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Role of Inflammation in the Pathogenesis of Diabetic Nephropathy

Review Article

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Abstract

Diabetic nephropathy is the major microvascular complication of diabetes mellitus and remains the leading cause of increased morbidity and mortality for diabetic patients. Recent evidence suggests that chronic subclinical inflammation is a key pathogenetic mechanism of the disease. Pro-inflammatory cytokines and particularly tumor necrosis factor and its receptors appear to play a major role in the process and are emerging novel biomarkers of the development and progression of diabetic nephopathy. Moreover, manipulation of the TNF superfamily system will hopefully provide a new therapeutic option for the disease.

Keywords: C-Reactive Protein; Diabetes Mellitus; Diabetic Nephropathy; Inflammation; Tumor Necrosis Factor-a; Tumor Necrosis Factor Receptors.

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Introduction

Diabetic nephropathy (DN), the major microvascular complication of diabetes mellitus (DM), remains the leading cause of increased morbidity and mortality for diabetic patients [1, 2]. The pathogenesis of DN is multifactorial and it has been considered to involve metabolic factors [renal polyols [3-6], advanced glycation end products (AGEs) [7-11]), hemodynamic factors (angiotensin II [12], endothelin I [4]), and oxidative stress [13], orchestrated by genetic and environmental factors. Moreover, recent evidence suggests that chronic subclinical inflammation is a key pathogenetic mechanism in the development and progression of diabetic nephropathy [14]. Although the form and severity of glomerular lesions vary widely in DN, tubulointerstitial infiltration by mononuclear cells and T lymphocytes is a common histologic finding, even at early stages of the disease. Tubulointerstitial infiltration can result from several metabolic and hemodynamic factors and oxidative stress. The above lead to activation of protein kinase cascade and transcription factors, such as nuclear factor-κB (NFκB) [14, 15], that initiate cell signalling pathways on glomerular and tubulointerstitial cells. The consequent production of inflammatory mediators, including pro-inflammatory cytokines, chemokines, and growth factors and the up-regulation of adhesion molecules on both leukocytes and endothelial cells, result in the initiation of a vicious cycle that eventually results in the development of glomerulosclerosis and tubulointerstitial fibrosis [14-16].

In 1991 Hasegawa et al. first suggested that pro-inflammatory cytokines could participate in the development of DN. The authors demonstrated that macrophages incubated with glomerular basement membranes from diabetic rats produced greater amounts of interleukin (IL) -1 and tumor necrosis factor (TNF) -α compared to macrophages incubated with membranes from normal rats. Production of these cytokines was probably induced by AGEs, as it was reduced after treatment with aminoguanidine, an AGE accumulation inhibitor [17]. Subsequently, accumulating evidence from experimental and clinical studies suggested that inflammation plays a key role in the pathogenesis of diabetic nephropathy. As a result, several inflammatory markers have been investigated as prognostic factors of disease development and as markers of disease severity.

C-reactive protein

C-reactive protein (CRP) is an acute phase protein, produced by the liver after stimulation by pro-inflammatory cytokines, including IL-1, IL-6 and TNF-α. CRP is considered to have several characteristics that play a key role in natural host defense. Specifically, CRP is a member of the pentraxin family of oligomeric proteins which are involved in innate immunity. Immunoregulatory func-

tions of CRP that lead to evolution of renal impairment include leukocyte migration, complement activation, platelet function regulation and clearance of cellular debris from sites of active inflammation [18]. There has been substantial experimental evidence and recent findings from clinical studies suggesting that CRP is a sensitive marker of subclinical inflammation, which is associated with insulin resistance, metabolic syndrome, hyperglycemia and Type 2 diabetes mellitus (DM) [18].

To the best of our knowledge, only few studies have investigated the association between albuminuria and CRP in diabetic patients, and results were controversial. In our recently published study, we did not observe any difference in CRP levels between normo- and micro-albuminuric patients and, moreover, no significant correlation was noted between severity of micro-albuminuria and CRP levels [19]. In agreement with our results, Choudhary and Ahlawat found that although CRP values were higher in patients with macro-albuminuria and they were positively correlated with the degree of albuminuria, no significant difference was observed between normo-albuminuric and micro-albuminuric diabetic patients [20]. Similarly, other investigators reported elevated CRP levels in diabetics either with or without microangiopathy compared to healthy controls, but no difference between normo- and micro-albuminuric diabetic patients [21-24]. In contrast to the above findings, some studies have shown that CRP levels can discriminate diabetic patients with normo-, micro- and macro-albuminuria [25, 26]. Finally, a recent prospective cohort study in Japan, which included 2,518 patients with Type 2 DM, demonstrated that elevated CRP levels were associated, independently of possible confounders, with a subsequent risk of developing (normo- to micro-albuminuria), but not progressing, diabetic nephropathy (micro- to macro-albuminuria) [27]. Overall, the findings of the reports up-to now suggest that classic inflammatory markers are mainly increased in patients with overt nephropathy and macro-albuminuria, which is probably associated with systemic activation of the inflammatory response.

