Proceedings of the International Conference on Modern Medicine and Global Health (ICMMGH 2023)
DOI: 10.54254/2753-8818/6/20230113

Research progress in the pathogenesis and treatment of diabetic nephropathy

Yedi Zhou

Department of Pharmacology, Nanjing University of Chinese Medicine Hanlin College, Taizhou, 225300, China

dorothy_zyd@163.com

Abstract. Diabetic nephropathy (DN) is one of the most common, frequent, age-related diseases, and it is also an important cause of chronic renal failure and end-stage renal diseases. It has always been one of the research hotspots. The high cost of treatment will bring a great burden to society and families. Therefore, it is very important to study the pathogenesis and treatment methods of DN. At present, many methods have been put forward for clinical diagnosis and treatment like Thiazolidinediones, renin inhibitor drug -aliskiren, tregs cells. These methods have their own advantages and disadvantages. However, the etiology of diabetic nephropathy is complicated and the course of the disease is long, and current treatments cannot achieve the expected target. Scholars also have studied many symptomatic treatment methods for different pathogenesis. However, the specific pathogenesis of DN has not yet been fully elucidated, and there is no special medicine for DN yet. This article briefly reviews the pathogenesis and treatments of DN based on the existing kinds of literature and new advances to provide some references for its clinical diagnosis and treatment.

Keywords: diabetic nephropathy, diabetes mellitus, pathogenesis, insulin resistance, metabolic disorders.

1. Introduction

Diabetic nephropathy is glomerulosclerosis caused by diabetic microangiopathy. Once formed, most patients will further develop into end-stage renal disease, and the 5-year survival rate of patients with end-stage renal disease is usually less than 20% [1]. The pathogenesis of DN is complex and caused by the interaction of multiple factors and pathways. At present, there are many clinical directions for the pathogenesis of diabetic nephropathies, such as Insulin resistance, Renin, Inflammatory Mechanisms Caused by Metabolic Disorders, etc. [2-4]. In the past, it was generally believed that proteinuria was an important sign of diabetic nephropathy, and urinary microalbumin was an important indicator for judging early diabetic nephropathy [5]. The appearance of urinary microalbumin heralded the initiation of diabetic nephropathy, but some patients with type 2 diabetes did not suffer from renal damage after renal damage. To rule out non-diabetic kidney injury, the diagnosis must be confirmed by renal biopsy. In addition, diabetes can lead to renal vascular damage and affect intrarenal blood flow, and clinical monitoring of renal blood flow by color Doppler ultrasound can provide a basis for early diagnosis of diabetic nephropathy, and has the characteristics of simple operation, non-invasive, and repeatable monitoring [6]. There are also many commonly used clinical treatment methods for diabetic nephropathy,

DOI: 10.54254/2753-8818/6/20230113

like Thiazolidinediones, renin inhibitor drug -aliskiren, tregs cells, etc. [7]. With the deepening of medical research, some new treatment programs have been developed, which have shown advantages in delaying the progression of the disease and improving the quality of life [8]. This article reviews the research progress of clinical diagnosis and treatment of diabetic nephropathy.

2. Pathogenesis of DN and its targeted treatment

2.1. Insulin resistance (IR) and Thiazolidinediones (TZD)

A large number of studies have shown that inflammation is closely related to the occurrence and development of insulin resistance in DN podocytes, and the expression of inflammatory factors in the serum of DN patients is increased [9]. Due to the existence of IR, obese patients are often accompanied by hyperinsulinemia, and their glomerular plasma flow and glomerular filtration rate increase significantly, manifesting as glomerular hypertrophy [10]. Insulin itself can directly act on the efferent arterioles, aggravating the state of glomerular hyperfiltration and hyperperfusion. In addition, insulin can stimulate multiple cytokines, such as insulin-like growth factor 1 (IGF-1) and IGF-2, which in turn further aggravate the occurrence of glomerular hypertrophy. Insulin can also increase the reabsorption of sodium in the renal tubules, leading to sodium and water retention in the body and the formation of hypertension. Under the stimulation of hyperinsulinemia, liver lipid Increased protein synthesis, and hyperlipidemia [11]. Hyperlipidemia can not only increase cytokine release and extracellular matrix (ECM) production by acting on low-density lipoprotein (LDL) receptors on mesangial cells, resulting in mesangial lesions, but also directly cause renal Injury of spherical podocytes and formation of FSGS-like lesions. Insulin can also increase the reabsorption of uric acid by the renal tubules, causing patients to have hyperuricemia, thereby aggravating renal damage [12].

