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Review

Diabetic nephropathy: Time to withhold development and progression - A review

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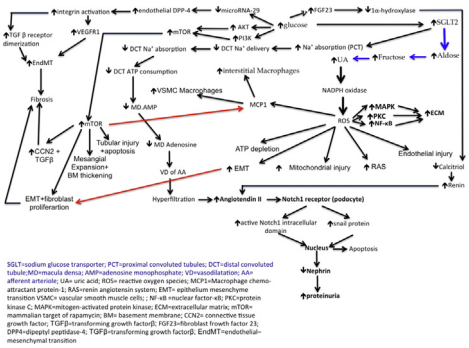
GRAPHICAL ABSTRACT



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ABSTRACT

The recent discoveries in the fields of pathogenesis and management of diabetic nephropathy have revolutionized the knowledge about this disease. Little was added to the management of diabetic nephropathy after the introduction of renin angiotensin system blockers. The ineffective role of the renin- angiotensin system blockers in primary prevention of diabetic nephropathy in type 1 diabetes mellitus necessitated the search for other early therapeutic interventions that target alternative pathogenic mechanisms. Among the different classes of oral hypoglycemic agents, recent studies highlighted the distinguished mechanisms of sodium glucose transporter 2 blockers and dipeptidyl peptidase-4 inhibitors that settle their renoprotective actions beyond the hypoglycemic effects. The introduction of antioxidant and anti-inflammatory agents to this field had also added wealth of knowledge. However, many of these agents are still waiting well-designed clinical studies in order to prove their beneficial therapeutic role. The aim of this review of literature is to highlight the recent advances in understanding the pathogenesis, diagnosis, the established and the potential renoprotective therapeutic agents that would prevent the development or the progression of diabetic nephropathy.

Introduction

Diabetic nephropathy (DN) is the most common cause of end-stage renal disease (ESRD) in most of the countries worldwide. One third of type 1 diabetes mellitus (T1DM) patients develop

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ESRD, while only 10–20% of type 2 diabetes mellitus (T2DM) patients progress to ESRD [1,2]. DN increases the overall 10-year mortality among diabetic patients at least 6 folds compared to healthy age matched non-diabetic individuals [3]. The earliest stage of DN is characterized by renal hyperfunction and hypertrophy [4]. Few years later, persistent increase in urine albumin excretion (UAE) develops. This stage is called the stage of incipient nephropathy characterized by UAE > 30 mg/day, >20 μg/min, or urine albumin:creatinine ratio (ACR) > 30 mg/g of creatinine. The persistent increase in UAE is initially associated with increased glomerular filtration rate (GFR). However, GFR shows consistent decline that becomes pronounced with the continuous increase of UAE above 300 mg/day, 200 μg/min, or when urine ACR exceeds 300 mg/g (Fig. 1)[5]. Progressive increase in blood pressure is usually associated with these renal changes. The 1st description of increased UAE was by Keen and Chlouverakis in 1963 [6]. The term "microalbuminuria" has gained popularity in 1982 after the publication of a 14-year longitudinal study that showed microalbuminuria as a predictor of increased risk of renal disease and mortality in T1DM [7]. The predictive value of microalbuminuria for renal and cardiovascular disease morbidity and mortality was later confirmed in T2DM [8]. These observations encouraged the use of renin angiotensin system blockers (RAS blockers) in patients with DN if they have incipient nephropathy [9]. However, a later study failed to demonstrate the predictive significance of microalbuminuria in DN progression [10]. Another study showed that in one third of T1DM patients that develop advanced renal disease, progression of microalbuminuria to overt proteinuria was not required for kidney disease progression [11]. These observations have lead to less enthusiasm to use RAS blockers in incipient nephropathy and to limit this mode of therapy to patients with overt nephropathy [12]. This trend was reflected in the attitude of many authorities to redefine DN as development of UAE > 300 mg/day in diabetic patients overlooking the earlier 3 stages. Consequently, treatment with RAS blockers became advised when the patients proceed to stage 4 DN. According to the new discoveries in experimental and clinical trials, a new strategy of DN treatment should be implemented. In this review, an updated approach to prevent, and control the progression of DN will be highlighted.