Tumor necrosis factor-α

TNF-α is a functional transmembrane homotrimeric protein that is produced by many cell types, including leukocytes, adipocytes and endothelial cells [24]. TNF-α is cleaved from the cell surface by a disintegrin and mettaloprotease protein-17 (ADAM-17) and it is released into circulation as a functional 17kDa soluble form. TNF-α acts through its receptors, TNF receptor 1 (TNFR1) and TNF receptor 2 (TNFR2). In plasma, TNF-α may be either free, or bound to circulating TNF-R1 and TNF-R2 [24, 28, 29]. Glycosylated forms of both receptors have been found in the urine [24, 28]. In response to stimulating factors, such as lipopolysaccharide, IL-1α and during inflammation, TNF-α and its receptors are expressed by activated native kidney cells (glomerular mesangial, epithelial and endothelial cells, and tubular epithelial cells) and monocytes-macrophages [30-32]. As a result, they stimulate the production of other cytokines (IL-8), acute phase proteins, growth factors and chemokines [monocyte chemoattractant protein (MCP)-1, and macrophage-colony stimulating factor (M-CSF)] by adjacent cells [23, 30]. Moreover, TNF-α upregulates the expression of adhesion molecules on leukocytes and endothelial cells that mediate adhesion of monocytes, lymphocytes, and granulocytes to activated endothelium and their subsequent migration [30, 33]. Since TNF-α is a pleiotropic cytokine, it exerts multiple effects that may promote renal damage in diabetic nephropathy through several mechanisms. It can cause vasoconstriction and reduction of glomerular blood flow through the production of endothelin-1. It interacts with the intracellular junctions of the glomerular filtration barrier and disrupts them increasing its permeability and resulting in the development of albuminuria [30, 34]. Increased production of TNF-α can also produce oxidative stress, through the activation of nicotinamide adenine dinucleotide phosphate (NADPH) in mesangial cells. Finally, TNF-α appears to have a direct apoptotic and cytotoxic effect on glomerular cells [30, 35].

Some experimental and clinical studies investigated the probable associations between serum or/and urine TNF-α levels with the development and progression of DN and with the severity of disease. Navarro et al. and Nakamura et al. reported increased expression of TNF-α mRNA in the glomeruli of diabetic compared to non- diabetic mice [36, 37]. In addition, Nakamura et al. reported a significant correlation between urinary albumin excretion and urinary TNF-α levels, as well as renal TNF-α expression. Of note, administration of an angiotensin enzyme inhibitor, enalapril, nearly completely abolished the increase in TNF-α mRNA expression to the level observed in control rats and decreased urinary cytokine excretion and albuminuria. The above data supported the hypothesis that inflammatory mechanisms may play a significant role in the development and progression of renal injury secondary to diabetes mellitus. In another experimental study, interstitial expression and urinary excretion of TNF-α were increased early in the course of the disease and preceded the rise in urinary albumin excretion (UAE) by about 2 weeks. Moreover, a second significant increase was observed after the onset of albuminuria, suggesting that this cytokine has an important role in the pathogenesis and progression of diabetic nephropathy, but its production is farther increased by albuminuria [38].

Recent studies in diabetic patients have demonstrated a correlation between urinary TNF-α levels and the presence and severity of albuminuria. We and others have shown that micro-albuminuric patients had significantly increased urinary TNF-α concentrations compared to normo-albuminuric patients and normal control subjects [19, 39]. In addition, we have recently demonstrated that urinary TNF-α levels are significantly and independently associated with the severity of micro-albuminuria [19]. Moreover, some studies suggested that TNF-α is predominantly involved in the progression of albuminuria during the early stages of diabetic nephropathy. Wu et al., [40] measured baseline levels of urinary TNF-α in 63 non-diabetic controls and 201 patients with Type 2 diabetes and different degrees of albuminuria and subsequently followed-up them for 28 months, with routine measurements of creatinine and UAE. The results showed that baseline urinary levels TNF-α were significantly elevated and correlated with the severity of albuminuria in patients with diabetes. During the follow-up, urinary TNF-α levels were found to be significantly associated with a rapid decline in the estimated glomerular filtration rate (eGFR) and the above correlation remained significant following adjustment for other progression promoters, including albuminuria, Similarly, Verhave et al. reported a correlation between urinary TNF-α levels and the rate of renal function decline in patients with diabetes Type 2 and macro-albuminuria during a median 2.1 years follow-up; however, the above association lost significance in the multivariate model [41]. Overall, these results suggested that inflammation is important in the pathogenesis of DN and indicated that TNF-α may be used as an independent predictor for the progression of DN at the early stage. Finally, in a very recently published prospective, randomized trial, adminis-