Thiazolidinediones (TZDs) is a new kind of drugs for the treatment of diabetes. It is thought to reverse the IR state in the body. YANG proved that thiazolidinedione (TZD) can improve podocyte insulin resistance, reduce podocyte injury and apoptosis by inhibiting the secretion of pro-inflammatory factors by macrophages, and improve renal function to delay renal failure, indicating that inflammatory response-related C -JNK pathway is the main signaling pathway of podocyte insulin resistance [13].

2.2. Renin and renin inhibitor drug-aliskiren

Angiotensin II (Ang II) is the most important biologically active substance in the renin-angiotensin system, and the abnormal activation of Ang II is involved in the occurrence of diabetic nephropathy and fibrosis [14]. AngII is not only involved in renal damage through hemodynamic effects but also through non-blood flow Kinetic action promotes mesangial cell proliferation and hypertrophy, leading to extracellular matrix accumulation and renal fibrosis [15]. AngII can induce the proliferation of glomerular mesangial cells, and significantly enhance the level of TGF-β/Smad signal transduction and type IV collagen [16].

Therefore, RAS is one of the main mechanisms of diabetic nephropathy. Blocking RAS can alleviate glomerulosclerosis and reduce proteinuria, thereby, delaying the progression of diabetic nephropathy. RAAS inhibitors can improve renal interstitial fibrosis in diabetes and reduce the production of fibrogenic growth factors. RAAS inhibitors can also prevent tubulointerstitial fibrosis by acting directly on proximal tubular epithelial cells and inhibiting hyperglycemia-induced growth factor production, thereby inhibiting fibroblast activation [17].

At present, aliskiren has become the first-line drug for the treatment of DN. By binding to the active site of renin, aliskiren blocks the binding of the substrate to the active site of renin and directly inhibits the catalytic activity of renin [18]. Inhibiting the rate-limiting step of the RAS cascade. Animal models of diabetic nephropathy show that aliskiren can reduce podocyte lesions, reduce glomerular pressure, inhibit glomerular interstitial fibrosis, reduce oxidative stress and other effects, reduce urinary protein excretion, and delay the progression of diabetic nephropathy [19]. In a multicenter randomized double-blind trial to study whether aliskiren combined with ACEI or ARB can benefit patients with diabetic nephropathy, the results show that the combination of the two not only reduces the cardiovascular events

DOI: 10.54254/2753-8818/6/20230113

of diabetic nephropathy, delay the progression of diabetic nephropathy, but also Adverse reactions such as hypotension, hyperkalemia, and acute kidney injury are more frequent than those of ACEI or ARB alone [20].

2.3. Inflammatory mechanisms caused by metabolic disorders and tregs cells

Metabolic disorders are the main initiating factors in the pathogenesis of DN inflammation. Long-term hyperglycemia leads to excessive accumulation of AGEs in the body. On the one hand, it can directly induce monocyte-macrophages, mesangial cells, and podocytes to secrete inflammatory cytokines, such as TNF. -α, IL-1α, IL-6, IL-12, ROS, etc., lead to the synthesis of extracellular matrix, glomerular proliferative lesions, renal tubular dysfunction, etc. [21]. In addition, AGEs can act on RAGE receptors on macrophages and mesangial cells, activate intracellular signaling pathways, mediate the activation of renal mesangial cells, and the infiltration and activation of inflammatory cells such as macrophages into renal tissue. Various chemokines, cell adhesion molecules, growth factors, and other cytokines further promote the proliferation of glomerular mesangial cells, and the accumulation of ECM, and form a complex network of interactions among innate renal cells, inflammatory cells and various cytokines, resulting in THE Waterfall effect, speed up the process of DN [22]. Persistent inflammation in DN can cause greater damage to the kidneys, and in severe cases, it will be accompanied by progressive fibrosis, eventually leading to end-stage renal disease [23].

Some studies have found that the development of nephropathy in patients with diabetes is related to the activation of circulating T cells and the increase of renal T cells. Although there is still no evidence that T cells have a direct role in the development of DN, existing studies have confirmed that the kidneys of diabetic animal models. The number of T cells in the body will increase exponentially, and the number of these increased T cells is correlated with the degree of proteinuria [24]. Another study found that Treg can induce macrophage differentiation into an anti-inflammatory phenotype. Therefore, not all CD4 + T cell activation will aggravate DN. Depletion of Tregs cells in mice with CD25 monoclonal antibody aggravated kidney damage [25]. It can be seen that Treg cells play a great role in delaying the occurrence and development of DN, and are expected to become another new target for the prevention and treatment of DN in the future.

