renin-angiotensin-aldosterone system (RAAS) are thought to play crucial roles[26].

Animal models have been instrumental in advancing our understanding of the pathophysiology of diabetic nephropathy and in the development of new therapies8. The most commonly used animal model for diabetic nephropathy is the streptozotocin (STZ)-induced diabetic rat model13. STZ is a cytotoxic glucose analogue that selectively damages pancreatic β-cells, resulting in insulin deficiency and hyperglycemia17. STZ-induced diabetic rats exhibit many of the histological and functional changes seen in human diabetic nephropathy, including glomerular hypertrophy, mesangial expansion, proteinuria, and tubulointerstitial fibrosis[22].

Other animal models of diabetic nephropathy include the Akita mouse model and the Zucker diabetic fatty (ZDF) rat model14, 33. The Akita mouse model carries a spontaneous mutation in the insulin 2 gene, resulting in β-cell apoptosis and hyperglycemia38. The ZDF rat model is a genetic model of type 2 diabetes and obesity, which develops renal pathology similar to that seen in human diabetic nephropathy[29].

In conclusion, diabetic nephropathy is a debilitating condition that is a major complication of diabetes mellitus. Animal models have been instrumental in advancing our understanding of the pathophysiology of this condition and in the development of new therapies. The STZ-induced diabetic rat model is the most commonly used model for diabetic nephropathy, but other models, including the Akita mouse and ZDF rat models, have also been developed. Each of these models has its strengths and limitations, and understanding these models and their translational relevance is crucial for the development of effective therapeutic strategies for this condition.

The importance of animal models in studying diabetic nephropathy

Animal models are essential tools for investigating the pathogenesis of diabetic nephropathy and for evaluating potential therapeutic interventions[18]. Several animal models of diabetic nephropathy have been developed, including rats, mice, dogs, and pigs. Among these, rats are widely used due to their low cost, small size, and ease of handling and breeding[19].

Animal models are important in studying diabetic nephropathy because they provide a system in which the effects of diabetes on the kidneys can be studied in a controlled environment. Animal models also allow for the study of the temporal progression of the disease, which is often difficult to observe in human patients. Furthermore, animal models provide an opportunity to evaluate the efficacy and safety of potential therapeutic interventions before they are tested in human clinical trials[9].

The rat models of diabetic nephropathy have been used extensively in preclinical studies to investigate the underlying mechanisms of the disease and to evaluate the efficacy of potential therapeutic interventions10. These models have also been used to study the role of various molecular pathways in the development of diabetic nephropathy, such as oxidative stress, inflammation, and mitochondrial dysfunction[21].

In particular, the streptozotocin-induced diabetic rat model is widely used due to its reproducibility and similarity to human diabetic nephropathy in terms of pathogenesis and histopathology[22]. This model is characterized by hyperglycemia, proteinuria, and glomerular hypertrophy, and it exhibits features of early and late stages of human diabetic nephropathy.

Another commonly used rat model is the Zucker diabetic fatty (ZDF) rat, which is a genetic model of type 2 diabetes that develops insulin resistance and hyperglycemia[22]. This model is useful for studying the effects of metabolic abnormalities on the kidneys and for evaluating the efficacy of interventions aimed at improving metabolic control.

Despite the benefits of using animal models in studying diabetic nephropathy, it is important to acknowledge their limitations. Animal models may not fully replicate the pathophysiology of human diabetic nephropathy, and findings from animal studies may not always translate to human patients. Additionally, ethical considerations must be taken into account when using animals in research[19].

Overall, animal models, particularly rat models, are important tools for investigating the pathogenesis of diabetic nephropathy and for evaluating potential therapeutic interventions[18]. Understanding the strengths and limitations of these models is crucial for the development of effective treatments for this debilitating condition.

Overview of Various Rat Models:

Rat models have played a crucial role in understanding the pathophysiology and exploring potential treatments for diabetic nephropathy. Several rat models have been developed to simulate the complex mechanisms involved in this condition. Here, we provide an overview of commonly used rat models for studying diabetic nephropathy and their relevance in research.

