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Review

# Novel therapeutic approaches for diabetic nephropathy and retinopathy

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ABSTRACT

Diabetes mellitus is a chronic disease that in the long-term increases the microvascular and macrovascular degenerative complications thus being responsible for a large part of death associated with diabetes. During the years, while preventive care for diabetic patients has improved, the increase in the prevalence of diabetes worldwide is continuous. The detrimental effects of diabetes mellitus result in microvascular diseases, which recognize hyperglycemia as major determinant. A significant number of potential therapeutic targets for the treatment of diabetic microvascular complications have been proposed, but the encouraging results obtained in preclinical studies, have largely failed in clinical trials. Currently, the most successful strategy to prevent microvascular complications of diabetes is the intensive treatment of hyperglycemia or the normalization of glycometabolic control achieved with pancreatic and islet transplantation. In this review, we focus on the novel therapeutic targets to prevent the development and progression of diabetic nephropathy and retinopathy microvascular complications.



**Contents**



## Introduction

Diabetes mellitus (DM) is a chronic disease characterized by hyperglycemia that in the long-term increases the likelihood of developing microvascular and macrovascular degenerative complications and causes an increase of morbidity and mortality [1]. Although preventive care for diabetic patients has improved during the last two decades and the rates of diabetes related complications have declined, a large burden of disease persists because of the continued increase in the prevalence of diabetes worldwide [2]. Diabetic complications are influenced by both genetic determinants of individual susceptibility and by independent accelerating factors such as hypertension, hyperhomocysteinemia and left ventricular dysfunction [3–5]. Hyperglycemia must be considered the major determinant of diabetic microvascular diseases, while free fatty acids associated to insulin resistance, must be considered the major determinant of diabetic macrovascular complications [6]. The main biological mechanisms of diabetic complications can be unified by the process of overproduction of superoxide radical oxygen species (ROS), the downstream intracellular signaling pathways and their modulators, which may serve as therapeutic target for the treatment of diabetic complications [6]. Among these targets we should mention the advanced glycation end products (AGEs) and their receptors, glucose transport

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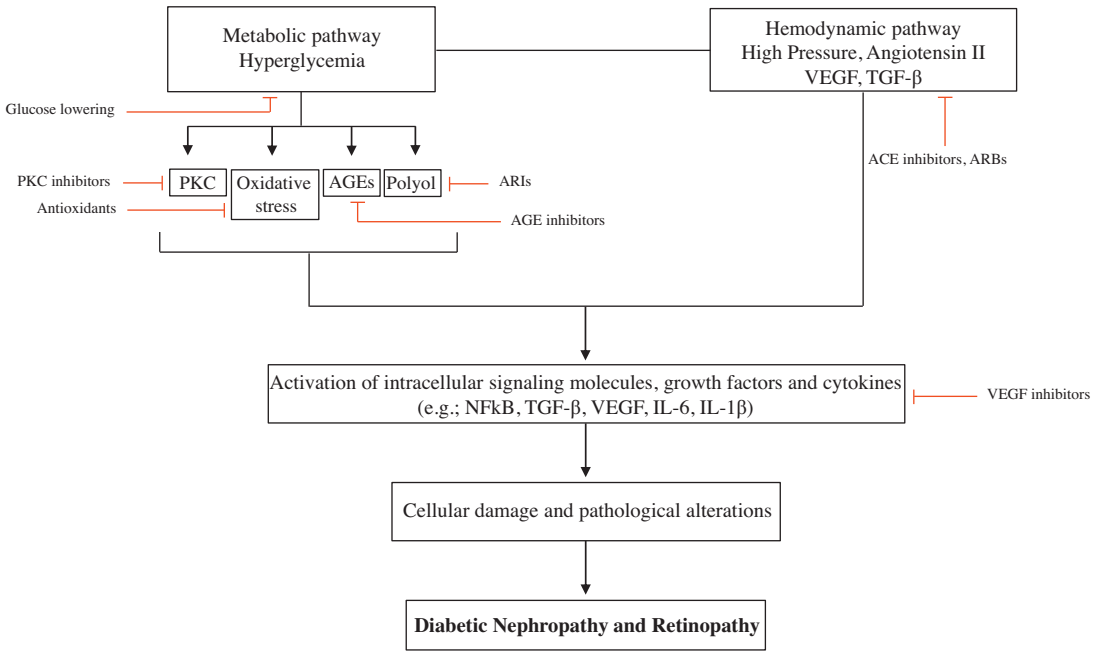


