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Mechanistic insight of diabetic nephropathy and its pharmacotherapeutic targets: An update

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ABSTRACT

Diabetic nephropathy (DN), a chronic complication of diabetes, is charecterized by glomerular hypertrophy, proteinuria, decreased glomerular filtration, and renal fibrosis resulting in the loss of renal function. Although the exact cause of DN remains unclear, several mechanisms have been postulated, such as hyperglycemia-induced renal hyper filtration and renal injury, AGEs-induced increased oxidative stress, activated PKC-induced increased production of cytokines, chemokines, and different inflammatory and apoptotic signals. Among various factors, oxidative stress has been suggested to play a major role underlying the onset and propagation of DN. It triggers several signaling pathways involved in DN, like AGEs, PKC cascade, JAK/STAT signaling, MAPK, mTOR, and SMAD. Oxidative stress-induced activation of both inflammatory and apoptotic signals are two major problems in the pathogenesis of DN. The FDA approved pharmacotherapeutic agents affecting against polyol pathway principally include anti-oxidants, like α-lipoic acid, vitamin E, and vitamin C. Kremezin and benfotiamine are the FDA approved AGEs inhibitors, another therapeutic target against DN. Ruboxistaurin, telmizartan, rapamycin, fenofibrate, aliskiren, and manidipine are some FDA approved pharmacotherapeutics effective against DN via diverse mechanisms. Beside this, some therapeutic agents are still waiting for FDA approval and few drugs without FDA approval are also prescribed in some countries for the management of DN. Despite the medications available in the market to treat DN, the involvement of multiple mechanisms makes it difficult to choose an optimum therapeutic agent. Therefore, much research is required to find out new therapeutic agent/strategies for an adequate pharmacotherapy of DN.

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1. Introduction

Diabetic nephropathy (DN), Kimmel Stiel-Wilson syndrome, or Nodular diabetic glomerulosclerosis and intercapillary glomerulonephritis is a major complication of diabetes. DN is the main cause of end stage renal dizease seriously affecting world population (Packham et al., 2012). It increases the rate of morbidity and mortality if not detected at early stage. Early diagnosis and essential management may delay the progression of this pathophysiology. It is characterized by morphological, ultrastructural, and functional changes of diabetic kidney followed by albuminuria (macro or micro), excessive deposition of extracellular matrix proteins, and thickening of the peripheral glomerular basement membrane (Jankun, 2012), which decreases glomerular filtration including expansion of the molecular matrix and loss of the charge barrier on the glomerular basement membrane (Parving, 2001; Rossing, 2006). DN is a multifunctional degenerative disorder where the mechanism of dizease progression is extremely complex due to the involvement of several factors like different cells, molecules, etc. (Elmarakby and Sullivan, 2012).

The term DN includes combination of several microvascular complications that often occur in diabetic kidney due to formation of advance glycation end products (AGEs), activation of protein kinase C (PKC) (Ojima et al., 2013), polyol pathway, mitogen activated protein kinases (MAPKs), poly(ADP ribose) polymerase (PARP), and release of inflammatory mediators (TNFα, IL2, IL1β, IL6, etc.), growth factors (VEGF, CTGF, etc.) and different chemokines (Juan et al., 2012). It has been observed that oxidative stress can trigger most of the degenerative pathways leading to DN. The onset and propagation of DN is extremely complex and has not been completely elucidated. The present review summarizes recent advances in understanding the biochemical and molecular mechanism(s) of DN and its possible pharmacotherapeutic targets.

2. Classification of DN

Long term exposure to diabetes induces renal complications and if untreated it leads to serious life threatening DN. Persons with long lasting diabetes will encounter histological and functional changes of the kidney before the onset of microalbuminuria (Fioretto and Mauer, 2007). Histological features show that DN comprizes three major lesions, first of all thickening of glomerular and tubular basement membranes followed by mesangial expansion and finally hyalinizes with loss of afferent and efferent arterioles. According to the new classification, Class I consists of thickening of the glomerular basement membrane (GBM). Class II represents mild (IIA) to severe (IIB) mesangial expansion. Thickening of GBM and the accumulation of mesangial matrix are the first changes which usually occur between 2 and 5 years of diabetes. The extent of mesangial expansion inversely associates with capillary filtration area, which participates in the progression from hyper-filtration to reduced glomerular filtration rate (GFR). Class III represents nodular glomerulosclerosis. Finally, Class IV is categorized as advanced DN comprizing more than 50% global glomerulosclerosis coupled with loss of podocyte (Fig. 1) (Tervaert et al., 2010). Arteriolar hyalinosis, glomerular capillary subendothelial hyaline (hyalinecaps), arteriosclerosis, and capsular-drops throughout the epithelial parietal surface of the Bowman capsule (e.g., the exudative lesions of DN) may also be present (Tervaert et al., 2010). Interstitial fibrosis participates to the rate of progression from moderate to severe reduction in GFR (Adler et al., 1986). Data on urinary biomarkers in human also support that the tubular injury plays a primary role in the development of early DN (Satirapoj et al., 2012).

3. Role of different molecules and molecular pathways involve in diabetic nephropathy and its probable pharmacotherapeutic targets

3.1. Role of Polyol pathway in diabetic nephropathy and its pharmacotherapeutic targets

3.1.1. Role of polyol pathway

Polyol pathway is an important means to diabetic nephropathy which is based upon two enzyme systems, namely aldose reductase (AR) which converts glucose to sorbitol with the help of its co-factor NADPH and sorbitol dehydrogenase (SDH) which causes transformation of sorbitol to fructose using NAD^+ as its co-factor (Fig. 2). Activation of these enzymes reduces the intracellular NADPH concentration leading to increased oxidative stress and activation of protein kinase C (Ramana, 2011). The reduction in NADPH concentration directly affects cellular oxidative defense