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Diabetic nephropathy: New insights into established therapeutic paradigms and novel molecular targets

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ABSTRACT

Diabetic nephropathy is one of the most prevalent microvascular complication in patients suffering from diabetes and is reported to be the major cause of renal failure when compared to any other kidney disease. Currently, available therapies provide only symptomatic relief and unable to treat the underlying pathophysiology of diabetic nephropathy. This review will explore new insights into the established therapeutic paradigms targeting oxidative stress, inflammation and endoplasmic reticulum stress with the focus on recent clinical developments. Apart from this, the involvement of novel cellular and molecular mechanisms including the role of endothelin-receptor antagonists, Wnt signaling pathway, epigenetics and micro RNA is also discussed so that key molecular switches involved in the pathogenesis of diabetic nephropathy can be identified. Elucidating new molecular pathways will help in the development of novel therapeutics for the prevention and treatment of diabetic nephropathy.

Contents

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1. Introduction

Being the cause of nearly 1 in 5 deaths, diabetes is an extremely prevalent and most common non-communicable lifestyle disease. The population living with diabetes is expected to rise from 366 million to 552 million by 2030, including nearly 183 million people with undiagnosed diabetes for long duration [1–3]. These figures equate to about three new cases every ten seconds or almost ten million new cases reported per year. With approximately 61.3 million people living with diabetes, India is second to China on the global scale [4,5].

Diabetic nephropathy (DN) is a major microvascular complication that accounts for 30–47% cases of end-stage renal disorders. Different factors involved in end-stage renal disease (ESRD) includes hemodynamic changes, inflammation, and hyperglycemia [6]. Initial stages of DN are characterized by lower amounts of proteinuria or microalbuminuria (albumin excretion of 30–299 mg/24 h), if unchecked, microalbuminuria progresses to an extensive proteinuria >500 mg in 24 h and manifests DN [7]. Mechanisms involved in development and progression of DN are still unclear. However, many researchers have shown a correlation between the degree of hyperglycemia and progression of DN complications. Moreover, better control over the glycemic state is associated with a decrease in the rate of progression of diabetic kidney disease and improvement of kidney functions in diabetic patients [8]. Besides this, tight glucose control is not the only way to control diabetic complication because even after that, diabetic patients continue to develop nephropathy and other vascular complications and metabolic memory is suggested to play an important role in this [9]. Metabolic memory is a term that has been used to define the process of remembering the prior hyperglycemic environment even after the establishment of normoglycemia [10]. The idea of metabolic memory first came into the frame from Diabetes Complications and Control Trial (DCCT) and Epidemiology of Diabetes Interventions and Complications (EDIC) trial. The clinical trial was started with an objective of comparison between intensive insulin therapy and conventional insulin therapy. Findings suggested that mechanisms involved in hyperglycemic metabolic memory were non-enzymatic glycation of cellular proteins and lipids along with increased levels of reactive oxygen and nitrogen species and epigenetical changes. Several other researchers independently reported other mechanisms involved such as nuclear factor kappa beta (NF-kβ) and activation of caspase-3 in diabetes associated complications by virtue of metabolic memory [11].

Prolonged hyperglycemia-induce chronic metabolic and hemodynamic changes which modulates various intracellular signaling pathways, transcription factors, cytokines, chemokines, and growth factors. Collectively, these changes stimulate structural abnormalities such as glomerular basement membrane thickening, podocyte injury and mesangial matrix expansion along with reduced glomerular filtration rate leading to the occurrence of glomerular sclerosis and tubule-interstitial fibrosis [12]. Various research groups have reported a myriad of molecular pathways which may be involved in the development and progression of diabetic nephropathy. These pathways include the activation of protein kinase C (PKC), increased oxidative stress, enhanced flux into the polyol and hexosamine pathways and increased transforming growth factor β (TGFβ). Other pathways involved are activation of mitogen-activated protein kinase (MAPK), increased formation of advanced glycation end products (AGEs), activation of endothelin receptors, Wnt signaling and epigenetical mechanisms [13]. Experiments on mesangial cells, endothelial cells and podocytes of the kidney showed hyperglycemia-mediated activation of these critical pathways [14].

The prevention and management of diabetic nephropathy should be multi-targeted, advocating a healthy lifestyle and targeting cellular and molecular switches involved in pathogenesis of same. The goal of the management is to reduce the risk of renal disease progression, as well as the risk of cardiovascular morbidities. In this review we have discussed new insights into the established therapeutic paradigms with a focus on recent clinical developments. Apart from this, we have also discussed novel cellular and molecular mechanisms associated with pathological changes during the development and progression of diabetic nephropathy.

2. Anti-inflammatory drugs as therapeutics against diabetic nephropathy

Diabetic nephropathy involves activation of chronic inflammatory cascade and enhanced immune response [15]. Development of diabetic nephropathy is associated with significant inflammatory cells infiltration along with an increase in plasma levels of C-reactive protein (CRP) and pro-inflammatory cytokines such as vascular cell adhesion molecule-1 (VCAM-1), interleukins (IL-1, IL-6, and IL-18) and tumor necrosis factor-α (TNF-α) [16]. Transcription factors such as NF-κβ, upstream stimulatory factor (USF) 1 and 2,