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A Review on Diabetic Nephropathy: New Insight into Established Therapeutic Approach

Jaheda Akter and Sanjida Islam*

Department of Pharmacy, International Islamic University Chittagong, Bangladesh

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***Corresponding author:** Sanjida Islam, Department of Pharmacy, International Islamic University Chittagong, Bangladesh

Abstract

Background: Diabetic nephropathy (DN) is a principle cause of morbidity and mortality in both type 1 and type 2 diabetes mellitus. DN plays a major role in development of cardiovascular disease, in particular heart failure, the incidence of which is about 15-fold greater in patient with diabetic nephropathy. Approximately 30-35% of patients with type 1 type 2 diabetes develops diabetic nephropathy. DN is represented by microalbuminuria and macroalbuminuria and morphological changes as like glomerular thickening, interstitial fibrosis, formation of nodular glomerulosclerosis and decreased endothelial cell fenestration. Additionally, the association of renin-angiotensin-aldosterone system, wnt signaling pathway and genetic factors are the major pathway in the progression of diabetic nephropathy.

Conclusion: This review is intended to establish a new insight into traditional therapeutic approach for diabetic nephropathy. Along with potential targets, novel approach such as epigenetic drugs and miRNA modulators may compliment the current therapeutic approach to improve renal function.

Keywords: Diabetic nephropathy; Microalbuminurea; Macroalbuminuria; Glomerulosclerosis

Introduction

Diabetic nephropathy is associated with increased albumin excretion, decreased glomerular filtration rate, glomerular lesion and increased arterial blood pressure [1]. DN can be divided into 5 stages of kidney dilapidation, and symptoms appear in stage 4. All patient should be screened for albuminuria at least once per year for kidney complication. The significant signs of step 4 are swelling of ankles, legs and hands because of water retention, hematuria, fatigue and nausea. If this condition remains untreated may lead stage 5, end-stage renal disease (ESRD) [2]. In stage 5, the kidney can no longer function to meet the daily requirement and microalbuminuria (>300mg/24h), progress to extensive proteinuria (>500mg in 24 h). Various factors linked with end-stage renal diseases are hemodynamic changes, inflammation and hyperglycemia [3]. The mechanism involved in the progression of DN is still on the question. Many researchers have determined an interrelationship between the degree of hyperglycemia and progression of DN complications [4]. As because a number of pathways involved in diabetic nephropathy, treatment should be multi-targeted, encouraging a healthy lifestyle and molecular targets associated in progression of DN. Available treatment procures only symptomatic alleviation and incapable of treating the underlying pathophysiology of diabetic nephropathy.

Pathogenesis of Diabetic Nephropathy

Role cytokines in diabetic nephropathy

Studies suggested that patient suffering from diabetic nephropathy have increased serum and urine level of tumor necrosis (TNF)-alpha [5]. It had been reported that TNF-alpha, IL-6, IL-1 associated in the progression of DN, found to be involved in the impairment of interglomerular hemodynamic [6].

Genetic association in diabetic nephropathy

Angiotensin-converting enzymes (ACE)

The dysfunctional ACE gene produce excess amount of aldosterone which causes fibrosis of blood vessels and aldosterone is also found to be associated with formation of extracellular matrix and fibronectin by mesangial cells by activation of the smad2-dependent TGFB1 pathway [7].

Oxidative stress in diabetic nephropathy

Oxidant species produced by oxygen metabolism and are required in different biological operation such as cell signalling, degenerative disease, aging etc [8]. Various pathophysiological mechanisms involved in DN pathogenesis in which increased

oxidant species have been recognized as the single underlying strenuous event therefore, elevated oxidant species accommodates a decisive central and significant role in the pathogenesis of diabetic nephropathy. In vitro and in vivo experimental models of diabetes have determined that metabolic (hyperglycemia, dyslipidaemia) and hemodynamic (systemic and glomerular hypertension) insults define the two principal drivers of oxidative stress in the diabetic kidney [9]. Overexpression of glucose transport because of metabolic- hemodynamic interaction, synergistically fuels an increase in oxidant species production and development of DN and other diabetic microvascular diseases. Oxidant species causes the damage in all the layers of the glomerular filtration barrier, functional alterations of the interaction between glomerular endothelial cells with glycocalyx layer and podocyte [10].

