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Pathogenetic Factors Development of Diabetic Nephropathy

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Abstract: Diabetic nephropathy is a specific kidney damage in diabetes mellitus, characterized by gradual sclerosis of renal tissue, which leads to loss of filtration, nitrogen excretory and other kidney functions. According to recent studies, diabetic nephropathy contains severe inflammatory element caused by metabolic disorders, protein overload and hemodynamic disorders.

Keywords: diabetic nephropathy, inflammation, proinflammation cytokines.

Diabetic nephropathy, which occurs in approximately one third of patients with diabetes, is characterized by significant cardiovascular risks and high mortality rates. Despite modern methods of correction of diabetic nephropathy, its prevalence is increasing due to the increasing incidence of diabetes mellitus in the general population, and the high risk of death in diabetic nephropathy correlates with the progression of diabetic nephropathy.

In the world in 2000, there were 171 million people with diabetes; in 2013, their number was already 382 million, and by 2035, according to forecasts, it will reach 592 million [20], i.e. 8-10% of the population of our planet. As a result, diabetes care costs will be at least $548 billion. Type 2 diabetes occurs in almost 85–95% of all diabetes cases [19]. In the United States alone, in 2011, the number of children and adults with diabetes was 25.8 million, and 79 million were prediabetic [5].

Diabetic nephropathy is characterized by structural and functional changes. In the initial stages of diabetic nephropathy, tubular hypertrophy is present, but later, along with arteriolar hyalinosis [53], interstitial fibrosis with tubular atrophy develops. Further progression leads to infiltration by macrophages and T lymphocytes. In the ultrastructural region, loss of podocytes and a decrease in the distance between endothelial cells are observed [46–50]. Functionally, there is early glomerular hyperfiltration and increased albumin excretion with the development of nephropathy, increased proteinuria and decreased glomerular filtration rate (GFR). Recent studies have shown that diabetic nephropathy develops a severe inflammatory element caused by metabolic disturbances [52], protein overload [37] and hemodynamic changes [22–35]. In diabetes, early hypertrophy of both the glomerular and tubuloepithelial structures develops in the kidneys. The mechanisms of these processes include the production of various growth factors and vasoactive substances, such as transforming growth factor b, angiotensin II, endothelin, thromboxane A2, insulin-like growth factor-1, fibroblast growth factor and platelet-derived growth factor [29].

In diabetic nephropathy, innate immune cells are restored and activated and produce proinflammatory cytokines. Macrophages and T cells accumulate in the glomeruli and interstitium even in the early stages of the disease.

The set of leukocytes includes three stages:

(a) selectin-dependent pumping of leukocytes on the endothelium,

(b) chemokine-dependent integrin activation and leukocyte adhesion;

(c) transmigration of leukocytes through the endothelium [25].

Proinflammatory cytokines produced by leukocytes, such as interleukin-1 (IL-1), tumor necrosis factor (TNF-α), and interferon-α (INF-), can induce native renal cells to produce a spectrum of chemokines. Elements of the diabetic environment, which include hyperglycemia and advanced glycation end products, are also powerful stimulators of chemokine production. These chemokines include interleukin-8, monocyte chemoattractant protein-1, INF-inducible protein, macrophage inflammatory protein-1 (MIP-1/CCL3), and RANTES (CCL5). The produced chemokines further direct the migration of additional leukocytes into the kidney and form the inflammatory cycle [16]. Macrophages are key inflammatory cells mediating renal inflammation in both experimental and diabetes mellitus. Activated macrophages produce a variety of proinflammatory, profibrotic and antiangiogenic factors. These macrophage-derived products include, TNF-α, IL-1, IL-6, reactive oxygen species (ROS), plasminogen activator inhibitor-1 (PAI-1), matrix metalloproteinases, transforming growth factor-a (TGF-a), platelet-derived growth factor (PDGF), angiotensin II and endothelin, but are not limited to [31].

F. Chow et al. [7] in an experiment on mice revealed that the accumulation and activation of macrophages is associated with long-term hyperglycemia, sedimentation of immune complexes in the glomeruli, increased production of chemokines and progressive fibrosis. Experimentally, in models of type 1 and type 2 diabetes, increased expression of intercellular adhesion molecule-1 (ICAM-1) was observed in the kidney. ICAM-1 serves as a ligand for LFA-1 on monocytes, which facilitates leukocyte adhesion and transmigration. In diabetic mice, blocking ICAM1 resulted in a significant reduction in albuminuria, glomerular and tubulointerstitial damage due to reduced macrophage accumulation in the kidney [6].