tration of pentoxifylline, in addition to renin-angiotensin system blockade, has been shown to further decrease proteinuria and to slow progression of renal disease in patients with Type 2 diabetes and stages 3-4 CKD during the 2 year follow-up period. In addition, pentoxifylline administration, was associated with decrease of urinary TNF-α levels whereas the latter remained unchanged in the control group [42].

Although undoubtedly there is an association between urinary TNF-α levels and the severity and progression of diabetic nephropathy, the probable value of serum TNF-α levels remains controversial. Navarro-González et al. reported a correlation between serum TNF-α levels and albuminuria [22]. In our study, however, no significant correlation was observed between the severity of micro-albuminuria and serum TNF-α levels. Moreover, and in agreement with the previous study, no correlation was observed between serum and urinary TNF-α levels, suggesting mainly intrarenal production of this cytokine and therefore local and non-systemic activation of the inflammatory response [22, 19]. The above hypothesis is further supported by the lack of correlation between micro-albuminuria and CRP, fibrinogen and serum TNF-α levels in our patients [19]. Finally, Niewczas et al. in the Joslin Kidney Study found that the risk- incidence rate of end-stage renal disease during 8 to 12 years follow-up was associated with elevated plasma concentrations of free and total plasma TNF-α levels, at baseline [29].

Despite extensive research, there are still unanswered questions regarding the implication of TNF-α in the initiation of inflammatory cascade and the pathogenesis of renal damage in diabetes mellitus [22, 35, 37, 38]. A hypothesis of activation of local inflammatory pathways in association with increased production and excretion of TNF-α, may provide an explanation of kidney damage at the early stages of diabetic nephropathy. In more advanced stages, a systemic inflammatory response may be activated and lead to the development of several micro-and macrovascular complications.

Tumor necrosis factor receptors

TNFR1 and TNFR2 are single transmembrane glycoproteins which belong to the TNF-α receptor superfamily and are referred to as markers of the TNF pathway. TNFR1 and TNFR2 have a molecular weight of 55 and 75 kDa respectively and are products of separate genes [43].

TNFR1 can be detected in all cell types, while TNFR2 is only expressed by oligodendrocytes, astrocytes, myocytes, thymocytes, endothelial cells, T lymphocytes and human mesenchymal stem cells. In kidney and under physiological conditions, TNF-α and TNFR2 are usually not present, whereas TNFR1 can be found in normal glomerular endothelium and is primarily localized within the Golgi apparatus [32, 43]. During inflammation and in response to stimulating factors, such as lipopolysaccharides and IL-1α, TNFR1 and TNFR2, are expressed in activated native kidney cells (glomerular mesangial, epithelial and endothelial cells, and tubular epithelial cells) and also in activated monocytes-macrophages [14, 16, 43]. Expression of TNFR2 is essential for the action of TNFR1. TNFR2 is a pro-inflammatory mediator which promotes cell migration, regeneration and proliferation and also enhances the role of TNFR1 by increasing the concentration of TNF-α available to TNFR1. TNFRs are cleaved from the cell surface by a disintegrin and metalloprotease protein-17 (ADAM-17), which results in the soluble forms of TNFRs [32]. There is a disagreement whether the soluble circulating levels of TNFRs are more important than the cellular signal transduction through these receptors. Moreover, mechanisms that regulate TNFRs have not been yet clarified although TNF-α was suggested to be the main regulating factor that induces shedding of TNFRs. However, this theory has not been confirmed in diabetic patients and definitely further investigation is required on the factors that influence the concentration and the role of TNFRs. Of note, serum levels of TNFRs are 100-500 times higher than those of TNF-α, which implies an additional role for TNFRs, besides that of binding TNF-α [43].