A large number of studies have shown that inflammation is closely related to the occurrence and development of insulin resistance in DN podocytes, and the expression of inflammatory factors in the serum of DN patients is increased [26].YANG proved that thiazolidinedione (TZD) can improve podocyte insulin resistance, reduce podocyte injury and apoptosis by inhibiting the secretion of pro-inflammatory factors by macrophages, and improve renal function to delay renal failure, indicating the inflammatory response. The related C-JNK pathway is the main signaling pathway of podocyte insulin resistance [27]. In addition, HAN et al. found that the level of IRS-1 serine phosphorylation in obese mice was reduced by knocking out the JNK gene in mice. This study once again proved that the activation of the JNK pathway is involved in insulin resistance [28]. ZHANG's study also showed that inflammatory factors can also inhibit insulin signaling and lead to insulin resistance by activating the JAK2/STAT 3/SOCS-1 pathway [29].

3. Conclusion

In fact, the above pathogenesis can be linked to a pathway - hyperglycemia. Hyperglycemia plays a connective role in the pathogenesis of DN. First, hyperglycemia can induce intracellular metabolic changes, namely by altering the ratio of glucose metabolites, fatty acids and amino acids, mitochondrial respiratory chain function, and uncoupling of respiratory chain proteins [30]. In addition, in the pathological state, the persistent high glucose state of DN patients can lead to a significant increase in the production of advanced glycation end products (AGEs), while renal function's damage causes a decrease in the clearance of AGEs, which eventually leads to a large accumulation of AGEs in the body, further aggravating the disease of Kidney damage.

Secondly, the excessive activation of the renin-angiotensin-aldosterone system (RAAS) can cause blood pressure regulation disorders and sodium-water balance to be disrupted, resulting in glomerular

DOI: 10.54254/2753-8818/6/20230113

"three highs" states, namely hypertension, hyperperfusion, and hyperfiltration, resulting in progressive damage to the kidneys and eventually renal fibrosis, which is closely related to the occurrence of DN [31]. The interaction between AGEs and the receptor for advanced glycation end-products (RAGE) activates a cascade of multiple intracellular signals that trigger inflammatory responses [32]. When the body's blood sugar rises, the main active product Ang II in RAAS is activated. The activated Ang II can induce the increase of reactive oxygen species (ROS) and cause podocyte apoptosis. Glomerular interstitial fibrosis eventually leads to DN [33]. So in the early stage of DN, the most significant thing is to control blood sugar.

DN is one of the most common complications of diabetes. Inflammation, insulin resistance, and autophagy caused by metabolic disorders may lead to the occurrence of DN, and these reasons will interact after the onset [34]. Although DN cannot be completely cured at present, and there is no specific drug for treatment, as long as active comprehensive treatment measures are taken, including the Renin-angiotensin system blockers, the drug of Thiazolidinediones and Tregs cells [35-37]. It can also play a role in delaying kidney damage. At the same time of treatment, it is necessary to formulate the best-individualized treatment plan for different populations, different physical conditions, and different etiologies to improve the quality of life of DN patients.

At present, there are various types of new hypoglycemic drugs and various mechanisms, which have shown a bright prospect for most DN patients. It is hoped that in the future, more targeted targets can be proposed for the pathogenesis of DN, and special medicines can be found. Treatments aimed at lowering blood pressure with multi-target therapy must be excellent treatments of DN.

References

[1] Umanath K, Lewis JB. Update on diabetic nephropathy:core curriculum 2018[J]. AmJ Kidney Dis,2018,71(6):884-895.Zhaochen Ma, Yudong Liu, Congchong Li, Yanqiong Zhang, Na Lin, Repurposing a clinically approved prescription Colquhounia root tablet to treat diabetic kidney disease via suppressing PI3K/AKT/NF-kB activation, Chinese Medicine, 10.1186/s13020-021-00563-7, 17, 1, (2022).

[2] Chao Chen, Dina Zhu, Shuai Zhang, Wensheng Zhang, Identification of circRNA/miRNA/mRNA regulatory network involving (+)-catechin ameliorates diabetic nephropathy mice, Food Science and Human Wellness, 10.1016/j.fshw.2021.12.023, 11, 3, (660-668), (2022).