Many studies have shown that infiltrating macrophages are associated with chronic local inflammation. Macrophages can interact with kidney cells and produce a proinflammatory environment that increases tissue damage and promotes scar formation. Macrophage-mediated injury has been shown to be amenable to new secondary prevention strategies [12].

F. Imani et al. [18] found that human and rat T lymphocytes express receptors for advanced glycation end products. Activation of CD4+ and CD8+ T cells by advanced glycation end products may trigger INF secretion by T cells, which causes further inflammation and oxidative stress in kidney tissue.

An analysis of 567 renal biopsies from patients with type 1 and type 2 diabetes showed that about 30% of glomerular lesions were induced by the immune complex and secondary focal glomerulosclerosis [17]. A number of modified proteins that develop in diabetes are potentially immunogenic. This involves human immune responses to oxidized low-density lipoproteins (LDL), which can subsequently lead to the formation of anti-oxidized LDL immune complexes [25]. Oxidized LDL immune complexes can also activate the classical complement pathway and induce the production of proinflammatory cytokines by human macrophages, including IL-1, IL-6 and TNF-α [1,43]. These immune complexes promoted glomerular fibrosis in in vitro studies by stimulating collagen production by mesangial cells [12].

Circulating immune cells such as monocytes congregate in the diabetic kidney due to upregulation of adhesion molecules such as ICAM-1. Chemokines (MCP-1) act as chemoattractants that promote the accumulation of immune cells in the kidney. These immune cells are activated by multiple signals via CSF-1, the receptor for advanced glycation end products, and Fcy receptors by the antioxidant immune complexes LDL. CSF-1 also promotes the maturation and proliferation of the monocyte into a macrophage. Activated immune cells, acting as inflammatory cells, produce proinflammatory cytokines and reactive oxygen species

that initiate a cell signaling cascade mediated by stress-activated protein kinases, p38 MAPK and JNK. These kidney cells then respond by producing chemokines such as MCP-1 and CSF-1 and profibrotic factors such as TGF-α, which increase extracellular matrix production by mesangial cells and interstitial fibroblasts. Ultimately, the diabetic kidney develops kidney cell damage and progresses to fibrosis [2].

Recent evidence suggests that multiple inflammatory cytokines are involved in the pathogenesis of diabetic nephropathy. Some of the major inflammatory cytokines that are believed to play an important role in diabetic nephropathy are listed in the table.

Table 1. Cytokines involved in inflammation in diabetic nephropathy

Cytokine	The role of inflammation in the kidneys in diabetes
ICAM-1	Adhesion molecule facilitating leukocyte adhesion to the endothelium and penetration into the diabetic kidney
VCAM-1	Adhesion molecule facilitating leukocyte adhesion to the endothelium and penetration into the diabetic kidney
MCP-1	Chemoattractant that stimulates the migration of macrophages into the diabetic kidney
TNF-	Promotes the production of reactive oxygen species, induces cell damage and increases endothelial permeability
IL-1	Promotes mesangial proliferation, glomerular hypertrophy, fibronectin production and increases endothelial permeability
IL-18	Increases the production of other cytokines (ICAM-1, IL-1, TNF-) and induces apoptosis of endothelial cells
Adiponectin	Reduces oxidative stress, TNF production and leukocyte-endothelial adhesion
Leptin	Causes oxidative stress, inflammation, hypertrophy and proliferation of vascular smooth muscle cells and disrupts endothelial function
Resistin	Promotes the expression of MCP-1, VCAM1, endothelin-1 and vascular smooth muscle cell proliferation

Tissue necrosis factor (TNF-a) is mainly produced by monocytes, macrophages and T cells. However, native kidney cells are also capable of producing TNF-α, including mesangial, glomerular, endothelial, dendritic and renal tubular cells [4]. TNF-a is involved in the conversion of monocytes to macrophages, reducing GFR through hemodynamic changes [13], as well as altering endothelial permeability [28]. According to the experiment, in patients with type 2 diabetes, the serum level of TNF-a is 3-4 times higher than in non-diabetic patients, while these levels in patients with diabetes with microalbuminuria are higher than in individuals with normal urine values [54].

