The Role of Inflammatory Cytokines in Diabetic Nephropathy

Juan F. Navarro-González*†‡ and Carmen Mora-Fernández†

*Servicio de Nefrología and †Unidad de Investigación, Hospital Universitario Nuestra Señora de Candelaria, Santa Cruz de Tenerife, and ‡Centro de Investigaciones Biológicas, Consejo Superior de Investigaciones Científicas, Madrid, Spain

ABSTRACT
Cytokines act as pleiotropic polypeptides regulating inflammatory and immune responses through actions on cells. They provide important signals in the pathophysiology of a range of diseases, including diabetes mellitus. Chronic low-grade inflammation and activation of the innate immune system are closely involved in the pathogenesis of diabetes and its microvascular complications. Inflammatory cytokines, mainly IL-1, IL-6, and IL-18, as well as TNF-α, are involved in the development and progression of diabetic nephropathy. In this context, cytokine genetics is of special interest to combinatorial polymorphisms among cytokine genes, their functional variations, and general susceptibility to diabetic nephropathy. Finally, the recognition of these molecules as significant pathogenic mediators in diabetic nephropathy leaves open the possibility of new potential therapeutic targets.


INFLAMMATORY CYTOKINES IN DIABETES MELLITUS

Cytokines are a group of pharmacologically active, low molecular weight polypeptides that possess autocrine, paracrine, and juxtacrine effects with characteristic features (Table 1).25 These molecules cluster into several classes (i.e., interleukins, tumor necrosis factors, interferons, colony-stimulating factors, transforming growth factors and chemokines), which are relevant humoral mediators in diabetic nephropathy. Less is known, however, about the role of inflammatory cytokines in diabetic renal injury.

The purpose of this review is to bring together current information concerning the role of inflammatory cytokines in the development and progression of diabetic nephropathy. Specific emphasis is placed on the mechanisms underlying the potential contribution of these molecules to renal injury. In addition, we examine data from genetic studies and discuss potential therapeutic strategies that target cytokines in the treatment of diabetic nephropathy.
Cytokines may influence signaling by receptors for other cytokines (transmodulation) 
Cytokines may influence signaling by receptors for another cytokine 
Cytokines may influence the production of another cytokine 

Constitutive production of cytokines is usually low or absent 
Production is regulated by various inducing stimuli at the level of transcription or translation 
Cytokine production is transient and the action radius may be short 
Cytokines produce their actions by binding to high-affinity cell surface receptors 
Most cytokine actions are attributed to altered patterns of gene expression in target cells 
Phenotypically, cytokine action leads to a variation in the rate of cell proliferation, changes in cell differentiation, and/or change in the expression of expected functions 
Cytokines often have multiple target cells and multiple actions (pleiotropy) 
Different cytokines may have an overlapping spectrum of actions (redundancy) 
Exposure of cells to various cytokines at one time may lead to qualitatively different responses (synergism/antagonism) 
Cytokines may alter the expression of receptors for another cytokine (transmodulation) 
Cytokines may influence signaling by receptors for other cytokines (trans-signaling) 
Cytokines may influence the production of another cytokine 

**Table 1. Characteristic features of cytokines**

- Constitutive production of cytokines is usually low or absent.
- Production is regulated by various inducing stimuli at the level of transcription or translation.
- Cytokine production is transient and the action radius may be short.
- Cytokines produce their actions by binding to high-affinity cell surface receptors.
- Most cytokine actions are attributed to altered patterns of gene expression in target cells.
- Phenotypically, cytokine action leads to a variation in the rate of cell proliferation, changes in cell differentiation, and/or change in the expression of expected functions.
- Cytokines often have multiple target cells and multiple actions (pleiotropy).
- Different cytokines may have an overlapping spectrum of actions (redundancy).
- Exposure of cells to various cytokines at one time may lead to qualitatively different responses (synergism/antagonism).
- Cytokines may alter the expression of receptors for another cytokine (transmodulation).
- Cytokines may influence signaling by receptors for other cytokines (trans-signaling).
- Cytokines may influence the production of another cytokine.

