Kermanshah University of Medical Sciences

Journal of Kermanshah University of Medical Science

Journal homepage: Htpp://journals.kums.ac.ir/ojs/index.php/jkums

Diabetic Nephropathy: Pathogenesis and Management

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Review Article

Article Info

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Received: 30 August, 2016
Accepted: 27 September, 2016
J Kermanshah Univ Med Sci. 2016; 20(3): 84-89

Abstract

Diabetic nephropathy (DN) is a major microvascular complication of diabetes mellitus and is the leading cause of end-stage renal disease (ESRD). Genetic, metabolic, systemic, and renal hemodynamic factors are involved in the pathogenesis of DN. Advanced glycation end products (AGEs), hypertension, oxidative stress, inflammation, and genetic susceptibility are risk factors for susceptibility to DN and its development. Management approaches of DN are based on the inhibitors of some components of the renin angiotensin aldosterone system (RAAS), AGEs, and protein kinase C (PKC) and combined antioxidants therapy with anti-inflammatory agents. The present review looks at some mechanisms involved in DN and its progression and also management approaches according to the inhibition of the risk factors of the disease.

Introduction

Diabetes mellitus is the most prevalent endocrine disorder (1). Diabetic nephropathy (DN) is one of the major microvascular complications of both type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) (2). DN develops in 30 to 35% of patients with diabetes mellitus, irrespective of blood glucose control (3). DN is manifested by microalbuminuria that subsequently can progress to macroalbuminuria. This diabetic complication is the leading cause of end-stage renal disease (ESRD) (4). In the United States, diabetes accounts for approximately 45% of cases with ESRD. The survival of diabetic dialysis patients is lower than non-diabetic patients (5).

The structural changes of the kidney such as glomerular mesangial expansion, thickening of the basement membranes, and the glomerular sclerosis in DN may be the same in various patients. However, the clinical manifestations of DN in different patients may not be similar (6).

In one third of patients with type 2 diabetes mellitus and excellent blood glucose control, DN develops, while in most patients, even with suboptimal blood glucose control and antihypertensive therapy DN is not appeared. So, a genetic susceptibility to DN has been suggested (7). Also, metabolic (poor glycemic control and hyperlipidemia), systemic, and renal hemodynamic factors are involved in the pathogenesis of DN (2). Due to the influence of genetic factors and metabolic control in the pathogenesis of DN, its development varies among diabetic patients (8).

Because of the involvement of some risk factors such as advanced glycation end products (AGEs), hypertension, oxidative stress, and inflammation and genetic susceptibility in the pathogenesis of DN, therapy approaches based on the inhibitors of some components of the renin angiotensin aldosterone system (RAAS), AGEs, and protein kinase C (PKC) have been developed for treatment and reducing DN progression. The present review looks at some mechanisms involved in DN and its progression and also therapy approaches according to the inhibition of the risk factors of the disease.

Hyperglycemia

In diabetic patients hyperglycemia increases the vasoconstrictor peptide of tissue angiotensin II (Ang II) which induces oxidative stress, glomerular hyperfiltration, endothelial damage, thrombosis, inflammation, and vascular remodeling (9). Hyperglycemia is involved in the development of DN through hypertrophy and thickening of the basement membrane, increased endothelial cell permeability to albumin, and enhanced matrix protein synthesis. Also, in the presence of hyperglycemia it might the levels of vasodilatory prostaglandins increase, which leads to enhance both renal perfusion and intraglomerular pressure and ultimately results in hyperfiltration. Further, aldose reductase converts excess glucose to sorbitol through the polyol pathway in the kidney. Increased intracellular sorbitol levels cause the depletion of intracellular myoinositol, resulting in afferent arteriolar vasodilatation, increased renal blood flow, and glomerular capillary pressure. Also, it has been suggested that the polyol pathway causes kidney damage by enhancing oxidative stress (10).

The activity of PKC in vascular smooth muscle and endothelial cells is enhanced in the presence of hyperglycemia that might be involved in the pathogenesis of DN (10).

Overexpression of some types of the Toll-like receptor (TLR), such as TLR2 and TLR4, in monocytes

is important mediators of metabolic inflammation during DN, and it has been reported to be positively associated with hemoglobin A_1c (HbA_1c) levels in diabetic patients (11).

The RAAS and hypertension

The RAAS plays a central role in the regulation of sodium metabolism, vascular tone, blood pressure, renal hemodynamic, and vascular modeling. This system is activated by hyperglycemia. In diabetic patients in the presence of hyperglycemia tissue Ang II increases, which affects glucose homeostasis and induces oxidative stress, which destroys beta cells. Increased Ang II causes glomerular hyperfiltration, endothelial damage, thrombosis, inflammation, and vascular remodeling (12, 13).