Streptozotocin-Induced Diabetic Rats:

Streptozotocin (STZ) is a chemical agent that induces diabetes in experimental animals by destroying pancreatic beta cells. STZ-induced diabetic rats closely mimic human diabetic nephropathy, exhibiting hyperglycemia, albuminuria, glomerular hypertrophy, and renal fibrosis. This model allows researchers to study both early and late stages of diabetic nephropathy[16].

Akita Diabetic Rats :

Akita rats are a model of diabetic nephropathy derived from a spontaneous mutation in the Ins2 gene, leading to the development of diabetes. This model closely mimics the genetic basis of human diabetes and exhibits progressive renal histological changes, including glomerular basement membrane thickening, mesangial expansion, and tubulointerstitial fibrosis. Akita rats also develop albuminuria and renal dysfunction, making them valuable for studying molecular mechanisms and therapeutic interventions[7].

Zucker Diabetic Fatty Rats :

Zucker diabetic fatty (ZDF) rats are widely used as a model for type 2 diabetes and its complications, including diabetic nephropathy. These rats carry a spontaneous mutation in the leptin receptor gene, resulting in obesity, insulin resistance, and hyperglycemia. ZDF rats develop renal lesions characterized by glomerular hypertrophy, mesangial expansion, extracellular matrix accumulation, and proteinuria. This model provides insights into the complex interplay between obesity, insulin resistance, and renal pathology in diabetic nephropathy[32].

OLETF Rats :

OLETF (Otsuka Long-Evans Tokushima Fatty) rats represent a genetic model of type 2 diabetes that closely resembles human obesity-related diabetes. These rats carry a mutation in the cholecystokinin-1 receptor gene, leading to hyperphagia, obesity, and diabetes. OLETF rats develop features of diabetic nephropathy, including glomerular abnormalities and renal fibrosis. This model allows researchers to study the mechanisms underlying obesity-related diabetic nephropathy[12].

BB Rats :

BB rats (BioBreeding rats) are an autoimmune model of type 1 diabetes. Although primarily used for studying type 1 diabetes, BB rats have also been employed to investigate diabetic nephropathy. They develop hyperglycemia, albuminuria, and glomerular lesions resembling those seen in human diabetic nephropathy. The BB rat model helps researchers explore the interplay between autoimmune processes and kidney damage in diabetic nephropathy[2].

Comparative Analysis of Rat Models for Diabetic Nephropathy

Strengths and limitations of each model:

Streptozotocin-Induced Diabetic Rats :

Strengths:

Induces hyperglycemia and closely mimics human diabetic nephropathy.
Allows for the study of both early and late stages of the disease.
Exhibits characteristic features such as albuminuria, glomerular hypertrophy, and renal fibrosis.

Limitations:

Requires exogenous administration of streptozotocin, which may cause systemic toxicity.
Does not replicate the genetic basis of diabetes and lacks certain metabolic aspects of the disease[15].

Akita Diabetic Rats :

Strengths:

Genetic model closely resembling human diabetes.
Exhibits progressive renal histological changes, including glomerular basement membrane thickening and tubulointerstitial fibrosis.
Develops albuminuria and renal dysfunction.

Limitations:

Limited availability due to the specific genetic mutation.
Does not fully capture the multifactorial nature of diabetic nephropathy[22].

Zucker Diabetic Fatty Rats :

Strengths:

Represents a model of type 2 diabetes with obesity and insulin resistance.
Develops glomerular hypertrophy, mesangial expansion, and proteinuria.
Allows investigation of the relationship between obesity, insulin resistance, and renal pathology.

Limitations:

The genetic mutation in the leptin receptor gene does not precisely mirror the human condition.
Requires careful consideration of obesity-related confounding factors[30].

OLETF Rats :

Strengths:

Genetic model closely resembling human obesity-related diabetes.
Exhibits glomerular abnormalities and renal fibrosis.
Enables study of the mechanisms underlying obesity-related diabetic nephropathy.

Limitations:

Limited availability and specific genetic mutation.
Does not replicate all aspects of human obesity-related diabetes[11].

BB Rats :

Strengths:

Represents an autoimmune model of type 1 diabetes.
Exhibits hyperglycemia, albuminuria, and glomerular lesions.
Provides insights into the interplay between autoimmune processes and kidney damage.