**Figure 1.** Intracellular cytokine-associated signaling pathways. JAK, Janus kinase; Tyk, Tyrosine kinase; STAT, signal transducer and activator of transcription; MYD88, myeloid differentiation factor-88; IRAK, IL receptor–associated kinase; TRAF, TNF receptor–associated factor; TAK, TGF-β-associated kinase; NIK, NF-κB-inhibiting kinase; IKK, inhibitor of NF-κB kinase; TRADD, TNF receptor–associated death domain; RIP, receptor interacting protein; MEKK, mitogen-activated protein kinase/Erk kinase kinase; JNK, c-Jun N-terminal kinase.

**INFLAMMATORY CYTOKINES IN DIABETIC NEPHROPATHY**

When considering the role of cytokines in pathophysiological processes underlying disease, it is necessary to take into account the fact that the activities of these molecules are very complex, as reflected by important features, including their pleiotropic actions—and thus a cytokine may trigger several different cellular responses depending on diverse factors, such as cell type, timing, and context. Cytokines share receptor subunits; act synergistically in many contexts, and, therefore, the association of two cytokines can markedly amplify their effects; cytokines stimulate the cells that produce them, or adjacent cells, or even can intervene through direct cell–cell interaction; and, finally, cytokines induce the expression of other cytokines and cytokine receptors (Table 1). In light of the data obtained from experimental and clinical studies, cytokines are often classified according to their pro- or anti-inflammatory activities.

In 1991, Hasegawa et al. reported that glomerular basement membranes from diabetic rats induced significantly greater amounts of TNF-α and IL-1 in cultured peritoneal macrophages than when these cells were incubated with basement membranes from nondiabetic rats. These new findings were the first to suggest that inflammatory cytokines may participate in the pathogenesis of diabetic nephropathy. Today, it is known that among inflammatory cytokines, IL-1, IL-6, IL-18 and TNF-α are relevant to the development of diabetic nephropathy, with diverse actions potentially involved in the development of complications (Table 2).

**IL-1**

In experimental models of diabetic nephropathy, renal expression of IL-1 increases, which is related to subsequent expression of chemotactic factors and adhesion molecules. IL-1 enhances the synthesis of ICAM-1 and vascular cellular adhesion molecule-1 by glomerular endothelial cells, and induces *de novo* synthesis and expression of ICAM-1 by glomerular mesangial cells and renal tubular epithelia. In addition, this cytokine induce transient expression of E-selectin by endothelial cells. IL-1 is also involved in the development of abnormalities in intraglomerular hemodynamics related to prostaglandin synthesis by mesangial cells. Treatment of glomerular mesangial cells with recombinant human IL-1 induces prostaglandin E2 synthesis and the release of a phospholipase A2 activity. In addition, pretreatment of resting mesangial cells with this cytokine results in an
Table 2. Potential role of inflammatory cytokines in diabetic nephropathy

<table>
<thead>
<tr>
<th>Potential Role</th>
<th>Description</th>
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<tbody>
<tr>
<td>Increase expression and synthesis of adhesion molecules</td>
<td>Proinflammatory effect</td>
</tr>
<tr>
<td>Increase expression of E-selectin</td>
<td>Proinflammatory effect</td>
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<tr>
<td>Increase synthesis of PGE2 and release of phospholipase A2 activity</td>
<td>Proinflammatory effect</td>
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<td>Amplification of secretory PGE2 responses to angiotensin II</td>
<td>Proinflammatory effect</td>
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<tr>
<td>Intraglomerular hemodynamic alterations</td>
<td>Proinflammatory effect</td>
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<tr>
<td>Increase in vascular endothelial cell permeability</td>
<td>Proinflammatory effect</td>
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<tr>
<td>Alterations in hyaluronan generation by proximal tubular epithelial cells</td>
<td>Proinflammatory effect</td>
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<tr>
<td>Induction of mesangial cell proliferation and cell contraction</td>
<td>Proinflammatory effect</td>
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<tr>
<td>Increases in fibronectin expression</td>
<td>Proinflammatory effect</td>
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<tr>
<td>Induction of apoptosis and necrotic cell death</td>
<td>Proinflammatory effect</td>
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<tr>
<td>Direct cytotoxicity to renal cells</td>
<td>Proinflammatory effect</td>
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<tr>
<td>Induction of reactive oxygen species</td>
<td>Proinflammatory effect</td>
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<tr>
<td>Alteration of tubular sodium reabsorption, renal protein content, and glomerular volume</td>
<td>Proinflammatory effect</td>
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<tr>
<td>Inhibition of endothelium-dependent relaxation</td>
<td>Proinflammatory effect</td>
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<td>Stimulation of plasminogen-activator inhibitor type 1 and tissue factor production</td>
<td>Proinflammatory effect</td>
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<td>Downregulation of tissue factor pathway inhibitor</td>
<td>Proinflammatory effect</td>
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<td>Reduction of thrombomodulin expression</td>
<td>Proinflammatory effect</td>
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<td>Stimulation of polymorphonuclear leukocytes and monocytes recruitment</td>
<td>Proinflammatory effect</td>
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<tr>
<td>Stimulation of adhesion molecules expression</td>
<td>Proinflammatory effect</td>
</tr>
<tr>
<td>Stimulation of synthesis and release of chemokines and growth factors</td>
<td>Proinflammatory effect</td>
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<tr>
<td>Induction of major histocompatibility complex antigens</td>
<td>Proinflammatory effect</td>
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<tr>
<td>PGE2, prostaglandin E2.</td>
<td>Proinflammatory effect</td>
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amplified secretory prostaglandin E2 response to angiotensin II.48 Furthermore, in vitro studies demonstrate that IL-1 directly increases vascular endothelial cell permeability.50