Methodology

In order to create this review, the authors looked for all the available literature concerned with this topic in pubmed, Ovid, Web of Science, Sciencedirect, Scopus, Cochrane Library, and Google Scholar beside the data they were collecting over the last 35 years during their attendance to meetings and workshops and during preparing their lectures in this piece of knowledge. In addition, clinicaltrials.gov website was frequently visited to look for running or just finished studies of the different therapeutic agents that have potential impact on the course of DN.

Pathogenesis of diabetic nephropathy

The effect of hyperglycemia is generally mediated through hemodynamic and multiple metabolic pathways. A stress upon the different pathogenic mechanisms that have therapeutic implications will be accomplished.

The glomerular hyperperfusion and hyperfiltration are owed to the decrease of the afferent arteriolar resistance. Increased glucose in glomerular ultrafiltrate stimulates sodium glucose transporter-2 (SGLT2) gene with consequent increased proximal tubular absorption of filtered sodium and glucose. SGLT2 in the apical membrane of the proximal tubular epithelial (PCT) cells is responsible for absorption of 90% of the glucose in the ultrafiltrate [13]. As a result, distal tubular sodium delivery decreases and hence distal tubular macula densa pays less energy in sodium absorption. Decreased energy expenditure decreases adenosine activity with consequent vasodilatation of afferent arterioles (Fig. 2) [14]. The increased glucose absorption raises intracellular glucose availability with consequent increased activity of polyol pathway that leads to increased fructose synthesis. Fructose metabolism leads to increased intracellular uric acid (UA) synthesis [15]. UA stimulates nicotinamide adenine dinucleotide phosphate (NADPH) oxidase enzyme causing increased intracellular oxidative stress, mitochondrial injury, adenosine triphosphate (ATP) depletion [16], endothelial injury, RAS activation and increased epithelial- mesenchyme transition (EMT). Excess fibroblasts infiltrate the interstitium with consequent progressive interstitial fibrosis (Fig. 3)[17].

Human glomerular mesangial cells (MCs) express NADPH oxidase [18]. ROS activates protein kinase C (PKC), mitogen-activated protein (MAP) kinase, and nuclear factor-κB (NF-κB) which eventually results in overproduction of extracellular matrix proteins (Fig. 4)[19].

Nuclear factor erythroid 2-related factor 2 (Nrf2) regulates the synthesis of many antioxidising and cytoprotective factors that can antagonize the oxidative stress and pro-inflammatory signals [20]. Nrf2 exists in the cytoplasm as an inactive complex bound to a repressor protein called Kelch-like ECH-associated protein 1 (Keap1). The free Nrf2 translocates to the nucleus where it binds to the promoter regions of genes encoding the antioxidant and phase 2 detoxifying molecules, activating their transcription. In addition, Nrf2 suppresses transcription of NF-kB [21]. Nrf2 is adaptively activated in diabetes but is not efficient enough to resist the oxidative stress provoked by hyperglycemia. The association between oxidative stress and inflammation with progression of DN directed attention towards Nrf2/Keap1 activators, as potential renoprotective agents.

Intrarenal RAS genes expression is induced in diabetes [22]. Mechanical strain increases angiotensin II (A2) production and up-regulates AT1R in podocytes [23]. Increased A2 maintains and aggravates glomerular hypertension. A2 caused *in vitro* loss of nephrin, the protein component of the slit diaphragm, in cultured podocytes [24]. Notch1 couples A2 with nephrin down regulation. Notch1 is a transmembrane receptor that plays a role in cell differentiation and renal development. Activation of Notch1 receptor

Fig. 1. Stages of Diabetic nephropathy. Stage 2 is characterized by the progressive increase in mesangial deposits on light microscopy without corresponding clinical or laboratory findings; ESRD = end stage renal disease when eGFR ≤ 15 mL/min/1.73 m^2.