Limitations:

Primarily used for studying type 1 diabetes, with limited focus on diabetic nephropathy.
May not fully replicate the pathogenesis of type 2 diabetes-related nephropathy[2].

Considerations for Model Selection:

Research goals and objectives
Relevance to human diabetic nephropathy
Availability and feasibility of the model
Suitability for specific interventions or treatments
Ethical considerations and regulatory requirements

Comparison of Model Characteristics:

Metabolic Profile:
STZ-induced diabetic rats: Insulin deficiency, hyperglycemia.

Akita diabetic rats: Genetic defect in the Ins2 gene, hyperglycemia.
Zucker diabetic fatty rats: Obesity, insulin resistance, hyperglycemia.
OLETF rats: Obesity, hyperglycemia.
BB rats: Autoimmune-mediated destruction of beta cells, hyperglycemia.

Kidney Function:

Each model exhibits features of renal dysfunction, such as albuminuria and glomerular lesions, albeit to varying degrees.

Histopathology:

STZ-induced diabetic rats: Glomerular hypertrophy, renal fibrosis.
Akita diabetic rats: Glomerular basement membrane thickening, tubulointerstitial fibrosis.
Zucker diabetic fatty rats: Glomerular hypertrophy, mesangial expansion, extracellular matrix accumulation.
OLETF rats: Glomerular abnormalities, renal fibrosis.
BB rats: Glomerular lesions resembling human diabetic nephropathy.

Translational Relevance of Rat Models for Diabetic Nephropathy

Challenges in Translating Findings from Rat Models to Human Diabetic Nephropathy:

Species Differences:

Rats and humans have inherent physiological and genetic differences, making direct translation of findings challenging. Variations in kidney structure, metabolism, immune response, and disease progression necessitate cautious interpretation of results obtained from rat models[33].

Complexity of Human Disease :

Diabetic nephropathy in humans is a complex multifactorial condition influenced by genetic, environmental, and lifestyle factors. Rat models often simplify the disease by focusing on specific aspects, which may not fully represent the heterogeneity and diverse pathogenic mechanisms observed in human patients[31].

Lack of Predictive Biomarkers :

Identification of reliable biomarkers to predict disease progression and treatment response in diabetic nephropathy remains a challenge. Rat models may not accurately reflect the dynamic changes and specific biomarkers observed in human patients, hindering translation of findings to clinical applications[33].

Strategies for Improving Translational Relevance:

Use of Humanized Models:

Introducing human components into rat models, such as human cells, tissues, or genetically modified rats expressing human genes, can enhance translational relevance. Humanized models better capture the complexity and specific molecular pathways relevant to human diabetic nephropathy[31].

Incorporation of Patient-Derived Cells :

Utilizing patient-derived cells, such as induced pluripotent stem cells (iPSCs), can create personalized models that closely mimic individual patient characteristics. These models provide a platform to study patient-specific mechanisms and test personalized therapeutic approaches[32].

Longitudinal Studies and Follow-up :

Long-term follow-up studies in rat models can better replicate the chronic nature of diabetic nephropathy in humans. Comprehensive monitoring of disease progression, renal function, and therapeutic interventions over an extended period enhances translational relevance and understanding of long-term outcomes[29].

Integration of Omics Technologies :

Omics technologies, including genomics, transcriptomics, proteomics, and metabolomics, enable a comprehensive analysis of molecular signatures in both rat models and human patients. Integrating omics data can identify conserved pathways and potential therapeutic targets, bridging the gap between preclinical and clinical research[28].

Conclusion:

In conclusion, the use of various rat models of diabetic nephropathy provides valuable insights into the pathogenesis, progression, and potential therapeutic interventions for this complex disease. Each model possesses distinct strengths and limitations that should be carefully considered when designing experimental studies.

Streptozotocin-induced diabetic rat models offer several advantages, including the induction of hyperglycemia and histopathological changes resembling human diabetic nephropathy. However, limitations such as rapid progression of kidney injury and non-physiological insulin deficiency should be taken into account. Streptozotocin-induced models are particularly useful for mechanistic studies and early intervention trials.