Finally, IL-1 dysregulates the generation of hyaluronan by renal proximal tubular epithelial cells. Primary cultures of human proximal tubular epithelial cells stimulated with IL-1 leads to a significant increase in hyaluronan concentrations in the culture supernatant.51 Increased production of glomerular hyaluronan initiates glomerular hypercellularity in experimental model of diabetes.52

IL-6

In 1991, Sekizuka et al.53 reported that serum levels of IL-6 were significantly higher in patients with type 2 diabetic nephropathy than the levels observed in diabetic patients without nephropathy, which suggests that this cytokine may play a role in the pathogenesis of diabetic nephropathy. Early after that report, Suzuki et al.54 analyzed kidney biopsies in patients with diabetic nephropathy by high-resolution in situ hybridization. These authors observed that cells infiltrating the mesangium, interstitium, and tubules were positive for mRNA encoding IL-6. Furthermore, they found a relationship between the severity of diabetic glomerulopathy (mesangial expansion) and expression of IL-6 mRNA in glomerular cells (mesangial cells and podocytes), which indicated that IL-6 may affect the dynamics of extracellular matrix surrounding those cells. More recent studies in type 2 diabetic patients demonstrate a significant association between IL-6 and glomerular basement membrane thickening, a crucial lesion of diabetic nephropathy and a strong predictor of renal progression.55,56

Recent studies by our group also show a significant overexpression of IL-6 in the diabetic rat kidneys, with an increase in the levels of mRNA encoding IL-6 in the renal cortex being directly associated with an elevation in its urinary excretion.45 Importantly, wet kidney weight, an accurate index of renal hypertrophy and one of the earliest renal changes during diabetes,57 is increased in diabetic rats and associated with renal mRNA expression of IL-6 and urinary excretion of this cytokine.45 Moreover, a direct correlation was observed between urinary levels and renal expression of IL-6 with urinary albumin excretion.45 These results support previous findings on the development of renal injury mediated by IL-6, which has been related to alterations in endothelial permeability, induction of mesangial cell proliferation, and increased fibronectin expression.54,58–60

IL-18

IL-18 is a potent inflammatory cytokine that induces IFN-γ,61 which in turn induces functional chemokine receptor expression in human mesangial cells.62 In addition, IL-18 leads to production of other inflammatory cytokines (including IL-1 and TNF-α), upregulation of ICAM-1, as well as apoptosis of endothelial cells.53–65 IL-18 is constitutively expressed in renal tubular epithelia,66 and recent studies demonstrate that infiltrating monocytes, macrophages, and T cells, along with proximal tubular cells, are potential sources of this cytokine.67,68

Serum and urinary levels of IL-18 have been reported increased in patients with diabetic nephropathy, with an independent relationship between these parameters and urinary albumin excretion.69–71 In addition, urinary excretion of β-2 microglobulin, a marker of tubulointerstitial injury, is also positively associated with serum IL-18.70 Moreover, in a longitudinal study, serum and urinary concentrations of this cytokine were directly correlated with albumin excretion rate, as well as with changes in albuminuria during the follow-up period.70