Monocyte chemoattractant protein 1 (MCP-1) promotes the migration and activation of monocytes and macrophages [15], increases the expression of adhesion molecules, and promotes the expression of other proinflammatory cytokines [21]. It is produced by various cells in the kidney, including monocyte-macrophages, mesangial cells, podocytes and tubular cells [14,38]. T Morii et al. [33] observed high levels of urinary MCP-1 in patients with type 2 diabetes and diabetic nephropathy, which correlated with albuminuria and N-acetyl-D-glucosaminidase (NAG) excretion as a marker of tubular injury [51].

Vascular cell adhesion molecule-1 (VCAM-1) is another molecule involved in leukocyte-endothelial adhesion, which facilitates the migration of leukocytes into the kidney during inflammation. VCAM-1 levels are increased in the kidneys of patients with diabetic nephropathy [33]. During diabetes, VCAM-1 expression is found in the vascular endothelium and in cells found in the kidneys [34]. Increased levels of soluble VCAM-1 in plasma are associated with progression of albuminuria in patients with type 1 and type 2 diabetes [25]. Interleukin-1. In the works of A.F. Rubio-Guerra et al. and J.F. Navarro et al. increased expression of IL-1 was found in experimental diabetic nephropathy [42]. In addition, IL-1 is capable of increasing the

permeability of endothelial cells [8], changing glomerular hemodynamics through the synthesis of prostaglandins, stimulating the proliferation of mesangial cells and fibroblasts, and inducing the production of TGF-B1 [41].

Interleukin-6. IL-6 is produced by endothelial cells, leukocytes, adipocytes and mesangial cells. An experiment revealed overexpression of IL-6 in the kidneys in diabetes, which correlates with renal hypertrophy and albumin excretion [9]. IL-6 has been suggested to mediate endothelial permeability, mesangial proliferation, and increased expression of phyrobectin [36]. IL-6 levels are increased in type 1 and type 2 diabetic patients with diabetic nephropathy [45], and IL-6 levels are higher in patients with overt proteinuria as opposed to those with microalbuminuria or normoalbuminuria [3].

Interleukin-18. IL-18 is a powerful inflammatory cytokine that induces IFN-γ [39] and produces other proinflammatory cytokines (IL-1 and TNF-α), increases the activity of ICAM-1 [10], as well as apoptosis of endothelial cells [34]. Tubular epithelial cells are the main source of IL-18, but recent studies have shown the production of IL-18 from monocyte-macrophages and T cells [48,49]. A. Nakamura et al. [35] found that serum and urinary IL-18 levels increased in patients with type 2 diabetes, correlating with urinary albumin excretion.

Adipokines. Adiponectin, leptin and resitin are cytokines produced by adipose tissue [11]. Adiponectin regulates insulin sensitivity and also has anti-inflammatory and antioxidant properties. Adiponectin suppresses TNF-FP-induced stimulation of adhesion molecules of endothelial cells and prevents the migration and adhesion of leukocytes [40]. In type 1 and type 2 diabetes mellitus, elevated serum adiponectin levels are positively correlated with both albuminuria and serum creatinine [44]. Another study found that micro- and macroalbuminuric patients with type 2 diabetes had higher leptin levels than normoalbuminuric patients [8,21].

Conclusions:

1. Inflammation plays a significant role in the progression of diabetic nephropathy. Evidence obtained in recent years suggests that the main driving factor in the inflammatory response in renal diabetes is not adaptive, but innate immunity. The major components of this immune response (infiltrating cell types, cytokines, signaling pathways) indicate that elements of the diabetic environment (hyperglycemia, advanced glycation end products, immune complexes) can activate kidney cells through the induction of stress-activated protein kinase, leading to the release of chemokines and increased molecule activity cell adhesion. These events promote the infiltration of the kidney by monocytes and lymphocytes, which are activated in the diabetic kidney and release harmful molecules such as proinflammatory cytokines and reactive oxygen species.

2. Leukocyte activity enhances the inflammatory response and contributes to cell damage and the development of fibrosis. It is expected that a better understanding of the inflammatory response in diabetic kidneys will help guide the selection of new anti-inflammatory strategies for the potential treatment of diabetic nephropathy.

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