In patients with T2DM, the inhibition of RAAS reduces the progression from normo- to micro- and micro- to macro-albuminuria and slows the development of ESRD (14). Also, the intra-renal RAAS plays an important role in the progression of DN. The alterations in the level of angiotensinogen, substrate of the rennin, can control the activity of the RAAS. In T2DM patients, the urinary excretion of angiotensinogen is significantly increased and is associated with an elevation in albuminuria and serum creatinine levels. Also, it has been demonstrated that urinary angiotensinogen levels increased before the onset of microalbuminuria, and it has been suggested that urinary angiotensinogen can be an early biomarker of intrarenal RAAS status in normo-albuminuric patients with T2DM compared with controls (15).

Systemic hypertension with extracellular matrix accumulation, increased glomerular permeability, proteinuria, and glomerular sclerosis has an essential role in the initiation and progression of DN (10). In most cases, albuminuria development is associated with a gradual increase in systemic blood pressure, and the blood pressure level closely relates to the rate of decline in the glomerular filtration rate (GFR) (16).

RAAS is a major mediator of renal injury that is activated by high glucose and mechanical stress with increased local formation of Ang II in the kidneys and subsequent pathophysiological changes associated with DN (17). Systolic blood pressure and renal function is regulated by the RAAS through two opposite pathways of Ang II production by angiotensin converting enzyme (ACE) that through binding to Ang II type 1 receptor (AT1R) elevates blood pressure. While in the other pathway, angiotensin converting enzyme-2 (ACE2) degrades Ang II to Ang (1–7), which exerts vasodilatory, antiproliferative, and apoptotic functions through the Mas receptor. In normal healthy conditions, both opposing pathways work together to maintain homeostasis (13, 17).

ACE2 acts as a compensatory mechanism during hyperglycemia-induced RAAS activation. ACE2 overexpression reduces fasting blood glucose and improves glucose tolerance in diabetic mice and ameliorates impaired glucose homeostasis. Therefore, ACE2 could be a novel target for the prevention of β-cell dysfunction in T2DM (18).

ACE2 expression is increased in early stages of the nephropathy, which plays a protective role. However, later in disease progression, the expression of ACE2 decreases leading to higher level of Ang II and the development of nephropathy (19). Ang (1–7) attenuates fibrogenic and pro-inflammatory pathways and relieves renal injury. Also, this heptapeptide limits ROS generation and normalizes antioxidant pathways. Ang (1–7) suppresses nuclear factor (erythroid-derived 2)-like 2 (Nrf2) stimulation of renal angiotensinogen expression, which counterbalances Ang II actions. The transcription factor of Nrf2 influences many signaling cascades that detoxify harmful substances and maintain cellular redox homeostasis. The pathway of the ACE2/Ang 1–7/MasR axis could be a target for future therapeutics (17). So, antihypertensive therapy for lowering blood pressure has a significant renoprotective and anti-albuminuric effects. Since high intraglomerular pressure is affected by the RAAS, the use of inhibitors of the RAAS and a low protein diet can significantly slow the rate of progression of glomerular injury (16).

It has been reported that, in the presence of high glucose and Ang II, collagen production by transforming growth factor (TGF)-β, a profibrotic cytokine, is stimulated (17).

A direct interaction between AGEs and the RAAS has been found, as angiotensin converting enzyme inhibitors (ACEI) and angiotensin II receptor blockers (ARB) have significantly attenuated in vitro and in vivo production of AGEs (17).

The onset and persistence of proteinuria is considered as one of the most important risk factors for the progression of kidney disease in diabetic patients. The first step strategy to reduce proteinuria in these patients is the use of ACEI or ARB. This therapy is beneficial for both type 1 and type 2 diabetic patients, even with low-grade proteinuria and normal GFR. Therapy with combined ACEI and ARB has shown efficient reduction in proteinuria, and adverse events were usually limited to hyperkalemia and renal impairment. Thus, dual blockade has been recommended in select cases with very high urinary protein excretion. Since blocking RAAS is not always enough to avoid proteinuria, other antiproteinuric treatments, such as direct rennin inhibitors or aldosterone blockers, have been suggested (20).

Due to ineffective suppression of the pressor arm of the ACE/Ang II/AT1R axis of the RAAS by ARB and ACEI, activation of the depressor arm (ACE2/Ang (1–7) /Mas axis) is a new therapeutic target for the treatment of diabetes complications (21).

Oxidative stress

Oxidative stress is a state of accumulation of reactive oxygen species (ROS) that results in disruption of normal cell function (16). Oxidative stress plays a key role in the pathogenesis of micro- and macro-vascular complications in diabetes (17). In the presence of oxidative stress the oxidation of proteins, lipids, carbohydrates, and DNA enhances leading to tissue and organ damage (22).