TNF-α

TNF-α is a pleiotropic inflammatory cytokine that is mainly produced by monocytes, macrophages, and T cells. In addition, and similar to other inflammatory cytokines, the expression and synthesis of TNF-α is not limited to hematopoietic cells. Thus, intrinsic renal cells, including mesangial, glomerular, endothelial, dendritic, and renal tubular cells are able to produce this cytokine.71–74 Furthermore, recent studies show that TNF-α can be stored within cells in a proactive form, and the TNF-α–converting enzyme can rapidly increase levels of the active cytokine.75

Reported actions of TNF-α on renal cells include the activation of second messenger systems, transcription factors, synthesis of cytokines, growth factors, receptors, cell adhesion molecules, enzymes involved in the synthesis of other inflammatory mediators, acute phase proteins, and MHC proteins.76 This variety of biologic activities results in diverse effects with a significant role in the development of renal damage in diabetes.

TNF-α is cytotoxic to renal cells and...
able to induce direct renal injury. In addition, other relevant TNF-α effects have been reported, such as induction of apoptosis and necrotic cell death, alterations of intraglomerular blood flow and GFR as a result of the hemodynamic imbalance between vasoconstrictive and vasodilatory mediators, as well as alterations of endothelial permeability. TNF-α alters the distribution of adhesion receptors involved in cell-cell adhesion (i.e., vascular endothelial-cadherin-catenin complexes) and prevents the formation of F-actin stress fibers. This results in restructuring of the intercellular junction leading to loss of endothelial permeability. On the other hand, TNF-α directly induces reactive oxygen species (ROS) in diverse cells, including mesangial cells. Recent experimental studies using isolated rat glomeruli demonstrate this cytokine activates NADPH oxidase through protein kinase C/phosophatidylinositol-3 kinase and mitogen-activated protein kinase pathways. Therefore, TNF-α, independent of hemodynamic factors, prompts the local generation of ROS, resulting in alterations of the barrier function of the glomerular capillary wall and leading to enhanced albumin permeability.

Experimental studies have consistently reported that mRNA encoding TNF-α and protein levels increase in glomerular and proximal tubule cells from diabetic rats. These investigations demonstrated a significant role of TNF-α in the development of renal hypertrophy and hyperfunction, two main alterations during the initial stage of diabetic nephropathy. TNF-α has a stimulatory effect on sodium-dependent solute uptake in cultured mouse proximal tubular cells, and in those studies diabetic rats exhibited enhanced urinary TNF-α excretion, sodium retention, and renal hypertrophy, which were prevented by administration of the anti-TNF-α agent TNFR:Fc, a soluble TNF-α receptor fusion protein. In addition to these data on renal hypertrophy and hyperfunction, mRNA levels and urinary TNF-α concentrations in the renal cortex directly and independently correlate with urinary albumin excretion. More importantly, studies that used the microdialysis technique demonstrate a significant increase in levels of TNF-α in renal interstitial fluid and urine (without evidence of cellular infiltrates in cortex or medulla), which precedes the development of albuminuria, suggesting a direct correlation between urine and renal interstitial fluid concentrations of TNF-α and urinary albumin excretion. Furthermore, shortly after the rise in albuminuria, urinary TNF-α concentration increases significantly, indicating a stimulatory effect for albuminuria on the production of renal TNF-α.

Finally, important data about the potential implications of TNF-α in diabetic nephropathy also derive from clinical investigations. Studies by our group and others found that diabetic patients with nephropathy have higher serum and urinary concentrations of TNF-α than non-diabetic subjects or diabetic patients without renal involvement. These studies suggest a direct and independent association between the levels of this cytokine and clinical markers of glomerular and tubulointerstitial damage, with a significant rise in serum and urinary TNF-α as diabetic nephropathy progresses.

**GENETICS OF DIABETIC NEPHROPATHY AND INFLAMMATORY CYTOKINES**

Only a modest number of individuals with diabetes will develop overt kidney disease (approximately one third to one half). The rates of development and progression of diabetic nephropathy reveal important interindividual variation, even when corrected for potential confounding influences. In addition, there is consistent familial aggregation of kidney disease (albuminuria, creatinine clearance, and end-stage renal disease) with renal histological changes. Today, there is mounting evidence for the role of genetic factors in diabetic nephropathy.