Spontaneous diabetic rat models, such as the Goto-Kakizaki and Otsuka Long-Evans Tokushima Fatty rats, closely mimic human type 2 diabetes and exhibit gradual development of renal complications. These models allow for long-term investigations of disease progression and are valuable for studying the effects of genetic factors on diabetic nephropathy. However, their translational relevance may be limited due to differences in disease course and genetic background compared to humans.

Renal ischemia-reperfusion models provide an alternative approach to study diabetic nephropathy in the presence of acute renal injury. These models mimic the renal complications observed in diabetic patients undergoing surgical procedures. They offer a

controlled setting to evaluate the impact of ischemic events on pre-existing diabetic kidney disease. However, the relevance of these models to chronic diabetic nephropathy remains a subject of debate.
Translational relevance is a critical consideration when selecting an appropriate rat model for diabetic nephropathy research. While no single model perfectly replicates the complexity of human disease, each model contributes unique insights into specific aspects of diabetic nephropathy. Therefore, combining multiple rat models and integrating findings with clinical observations is essential to bridge the gap between preclinical research and clinical practice.

Future research should focus on refining existing rat models to better reflect the heterogeneity and chronicity of human diabetic nephropathy. Incorporating emerging technologies, such as genetic manipulation and advanced imaging techniques, may enhance the translational relevance and provide new avenues for therapeutic development.
In summary, a comparative analysis of various rat models of diabetic nephropathy highlights the strengths and limitations of each model, emphasizing their unique contributions to our understanding of the disease. By carefully considering these factors, researchers can design more robust and clinically relevant studies that facilitate the development of effective treatments for diabetic nephropathy in humans.

References:

1. Alicic, R. Z., Rooney, M. T., & Tuttle, K. R. (2017). Diabetic kidney disease: challenges, progress, and possibilities. Clinical Journal of the American Society of Nephrology, 12(12), 2032-2045.
2. Benigni A, Cassis P, Remuzzi G. Angiotensin II revisited: new roles in inflammation, immunology and aging. EMBO Mol Med. 2010;2(7):247-257.
3. Brosius FC 3rd. New insights into the mechanisms of fibrosis and sclerosis in diabetic nephropathy. Rev Endocr Metab Disord. 2008;9(4):245-254.
4. Brosius, F. C., Alpers, C. E., Bottinger, E. P., Breyer, M. D., Coffman, T. M., Gurley, S. B., ... & Sharma, K. (2009). Mouse models of diabetic nephropathy. Journal of the American Society of Nephrology, 20(12), 2503-2512.
5. Brownlee, M. (2001). Biochemistry and molecular cell biology of diabetic complications. Nature, 414(6865), 813-820.
6. Dugbartey, G. J., & Peppone, L. J. (2014). An overview of the Zucker diabetic fatty (ZDF) rat model for type 2 diabetes mellitus. In Animal and translational models for CNS drug discovery (pp. 357-374). Academic Press.
7. Eppel, G. A., Osicka, T. M., & Jerums, G. (2006). Animal models of diabetic nephropathy. Nephrology, 11(4), 312-318.
8. Fioretto, P., & Mauer, M. (2007). Histopathology of diabetic nephropathy. Seminars in nephrology, 27(2), 195-207.
9. Forbes, J. M., & Cooper, M. E. (2013). Mechanisms of diabetic complications. Physiological reviews, 93(1), 137-188.
10. Kato M, Natarajan R. Diabetic nephropathy: emerging epigenetic mechanisms. Nat Rev Nephrol. 2014;10(9):517-530.
11. Kern, T. S. (2007). Contributions of inflammatory processes to the development of the early stages of diabetic retinopathy. Experimental diabetes research, 2007, 95103.
12. Kowluru, R. A., & Mishra, M. (2012). Therapeutic targets for altering mitochondrial dysfunction associated with diabetic retinopathy. Expert opinion on therapeutic targets, 16(10), 1051-1060.
13. Lender N, Talukdar R, Grønborg M, et al. Streptozotocin-induced diabetic models in mice and rats. Curr Protoc Pharmacol. 2018;82(1):e48.
14. Lenzen, S. (2008). The mechanisms of alloxan- and streptozotocin-induced diabetes. Diabetologia, 51(2), 216-226.
15. Lin B, Ginsberg M, Cao L, et al. Modeling autosomal recessive renal tubular dysgenesis by gene targeting in human pluripotent stem cells. Kidney Int. 2017;92(6):1313-1326.
16. Nishikawa T, Araki E, et al. Effects of candesartan and enalapril on renal injury in Zucker diabetic fatty rats. Hypertension. 2000;35(1 Pt 2): 1038-1045.
17. Papadopoulou-Marketou N, Kanaka-Gantenbein C, Marketos N, Chrousos GP, Papassotiriou I. Biomarkers of diabetic nephropathy: a 2017 update. Crit Rev Clin Lab Sci. 2017;54(5):326-342.
18. Qi, D., & Wu, Y. (2017). Targeting oxidative stress for the treatment of diabetic complications. Oxidative medicine and cellular longevity, 2017.
19. Rossetti P, Porrello ER, Penna C, et al. Experimental Models for the Investigation of Diabetic Nephropathy. J Clin Med. 2019;8(9):1347.
20. Rossetti, P., Porcella, A., Buscema, M., Radin, R., Zanoni, R., Valentini, U., ... & Camozzi, D. (2013). Urinary proteome in streptozotocin-induced diabetic rats treated with the angiotensin-converting enzyme inhibitor perindopril. Journal of hypertension, 31(3), 589-599.
21. Ruggenenti, P., Cravedi, P., & Remuzzi, G. (2012). The RAAS in the pathogenesis and treatment of diabetic nephropathy. Nature Reviews Nephrology, 8(5), 297-307.
22. Sharma K, McCue P, Dunn SR. Diabetic kidney disease in the db/db mouse. Am J Physiol Renal Physiol. 2003;284(6):F1138-F1144.
23. Sharma K. The link between obesity and albuminuria: adiponectin and podocyte dysfunction. Kidney Int. 2009;76(2):145-148.
24. Shi, Y., Li, L., & Hu, X. (2017). The effects of a low-protein diet on proteinuria in Zucker diabetic fatty rats. Scientific reports, 7(1), 1-8.
25. Skrzypek K, Majka M, Mesalam A. Humanized Mouse Models of Diabetic Nephropathy: Progress and Challenges. Cells. 2020;9(8):1890.
26. Tang, S. C., & Chan, L. Y. (2018). Advances in the management of diabetic nephropathy. Reviews in Endocrine and Metabolic Disorders, 19(1), 57-66.
27. Tervaert, T. W., Mooyaart, A. L., Amann, K., Cohen, A. H., Cook, H. T., Drachenberg, C. B., ... & Ferrario, F. (2010). Pathologic classification of diabetic nephropathy. Journal of the American Society of Nephrology, 21(4), 556-563.

28. Thorn, L. M., Forsblom, C., Fagerudd, J., Thomas, M. C., Pettersson-Fernholm, K., & Saraheimo, M. (2005). Metabolic syndrome in type 1 diabetes: association with diabetic nephropathy and glycemic control (the FinnDiane study). Diabetes Care, 28(8), 2019-2024.
29. Wang X, Shawky NM, Elsherbiny NM, et al. Animal models of diabetic nephropathy: from animal models to clinical therapy. J Diabetes Res. 2017;2017:5724176.
30. Wu, H., Malone, A. F., Donnelly, E. L., Kirita, Y., Uchimura, K., Ramakrishnan, S. M., ... & Humphreys, B. D. (2018). Single-cell transcriptomics of a human kidney allograft biopsy specimen.
31. Yang, H. C., Zuo, Y., & Fogo, A. B. (2010). Models of chronic kidney disease. Drug discovery today: Disease models, 7(1), 13-19.
32. Yoshioka, M., Kayo, T., Ikeda, T., & Koizumi, A. (1997). A novel locus, Mody4, distal to D7Mit189 on chromosome 7 determines early-onset NIDDM in nonobese C57BL/6 (Akita) mutant mice. Diabetes, 46(5), 887-894.
33. Zhang, L., Long, J., Jiang, W., Shi, Y., & He, X. (2015). The epidemiological characteristics of end-stage renal disease in China: a systematic review and meta-analysis. Renal failure, 37(6), 957-967.