[3] Oyunchimeg Buyadaa, Agus Salim, Jedidiah I. Morton, Karin Jandeleit-Dahm, Dianna J. Magliano, Jonathan E. Shaw, Examining the factors contributing to the association between non-albuminuric CKD and a low rate of kidney function decline in diabetes, Therapeutic Advances in Endocrinology and Metabolism, 10.1177/20420188221083518, 13, (204201882210835), (2022).

[4] Sharma K, McCue P, Dunn SR: Diabetic kidney disease in the db/db mouse. Am J Physiol Renal Physiol 284:F1138–F1144,2003

[5] Lorenz JN: A practical guide to evaluating cardiovascular, renal, and pulmonary function in mice. Am J Physiol Regul Integr Comp Physiol 282:R1565–R1582,2002

[6] Tan HongBao, Zhao Qian,and Chen Li."Penehyclidine hydrochloride suppresses inflammation response and reduces podocyte injury in diabetic nephropathy by targeting fibrinogen-like protein 2." International Immunopharmacology 107.(2022). doi:10.1016/J.INTIMP.2022.108680.

[7] Yang Tingting, et al."Corrigendum to ‘Targeting mammalian serine/threonine-protein kinase 4 through yes-associated protein/TEA domain transcription factor-mediated epithelial-mesenchymal transition ameliorates diabetic nephropathy orchestrated renal fibrosis [Metabolism Clinical and Experimental 108 (2020) 154258]." Metabolism 130.(2022). doi:10.1016/J.METABOL.2021.154963.

[8] Han MS, Jung DY, MOREL C, et al.JNK expression by macrophages promotes obesity-induced insulin resistance and inflammation[J].Science, 2013, 339 (6116) :218-222.

DOI: 10.54254/2753-8818/6/20230113

[9] Kambham N, Mark kowitz GS, ValeriA Metal. Obesity relate dglomerulopathy). : A nemergingepidemic. Kidney Int, 2001, 59:1489
[10] Cistola David P.,and Dwivedi Alok K.."Compensatory Hyperinsulinemia is a Hidden Risk Factor for Type 2 Diabetes: CARDIA 30-year Follow Up." Metabolism 128.S(2022). doi:10.1016/J.METABOL.2021.155061.
[11] Reaven GM.Thekidney: An unwilling accomph ice insyndromeX.AmJKidneyDis, 1997, 30:928
[12] Yang H C, Ma L J, Ma J, et al.Peroxisome proliferator-activated receptor-gamma agonist is protective in podocyte injury-associated sclerosis[J].Kidney Int, 2006, 69 (10) :1756-1764.
[13] Lv LL, Liu BC.Role of non-classical reninangiotensin system axis in renal fibrosis[J].Frontiers in physiology,2015,6:117.
[14] Rahimi Z. The Role of Renin Angiotensin Aldosterone System Genes in Diabetic Nephropathy [J]. Canadian journal of diabetes, 2016, 40(2):178-183.
[15] Chen Xiangmei, Li Yan, Li Wenge, Zhao Shuzhen, Ye Yizhou. "Discussion on the mechanism of angiotensin-converting enzyme inhibitors reducing glomerulosclerosis." Chinese Journal of Nephrology. 03(1998).
[16] Koszegi S, Molnar A, Lenart L,et al.RAAS inhibitors directly reduce diabetes induced renal fibrosis via growth factor inhibition[J].J Physiol, 2019,597(1):193-209.
[17] Rakusan D, Kugal P, Kramer H J, et al. Persistent antihypertensive effect of aliskiren is accompanied by by reduced proteinuria and normalization of glomerular area in Ren-2 transgenic rats[J].Am J Physiol Renal Physiol,2010,299(4):758-766.)
[18] Dong Y F, Liu L, Lai Z F, et al. Aliskiren enhances protective effects of valsartan against type 2 diabetic nephropathy in mice[J]. J Hypertens, 2010, 28(7): 1554-1565.
[19] Parving H H, Brenner B M, Mcmurray J J, et al. Ailitude Investigators. Cardiorenal end points in a trial of aliskiren for type 2 diabetes[J].N Engl J Med, 2012, 367(23):2204-2213.
[20] A/L B Vasanth Rao VR, Tan SH, Candasamy M, et al. Diabetic nephropathy: an update on pathogenesis and drug development[J]. Diabetes Metab Syndr, 2019, 13 (1) : 754 − 762.doi: 10.1016 / j.dsx .
[21] Kumar P.A, Chitra P.S, Reddy G.B. Advanced glycation end products mediated cellular and molecular events in the pathology of diabetic nephropathy[J]. Biomolecular Concepts, 2016, 7(5): 293-300.
[22] Peng X, Xiao Z, Zhang J, et al. IL-17A produced by both γδT and Th17 cells promotes renal fibrosis via RANTES-mediated leukocyte infiltration after renal obstruction[J]. J Pathol, 2015,235(1):79-89. doi:10. 1002/path. 4430.
[23] Kim YG,Kim SM,Kim KP, etal. The role of inflammasome-dependent and inflammasome-independent NLRP3 in the kidney[J]. Cells,2019,8(11):1389. doi:10. 3390/cells8111389
[24] Chikoti S, Mahwish UN, Raju SB,et al. Gender bias in the genetic vulnerability towards type 2 diabetes and diabetic nephropathy:role of forkhead box protein3 transcription factor gene variants[J]. Gene,2021,774:145426. doi:10. 1016/j. gene. 2021. 145426.
[25] Wada J, Makino H.Inflammation and the pathogenesis of diabetic nephropathy[J]. Clin Sci (Lond) , 2013, 124 (3) :139-152.
[26] Yang H.C, Ma L.J, Ma J, et al.Peroxisome proliferator-activated receptor-gamma agonist is protective in podocyte injury-associated sclerosis[J].Kidney Int, 2006, 69 (10) :1756-1764.
[27] Han M.S, Jung D.Y, Morel C, et al.JNK expression by macrophages promotes obesity-induced insulin resistance and inflammation[J].Science, 2013, 339 (6116) :218-222.
[28] Zhang Y, Zhou B, Deng B, et al.Amyloid-beta induces hepatic insulin resistance in vivo via JAK2[J].Diabetes, 2013, 62 (4) :1159-1166.
[29] Kitada M,Ogura Y,Monno I,et al.Regulating Autophagy as a Therapeutic Target for Diabetic Nephropathy[J].Current Diabetes Reports,2017,17(7):53.
[30] Ren Hongru, et al."Prescription patterns of sodium and calcium polystyrene sulfonate in patients with hyperkalemia and chronic kidney disease receiving RAAS inhibitors.." Clinical kidney journal 15.9(2022). doi:10.1093/CKJ/SFAC077.