Hypertension, poor glycemic control, and albuminuria, the main known risk factors for diabetic nephropathy, do not explain all of the interindividual variability for the rates of developing nephropathy. Many studies have examined the variability of candidate genes in diverse pathogenic pathways for this complication, including the renin-angiotensin, nitric oxide, and bradykinin systems. There has been no consistent or replicated evidence for the contribution of a set of candidate genes or surrogate markers for diabetic nephropathy risk. It is important to note that diverse factors, including small sample size, incomplete genetic dissection of the polymorphisms in the candidate gene, and extensive genetic and phenotypic heterogeneity, may contribute to explain the failure to identify risk genes.
Although >99% of human genes are shared across same the population, variations in sequence may have great predictive relevance. Single nucleotide polymorphisms (SNPs) are sequence variations that occur when a single nucleotide in the genome is altered. SNPs, which make up approximately 90% of all human genetic variation, occur in every 100 to 300 bases along the 3 billion–base human genome. Approximately 300,000 SNPs are thought to have functional significance because they occur in coding regions, splice junctions, and promoter regions. Some of these SNPs have a major impact on the susceptibility to disease or on human response to disease or to a drug.

Cytokine genes influence nuclear transcription and cell function with several allelic polymorphisms having demonstrable effects in human disease. Because inflammatory cytokines significantly modulate the pathogenesis of diabetic nephropathy, their genetic variability may affect the susceptibility to renal progression (Figure 2). Genes encoding IL-1 and IL-1 receptor antagonist (IL-1Ra), a naturally occurring antiinflammatory agent, map to the long arm of chromosome 2. The IL-1β gene has two base exchange (C→T) polymorphic sites at promoter −511 and exon 5+3953, whereas IL-1Ra gene (IL-1RN) contains a variable number of 86 bp tandem repeat sequence in intron 2. There is a significant association between carriage of IL-1β allele 2 (−511 C/T polymorphism) and IL-1RN allele 2 (2 copies of the repeat sequence) with diabetic nephropathy.

Concerning IL-6, the gene encoding this cytokine is located at chromosome 7p21, whereas the gene encoding the IL-6 receptor (IL-6R) maps to chromosome 1q21, with diverse polymorphic regions at both genes. A C/G polymorphism at position −634 in the promoter region of the IL-6 gene is a potential genetic susceptibility factor for the progression of diabetic nephropathy. In that study, Kitamura et al. found a significant positive association of the IL-6 −634 G/G homozygote with macroalbuminuria in type 2 diabetic patients from Japan. More recently, Wang et al. identified a previously unreported amino acid change (V385I) that is associated with type 2 diabetes and diabetic nephropathy. This variant has been not previously seen in whites, Pima Indians, or Koreans.

Finally, the TNF-α gene located on chromosome 6p is highly polymorphic. Most of the variants are SNPs, but there are also various dinucleotide repeats (GA). Polymorphism of the TNF-α gene at the −308 position is significantly related to an increased risk of kidney failure in patients with type 2 diabetes.

The rationale for studying cytokine gene polymorphisms in diabetic nephropathy is based on diverse aspects: It gives us a better understanding of the origin and pathogenesis of this complication; it improves our knowledge of interindividual variation in the development and progression of diabetic nephropathy; in a clinical setting, it may permit the identification those patients at high risk for susceptibility, severity, or poor clinical outcome; it helps us understand the interindividual responses to therapeutic strategies; and, it may identify new targets for drug development and, therefore, novel interventions to prevent or delay diabetic nephropathy. However, the cytokine network is highly complex, with multiple interactive signals of gene activation and suppression. Thus, the association of individual polymorphisms in cytokine genes may be noninformative, whereas specific combinations of cytokine genotypes may be much more relevant.

THERAPEUTIC IMPLICATIONS OF INFLAMMATORY CYTOKINES

Despite the benefits derived from the current therapeutics for diabetic nephropathy, mainly strict control of glucose and BP as well as blockade of the renin-angiotensin system, these strategies still provide imperfect protection against renal progression. This imperfection points to the need for newer therapeutic agents that have potential to affect primary mechanisms contributing to the pathogenesis of diabetic nephropathy. Nephropathy occurs as a result of an interaction between metabolic and hemodynamic factors, which activate diverse pathways that lead to renal damage. Growing evidence highlights the importance of inflammatory mechanisms in the development and progression of diabetic nephropathy. Therefore, investigation into antiinflammatory strategies may offer new approaches of further effect. In fact, blockade of the renin-angiotensin-aldosterone system, the current principal strategy in the treatment of diabetic nephropathy, provides pleiotropic, antiinflammatory actions potentially relevant in the therapeutic approach to this complication. Other new therapies against inflammatory molecules and pathways germane to diabetic nephropathy therapies may be on the horizon.