Conventional Drugs for Diabetic Nephropathy

Glucose lowering agent in diabetic nephropathy

Sodium-glucose cotransporter 2 (SGLT2) inhibitors have been used for reducing hyperglycemia because SGLT2 is responsible for reabsorbing of the glucose in the glomerular infiltrate. Empagliflozin, an SGLT2 inhibitor, slower the progression of kidney diseases [11]. Dipeptidyl peptidase -4(DPP-4) inhibitors such as linagliptin and saxagliptin (SAVOR-TIMI 53 trial) known to reduce the amount of albuminuria [12].

Cyclooxygenase (COX) and Xanthine oxidase (XO) inhibitor in diabetic nephropathy

Aspirin as a non-specific and others specific COX-2 inhibitors improve glomerular lesion, in pre-clinical models of diabetes [13]. Purine xanthine oxidase (XO) inhibitor reduce inflammation and oxidative stress in diabetic nephropathy [14].

Hydroxy-3-methylglutaryl coenzyme A reductase inhibitors and diabetic nephropathy

It was reported that statins amend renal dysfunction and reduce renal injury by inhibition of isoprenylation of Ras and Rho GTPases. Which may lead to decreased monocyte/macrophage infiltration and activating protein-1 (AP-1) in the glomerulus, adhesion of molecules, decreased mesangial proliferation and decreased accumulation of extracellular matrix and fibrosis [15].

Endothelin receptor antagonist in diabetic nephropathy

Avosentan, an endothelin-1 receptor A antagonist, found to reduce albuminuria. A study conducted on randomized controlled trial on 56 patients treated with oral bosentan for 4 weeks improves peripheral endothelial function [16].

Antioxidants against diabetic nephropathy

Pyridoxamine can remove free radicals and carbonyl product, and block the synthesis of AGEs. Pyridoxamine phase II trials showed the normal renal function had lower average serum creatinine level. Currently PIONEER -CSG -17 trial investigating to prove such benefit about use of pyridoxamine [17]. It has been reported that teneligliptin is a DPP-4 inhibitor with antioxidant.

MicroRNA and diabetic nephropathy

Under hyperglycemia conditions, up regulated micrRNAs result in pathogenesis of diabetic nephropathy [18]. It was suggested, miR-192 & miR-200 contribute to stimulate of TGF-beta 1 and fibrosis, which may consequently cause renal damage [19]. Therefore, miRNA may inhibit diabetic nephropathy by regulating various biological processes. Application of kidney protective miRNAs and knockout of inducing miRNA could be some of the approaches to restoring renal function in diabetic nephropathy [20].

Future Prospect of Drugs for Diabetic Nephropathy

Recent studies are gathering the evidence about involvement of autophagy with DN because of its cryoprotective activity in the kidney [21]. mTOR may suppress autophagy. mTORC1 inhibitors such as rapamycin or sirolimus have been found to be effective as renoprotective agents except for the negative effect on renal function and proteinuria [22].

Update on Recent Clinical Trials

Due to the distinct and complicated pathogenic mechanism associated with DN the failure rate of potential new drugs in clinical trials above 90% with only a fistful of these therapies achieving phase III trials. Summarizing the outcome of recently completed clinical trials in the past 5 years (2013-2018) and shown in Table 1 [23].

Table 1: Summarizing the outcome of recently completed clinical trials in the past 5 years (2013-2018).

Drug	Target	Outcome
LY3016859	Epidermal growth factor ligand inhibitor	Reduced proteinuria and albuminuria
Lipo-prostaglandin E1	Cytokine & Angiopoietin inhibitior	Improve renal hypoxia
N-accetylcysteine	Antioxidants	Reduced albuminuria
Baricitinib	Janus kinase inhibitor	Lower UACR
PF-04634817	Chemokine inhibitor	Reduction in UACR, blood pressure

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Conclusion

Diabetic nephropathy remains one of the most prevalent and life-threatening complications of diabetes. Diabetic nephropathy cases increasing rapidly around the world. Recently available therapies provide only symptomatic relief and not capable to treat underlying pathophysiology of diabetic nephropathy. This review has discussed the many factors and pathophysiological mechanisms associated with the progression of diabetic nephropathy, targets and therapeutic approaches to reduce renal impairment and improve kidney function. It also provided with new insights into the treatment of diabetic nephropathy. Novel biomarkers holding strong potential requires further clinical studies. The review also focused on the future prospect of drug for the treatment of diabetic nephropathy and update of recent clinical trials of targets for the treatment of diabetic nephropathy. A combination of therapies with epigenetic drugs and miRNAs modulators may fulfil the current treatment strategy of diabetic nephropathy.

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