During the progression of diabetes mellitus, high blood glucose and high blood pressure cause the excessive production of various ROS by both the NADH

system and mitochondria. The excessive production of intracellular ROS is a common pathway through which hyperglycemia induces renal injury. In long-term ongoing hyperglycemia, ROS causes direct and indirect damage in kidneys. ROS through stimulation of some mediators in the signaling pathways of the cellular responses such as extracellular regulated protein kinases (ERK), p38 mitogen-activated protein kinases (p38 MAPK), NF-kB, and activator protein-1 (AP-1), that may be involved in the development of DN. In the presence of oxidative stress that results from the induction of inflammatory responses by hyperglycemia, a significant destruction in the normal structure and function of the kidney leads to fibrosis. The presence of hyperglycemia with metabolic and hemodynamic disturbances in the kidneys triggers the molecular pathways that contribute to glomerular injury (16, 23, 24).

Two biomarkers of oxidative stress in patients with kidney disease are advanced oxidation protein products and isoprostane, a product of polyunsaturated fatty acid oxidation (25, 26). Also, 8-hydroxy-2-deoxyguanosine is an oxidative stress marker for DN (24).

Inflammation

It has been suggested that inflammation is a key factor in the progression of DN. Chronic inflammation contributes to DN through a direct effect of proinflammatory mediators on cellular signaling and by inducing oxidative stress (27).

Inflammation results in the production of a variety of cytokines and acute phase proteins. Interleukin 1 (IL-1), IL-6, IL-18, and tumor necrosis factor-**α** (TNF-**α**) are the main inflammatory cytokines that affect the DN development (28, 29). Nrf2, a redox-sensitive transcription factor, is implicated in inflammation and related disorders. Nrf2 activation in diabetes has a therapeutic potential through the control of oxidative stress and the regulation of inflammatory cytokines (30).

Treatment with mycophenolate mofetil protects the kidney by an antioxidant mechanism, regulated at least in part by the Nrf2/Keap1 system, in addition to its well-known anti-inflammatory effects (27).

It has been proposed that DN comprises a heavy inflammatory element triggered by metabolic disorders, protein overload, and hemodynamic abnormalities. In addition to glomerular involvement, the tubular epithelial cells also play an important role in orchestrating renal inflammation in DN (31).

AGEs are modifications of proteins or lipids that become nonenzymatically glycated and oxidized after contact with aldose sugars. These compounds activate nuclear factor kappa B (NF-*κ*B) in tubular epithelial cells and TGF-*β*-Smad signaling in mesangial cells. The activity of AGEs is mediated by their specific receptor, RAGE. The inhibition of AGEs by alagebrium results in normalization of the renal expression of RAGE and restores PKC activity to the control level (17).

High glucose mediates an inflammatory response by the activation of macrophages, mainly through transforming growth factor-β-activated kinase 1 (TAK1)/MAPKs, and TAK1/NF-κB-dependent pathways, which results in the polarization of macrophages towards a pro-inflammatory phenotype, and development of DN. TAK1 has an important role in innate immune responses and kidney disease. TAK1 is critically involved in macrophage activation (32).

Genetic susceptibility

A genetic predisposition to the development of DN has been suggested. The ACE gene is the most studied gene to be involved in the pathogenesis of DN (both micro- and macro-albuminuria) and progression from micro- to macro-albuminuria (2). The presence or absence of a 287 base pairs insert in intron 16 of the ACE gene, designated as ACE insertion/deletion (I/D) polymorphism (rs1799752), is the most studied variant of the ACE gene. The physiologic importance of this polymorphism is the association of the D allele with the highest systemic and renal ACE activity. The lower ACE activity might be one of the mechanisms underlying the protective effect of the ACE II genotype against nephropathy. The presence of this allele leads to increased GFR (4, 33). The frequency of ACE alleles varies in different ethnic groups also DN is more common in non-White populations, specifically African-Americans, Native Americans, Mexican-Americans, Asian-Americans, and those of Pacific Island descent (10). The presence of ACE I/D polymorphism may lead to susceptibility to DN (10).

The AT1R gene, one of the receptors of the angiotensin II and III is located on chromosome 3q21-q25. One of the well-studied polymorphisms of this gene is the AT1R A1166C (rs5186), located in the 3′-untranslated region of the gene (4). This polymorphism may be involved in post-transcriptional modification of AT1R mRNA (34). Many studies demonstrated an association between AT1R A1166C polymorphism and DN, especially in patients with T2DM (35–37). This association might be due to higher AT1R CC expression and increased AT1R for binding to Ang II as well as the higher affinity of this variant receptor for Ang II (38).

The vasodilator molecule nitric oxide (NO) is produced from L-arginine by endothelial nitric oxide synthase (eNOS). NO regulates endothelial function and plays an important role in the maintenance of homeostasis. The presence of eNOS variants through reduced production of NO might further complicate endothelial dysfunction and nephropathy. Studying polymorphisms of eNOS has demonstrated that the allele of eNOS 4a of the eNOS 4a/b or 894T allele of G894T alone increases the risk of developing DN, although the effect is modified by the concomitant presence of both alleles (39).