In a recent study, Utamura et al. demonstrated that mycophenolate mofetil, an immunosuppressive antiinflammatory drug, largely prevented the development of albuminuria and glomerular injury in experimental diabetic nephropathy. The beneficial effect of mycophenolate mofetil was not related to any effect on glomerular hemodynamics or improvement of metabolic control, and, therefore, the authors conclude that benefit probably resulted directly from its immunosuppressive and antiinflammatory properties.

Inhibition of inflammatory cytokines as therapy for diabetic nephropathy, also derive from studies on the modulation of TNF-α. Moriwaki et al. recently reported the effect of the chimeric anti–TNF-α antibody, infliximab, on diabetic nephropathy. In that study, diabetic rats treated with infliximab showed a reduction of albuminuria as well as decreased urinary excretion of TNF-α. Previous studies with pentoxyfylline (PTF) also suggest that inhibition of TNF-α may be therapeutic in the treatment of diabetic nephropathy.

PTF is a methylxanthine-derived phosphodiesterase inhibitor that possesses significant antiinflammatory properties. The drug inhibits transcription of the TNF-α gene and reduces lev-
els of mRNA encoding TNF-α. In addition, PTF shows a significant effect in modulating IFN-γ, IL-1β, and IL-6. In different models of renal disease where TNF-α plays a central role, such as lupus nephritis and crescentic glomerulonephritis, PTF prevents or attenuates renal injury. Regarding diabetic nephropathy, recent experimental studies show that administration of PTF prevents an increase in renal expression, synthesis, and excretion of TNF-α during diabetes, which was directly and significantly associated with a reduction in renal sodium retention, renal hypertrophy, and urinary albumin excretion. 

In addition to these experimental results, clinical trials have demonstrated that PTF significantly reduces clinical markers of glomerular and tubulointerstitial injury in diabetic subjects. Electrophoretic analysis of urinary protein after PTF administration show this drug is able to reduce the urinary excretion of both high molecular (Ig G, ceruloplasmin, transferrin, and albumin) and low molecular weight proteins (α1-antitrypsin, α1-acid glycoprotein, collagenase inhibitor, α1-microglobulin, trypsin inhibitor, lysozyme, and β2-microglobulin). 

This antiproteinuric effect of PTF has been recently analyzed in comparison with angiotensin-converting enzyme inhibition in type 2 diabetic patients, and the results of these studies indicate that PTF is equivalent in efficacy and safety to captopril. Finally, addition of PTF to blockers of the renin-angiotensin system, both angiotensin-converting enzyme inhibitors or angiotensin II type 1 receptor blockers, provides an additive and significant reduction of urinary albumin excretion. This beneficial effect on albuminuria is independent from BP and glycemic control. However, it is significant and directly related to a reduction in urinary excretion of TNF-α.

CONCLUSIONS

Providing diabetic patients protection from the development and progression of renal injury remains a challenge for nephrologists. Because of the pathogenic complexity of diabetic nephropathy, new therapeutic interventions targeting primary mechanisms contributing to renal damage are critical for the future treatment of this complication. Inflammatory cytokines exert an important diversity of actions implicated in diabetic nephropathy, from development to the initial stages of diabetes to progression and to late stages of renal failure. The recognition of these molecules as significant pathogenic factors in this complication will provide new therapeutic targets. The development of new techniques for examining changes in the expression of pathogenic genes involved in inflammatory pathways as well as better ability to assess interindividual genetic variability will undoubtedly uncover important information regarding the pathogenic mechanisms of diabetic nephropathy. Likewise, this effort will also facilitate the identification of high-risk patients and perhaps lead to novel and unexpected therapies. From a therapeutic perspective, limited experience is available regarding the inhibition of inflammatory cytokines in diabetic nephropathy. To date, studies have focused on the effect of PTF on urinary albumin excretion, showing a beneficial antiproteinuric effect of this drug. However, further clinical trials are necessary to examine the potential renoprotective efficacy of PTF and other antiinflammatory cytokinins in establishing remission or even regression of diabetic nephropathy.

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DISCLOSURES

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