Recent studies in diabetic patients have shown that elevated concentrations of circulating TNFRs were strongly associated with renal function during follow-up but not with the presence or severity of albuminuria. Lin et al. studied eGFR decline over 11 years in 516 women with Type 2 diabetes mellitus in the Nurses' Health Study. Comparing the highest with the lowest quartile, soluble TNFR2 levels were independently associated with an eGFR decline of > or = 25% and this association was stronger in obese women. Of note, no lipids and other markers of inflammation (CRP, fibrinogen, E-selectin, intercellular adhesion molecule 1, leptin or adiponectin) were significantly associated with eGFR decrease after multivariable adjustment [44]. More recently, in the aforementioned study of Niewczas et al. the risk of end-stage renal disease during the 8 to 12 years of follow-up was strongly associated with elevated baseline plasma concentrations of circulating TNFR1 and TNFR2 [29]. This correlation was evident in both proteinuric and non-proteinuric patients and remained significant after adjustment for clinical covariates including urinary albumin excretion. As we mentioned above, free and total plasma TNF-α levels also tended to predict progressive nephropathy, but less significantly than their receptor levels [29]. In addition, a very recent study in American Indians reported that baseline TNFRs levels were associated with the risk of end-stage renal disease defined as dialysis, kidney transplant, or death attributed to diabetic kidney disease during a median follow-up of 9.5 years after adjusting for age, gender, mean blood pressure, HbA1c, urinary albumin-to-creatinine ratio, and measured by iothalamate GFR [45]. In addition, in Japanese Type 2 diabetic patients without overt proteinuria baseline serum levels of soluble TNFR1 and TNFR2 were found to predict a greater decline in eGFR rate after 5 years. Moreover, patients with high level of both TNFR1 and TNFR2 showed a 4-fold higher risk for a GFR decline of ≥ 25% than those with high level of only one receptor or low level of both receptors and these associations were enhanced in diabetic women [46]. Of note, Fernandez-Real et al. in patients with Type 2 diabetes and normo- or micro-albuminuria demonstrated a correlation between soluble TNFR1, but not TNFR2, and mesangial expansion in renal biopsies which remained significant after controlling for age, body mass index and blood pressure. In contrast, albumin excretion rate was not significantly associated with either mesangial expansion or TNFR1 and TNFR2 levels [47]. Elevated plasma concentrations of TNFRs have been also shown to predict stage 3 CKD among patients with Type 1 diabetes. Gohda et al. followed two cohorts comprising 628 patients with Type 1 diabetes, normal renal function, and no proteinuria for over 12 years. Concentrations of TNFR1 and TNFR2 were found to be strongly associated with risk for early renal decline (eGFR less than 60 ml/min per 1.73 m^2). The risk associated with high TNFR1 values was slightly less than that associated with high TNFR2 values. TNFR levels were unrelated to baseline free TNF-α level and re-

mained stable over long periods within an individual. Moreover, renal decline was associated only modestly with total TNF-α concentration and appeared unrelated to free TNF-α [48].

Overall the findings of the studies up-to-now suggested that measurement of serum TNFR levels may identify diabetic patients on high- risk of declining renal function but also raised questions on the importance of micro-albuminuria to the pathogenesis of renal dysfunction in Type 2 DM. Of note, an interesting recent experimental study investigated whether TNF-α inhibition with a soluble TNFR2 fusion protein, etanercept, improves the early stage of DN in the Type 2 diabetic model of the KK-A(y) mouse and also which TNF pathway, TNFR1 or TNFR2, is predominantly involved in the progression of this disease [49]. Administration of etanercept was associated with a dramatic improvement of albuminuria but also of glycemic control. Renal mRNA and/or protein levels of TNFR2, but not TNF-α and TNFR1, in etanercept-treated mice were significantly decreased compared with untreated mice. Finally, mRNA levels of intercellular adhesion molecule-1, vascular cell adhesion molecule-1, and monocyte chemoattractant protein-1 and the number of macrophages were all decreased after treatment. The above results indicated that etanercept may improve the progression of the early stage of diabetic nephropathy predominantly through inhibition of the pro-inflammatory action of the TNF-α-TNFR2 pathway [49].

Conclusion

Diabetic nephropathy remains the leading cause of increased morbidity and mortality and an urgent need exists to identify novel biomarkers and to develop new therapeutic strategies. However, identification of diabetic patients at high risk of developing progressive nephropathy is a challenge considering the complexity of the multiple pathophysiological processes involved in the development and progression of the disease. Recent evidence suggests that inflammation plays a key role in the disease and accordingly the probable value of several inflammatory biomarkers as predictors of disease development and progression is under investigation, Among them TNF-α appeared to play a key role in the development of albuminuria and TNF-α-TNFR signaling pathways emerged as promising predictors of renal function decline. However, the value of these biomarkers should be examined in large, prospective, multicenter trials with long-term follow-up period in order to determine their usefulness in daily clinical practice. Moreover, although several ways of specifically manipulating the TNF superfamily system already exist, whether or not these drugs provide new targets for intervention and more effective treatment options for diabetic patients is still to be revealed.

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