Management of DN

Intensive glycemic control (a mean HbA1c of 7%) compared to a mean HbA1c of 9.1% is useful in reducing the risk of onset of microalbuminuria or clinical albuminuria (40).

Arterial hypertension is a key risk factor for kidney damage. The first line treatment of DN is using ARB and ACEI, which improve markers of the kidney disease and slow kidney disease and improve cardiovascular diseases (2). However, although the combination treatment with an ACEI supplemented by an Ang II

receptor-blocking agent provides a more complete blockade of the RAAS and a better control of hypertension, this treatment may increase adverse events, such as hyperkalemia or acute kidney injury (41). Further, combined treatment by an ACEI/ARB and a mineralocorticoid receptor blocker is effective in decreasing albuminuria in diabetic nephropathy but increases the risk of hyperkalemia (42).

Different responses to therapy according to ACE I/D genotypes and stage of diabetic nephropathy has been indicated. In macroalbuminuric patients with DD genotype a better response to angiotensin II receptor antagonist (losartan) had been obtained while in normoalbuminuric patients with DD genotype administration of captopril (an ACE inhibitor) was more effective on lowering serum ACE activity (43). Also, a better response to captopril compared to losartan was obtained with a significant reduction of ACE activity in diabetic patients without nephropathy carrying the DD genotype. However, losartan therapy has a beneficial effect in microalbuminuric patients with II genotype compared to ID and DD genotypes (44).

While some clinical studies report the effectiveness of antioxidants for the treatment of DN, other reports fail to establish an improvement in DN with antioxidant treatment. However, combined antioxidants therapy with anti-inflammatory agent might be useful in the improvement of albuminuria and HbA_{1C} levels in diabetic patients (45).

In vivo and in vitro experiments suggest an important role for the NADPH oxidases of the Nox family, and in particular the homologue Nox4, in the pathogenesis of DN that is the major source of ROS in the diabetic kidney. Thus, Nox homologs and their associated subunits could be considered as relevant therapeutic targets for the treatment of DN through the generation and development of agents able to inhibit the Nox enzymes in a homolog-specific manner (46).

Chemokine C–C motif ligand 2 (CCL2) is involved in DN through inflammatory responses. So, inhibition of the CCL2 receptor could be a target in the treatment of DN (47).

Novel therapies with renoprotective effects such as thiazolidinediones (TZD) which are peroxisome proliferator activator receptor-gamma agonists have been suggested but it seems they may not have a major role in the treatment of DN. Also, dipeptidyl pepetidase-4 (DPP-4) inhibitors which suppress the degradation of glucagon-like peptide, an incretin that increases insulin and suppresses glucagon release, are novel candidates undergoing clinical trials for their potential for retarding DN progression. Further, activators of vitamin D receptor as anti-inflammatory and anti-proteinuric agents might be considered for retarding DN progression (31).

The lower level of vitamin D in diabetic patients compared to healthy individuals has been indicated (48). Alteration of vitamin D metabolism in DN patients is one of the mechanisms involved in the reduction of the bone mineral density in diabetic patients (49). It has been reported that the administration of a vitamin D receptor activator in combination with RAAS inhibitors (ACEI or ARB) has an additional benefit in lowering albuminuria in patients with DN (50).

Due to the association of the activation of NF-κB and pro-inflammatory chemokines/cytokines in tubular epithelial cells with the extent of the proteinuria and interstitial cell infiltration, targeting some of NF-κB-related inflammatory molecules as therapeutic potential has been proposed (31).

Conclusion

In diabetic patients, hyperglycemia through induction of oxidative stress and over expression of potential important mediators of metabolic inflammation is involved in the development of DN. Chronic inflammation through a direct effect of proinflammatory mediators of cellular signaling and also by creating a state of oxidative stress contributes to DN**.** Also, RAAS is activated by high glucose and mechanical stress with increase local formation of Ang II in the kidneys and subsequent pathophysiological changes associated with DN. In addition, a genetic susceptibility to DN based on ethnic difference in susceptibility to DN and the role of ACE I/D polymorphism has been suggested.

The first line treatment of DN is using ACEI and ARB or a combined treatment by an ACEI/ARB and a mineralocorticoid receptor blocker. Combining antioxidant therapy with an anti-inflammatory agent might be useful in the improvement of albuminuria and HbA_{1C} levels in diabetic patients. Also, inhibition of Nox enzymes and or the CCL2 receptor could be a target in the treatment of DN. Further, DPP-4 inhibitors and activators of vitamin D alone or in combination with RAAS inhibitors (ACEI or ARB), and targeting some NF-κB-related inflammatory molecules have therapeutic potential.

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