DOI: 10.54254/2753-8818/6/20230113

[31] Wahab Nur Ainina Abd, et al."Abietic acid ameliorates nephropathy progression via mitigating renal oxidative stress, inflammation, fibrosis and apoptosis in high fat diet and low dose streptozotocin-induced diabetic rats." Phytomedicine 107.(2022). doi:10.1016/J.PHYMED.2022.154464.

[32] Hu S Y, et al."Protective effect of berberine in diabetic nephropathy: A systematic review and meta-analysis revealing the mechanism of action." Pharmacological Research 185.(2022). doi:10.1016/J.PHRS.2022.106481.

[33] Gaspar Joana M., Carvalho Humberto M.,and Camacho Morales Alberto."Editorial: Metabolic Disorders Associated With Autism Spectrum Disorders: Approaches for Intervention ." Frontiers in Neuroscience 15.(2021). doi:10.3389/FNINS.2021.809978.

[34] Tang GY, et al."Clinical efficacies, underlying mechanisms and molecular targets of Chinese medicines for diabetic nephropathy treatment and management." Acta Pharmaceutica Sinica B 11.9(2021). doi:10.1016/J.APSB.2020.12.020.

[35] Liu XJ, et al."A Review of Traditional Chinese Medicine on Treatment of Diabetic Nephropathy and the Involved Mechanisms.." The American journal of Chinese medicine .(2022). doi:10.1142/S0192415X22500744.

[36] SteppanCM, BaileyST, B hatSetal. The hormoneresistin link so besity to diabetes.Nature, 2001, 409:307

[37] Wang Yun Qian, et al."Retracted: Resistin-Like Molecule Beta (RELM-β) Regulates Proliferation of Human Diabetic Nephropathy Mesangial Cells via Mitogen-Activated Protein Kinases (MAPK) Signaling Pathway." Medical Science Monitor 28.(2022). doi:10.12659/MSM.936542.