**Fig. 1.** Signaling pathways and common therapeutic approaches for diabetic nephropathy and retinopathy. *Abbreviations*: AGEs, advanced glycations end products; PKC, protein kinase C; TGF-β, transforming growth factor beta; IL-6, interleukin-6; VEGF, vascular endothelial growth factor; NFκB, nuclear factor kappa-light-chain-enhancer of activated B cells; IL-1β, interleukin-1 beta; ARBs, angiotensin II receptor blockers; ARIs, aldosterone reductase inhibitors; ACE, angiotensin-converting enzyme.

molecules, nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB), protein kinase C (PKC), inflammatory molecules such as adipokines, chemokines, adhesion molecules and pro-inflammatory cytokines [6,7]. Furthermore, pro-fibrotic molecules as epidermal growth factor, vascular endothelial growth factor (VEGF), connective tissue growth factors (CTGF) and the transforming growth factor beta (TGF-β), which are considered to potentiate the morphological alterations related to diabetic complications have also been studied [7]. In recent times, epigenetic alterations, including histone, methylation and microRNAs have demonstrated their potential role as novel therapeutic targets in the area of diabetic complications [8]. An elevated number of new potential agents are the focus of clinical trials or are in pre-clinical investigations. We focus here on a novel therapeutic approaches to prevent the development and progression of diabetic nephropathy and retinopathy microvascular complications [9] (Fig. 1).

## Diabetic nephropathy

Diabetic nephropathy (DN) is a leading cause of end stage renal disease and it seems to occur as a result of an interaction among inflammatory, metabolic and hemodynamic factors [10] (Fig. 1). The progression to end stage renal disease, favored by hyperglycemia and hypertension, is characterized by microalbuminuria and macroalbuminuria. Typically these factors induce structural abnormalities of the glomerulus, tubular epithelial cells, interstitial fibroblasts and vascular endothelial cells [11]. Over the past decade, there have been important advances in understanding the pathogenesis of diabetic nephropathy, with particular focus on inflammatory status and oxidative stress. Glucose-dependent pathways, such as advanced glycation, play an important role in the development of diabetic renal disease [12]. In addition, the accumulation of extracellular matrix seems to be the consequence of pro-sclerotic action of growth factors, including TGF-β and CTGF [13]. It is also increasingly clear that angiotensin II can enhance AGEs accumulation in the kidney and AGEs can directly modulate expression of key components of the renin-angiotensin system (RAS). Thus, it seems that metabolic and hemodynamic stimuli, triggered by diabetes, interact to increase injury and the progression of renal damage [14]. Furthermore, as observed in type 1 diabetes (T1D), the onset of nephropathy is associate with inflammatory cells infiltration and increase of C-reactive protein and inflammatory cytokines such as interleukin-1 beta (IL-1β) and vascular cell adhesion molecule 1 [15]. In addition, in type 2 diabetes (T2D), the development of nephropathy is associated with the activation of $CD8^+$ T cells and with the increase of interleukin-6 (IL-6) [7,16,17].

### *Systemic control*

Several large cohort studies have shown the efficacy of strict glycemic control treatment on the development of DN. In particular two studies, the Diabetes Control and Complications Trial (DCCT) [18] and the Epidemiology of Diabetes Interventions and Complications (EDIC) [19], resulted in clinically important, long-lasting reductions in incidence of kidney disease. In these studies, intensive diabetes therapy in T1D patients reduced the risks of microalbuminuria, macroalbuminuria and impaired glomerular filtration rate (GFR) [18,19]. Studies performed in pancreas-transplanted patients as well as in Langherans islet transplant recipients, confirmed that strict glycemic control might slow the rate of kidney damage, even if overt proteinuria has developed [20]. The efficacy of prolonged euglycemia on diabetic nephropathy has been further demonstrated in T1D patient recipients who received pancreas transplantation alone [21]. When compared with a control group treated with conventional insulin therapy at a five years follow up, these with recipients of pancreas transplantation showed histological changes associated with DN (*e.g.*; increased mesangial and glomerular volume). After 10 years of successful pancreas transplantation, significant reductions were observed in the thickness of the glomerular basement membranes and of the mesangial fractional volume [21]. Antihypertensive drugs that interrupt the RAS, such as angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs), are currently considered