Markers of Inflammation and Oxidative Stress in the Development and Progression of Renal Disease in Diabetic Patients

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Key Words

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Abstract

The prevalence of diabetes is increasing and has already reached pandemic proportions. Diabetes is a well-known risk factor for chronic kidney disease. Diabetic kidney disease (DKD) occurs in up to 40% of people with type 1 or 2 diabetes and is nowadays the leading cause of end-stage renal disease (ESRD). Among several factors involved in the development and progression of DKD are also inflammation and oxidative stress. Unfortunately, there is a paucity of sensitive and specific biomarkers for the early prediction of patients who will develop DKD or will progress to ESRD. This review summarizes the evidence regarding the prognostic value and benefits of targeting markers of inflammation (pro-inflammatory cytokines, tumour necrosis factor- α (TNF- α) and TNF- α receptors, adhesion molecules, chemokines) and markers of oxidative stress. Some of these biomarkers are promising, but further studies are needed before they can be used in clinical practice.

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Introduction

The prevalence of diabetes is increasing worldwide, mainly due to the increase in type 2 diabetes. Diabetic kidney disease (DKD) is the leading cause of chronic kidney disease in developed countries. Several factors are involved in the development and progression of DKD including hyperglycaemia, obesity, hypertension, smoking, hereditary and advanced age. Although current treatment strategies can slow the progression of DKD, the burden of the disease remains high and many patients with DKD continue to progress to end-stage renal disease (ESRD). In recent years, the role of inflammation and oxidative stress has been emphasized. Oxidative stress can increase the production of inflammatory cytokines and an increase in inflammatory cytokines can stimulate oxidative stress. It is important to identify patients who will develop DKD and/or will progress to ESRD. In this paper, the possible role of the biomarkers of inflammation and oxidative stress in serum and urine will be presented.

Markers of Inflammation

Pro-Inflammatory Cytokines

The most important function of cytokines is the regulation of the inflammatory process, and studies suggesting their role in DKD were first published 25 years ago.

In the multi-centre Finnish Diabetic Nephropathy Study (FinnDiane), type 1 diabetic patients were included and divided into 3 groups according to their albumin excretion rate (normo- to macroalbuminuria) [1]. Interleukin-6 (IL-6), a cytokine produced by many cells, increased in serum in parallel with the severity of albuminuria, while a multiple regression analysis showed that albuminuria, high-density lipoprotein-cholesterol and the duration of diabetes were independently associated with serum IL-6 [1]. In a study by Wolkow et al. [2], the baseline urinary concentrations of 5 inflammatory markers, IL-6, IL-8, monocyte chemoattractant protein 1 (MCP-1), interferon γ -inducible protein 10, and macrophage inflammatory protein 1 δ , were higher in type 1 diabetic patients with an early progressive kidney function decline compared to those with a stable kidney function. In a Japanese study by Moriwaki et al. [3], type 2 diabetic patients and healthy volunteers were included. Significant differences in serum levels of IL-18 were observed between the patients and control subjects, whereas those of IL-6 was not different between the 2 groups [3]. IL-6 and IL-18 levels were increased in diabetic patients with microalbuminuria or albuminuria compared to those without albuminuria [3]. Serum and urinary IL-18 and serum IL-6 levels were also significantly elevated in patients with type 2 diabetes compared to control subjects in a study by Nakamura et al. [4]. Albuminuria was independently associated with serum and urinary IL-18 levels, and serum and urinary IL-18 levels correlated positively with albuminuria after 6 months and with changes in albuminuria during the follow-up period [4].

TNF- α and TNF- α Receptors

Tumour necrosis factor- α (TNF- α) is produced mainly by monocytes and macrophages. In 2 studies, Navarro et al. [5] reported a significant association between serum TNF- α and proteinuria in diabetic patients with normal renal function and microalbuminuria, as well as in subjects with overt nephropathy and renal insufficiency [6]. A significant increase in urinary TNF- α was found as diabetic nephropathy progressed [5, 6]. A multivariate analysis showed a significant and independent relationship between urinary TNF- α and albuminuria. Similar results were found by Moriwaki et al. [3], where significant differences in the serum levels of TNF- α were observed between the type 2 diabetic patients and control subjects. In patients with microalbuminuria or albuminuria, TNF- α levels were significantly increased compared to those without albuminuria [3]. Interestingly, in the study by Niewczas et al. [7] only the serum levels of soluble

forms of receptors 1 and 2 for TNF- α , and not TNF- α , were found to be associated with the glomerular filtration rate in a multivariate analysis. In a prospective study by Niewczas et al. [8], patients with type 2 diabetes were followed for 12 years and it was found that only plasma TNF receptors 1 and 2 were associated with a risk for ESRD. TNF receptor 1 also predicted a risk for ESRD after adjusting for clinical covariates [8]. In another prospective study where patients with type 1 diabetes, normal renal function and no proteinuria (defined as UACR <30 $\mu\text{g}/\text{min}$) were followed for 12 years, an early decrease in glomerular filtration rate was associated with circulating TNF receptors 1 and 2 levels but not with TNF- α levels [9].

Although these studies suggest that serum TNF- α receptor levels are associated with the development and progression of diabetic nephropathy, the exact mechanisms linking TNF- α receptors with diabetic nephropathy are not known. Interestingly, this association is stronger in diabetic patients without proteinuria. Thus, high concentrations of TNF- α receptors are strong predictors of early and late renal function loss in diabetic patients with and without proteinuria.

Adhesion Molecules

The migration of leukocytes from vascular lumen to inflammatory sites is mediated by adhesion to endothelial cells. Leukocyte adhesion is promoted by adhesion molecules expressed on leukocytes and endothelial cells.

In type 1 diabetic patients, the plasma concentration of intercellular adhesion molecule-1 (ICAM-1) was elevated in patients with microalbuminuria and overt nephropathy compared to healthy subjects [10]. Plasma concentrations of ICAM-1 were similar in healthy controls and normoalbuminuric type 1 diabetic patients [10]. Plasma vascular adhesion molecule-1 (VCAM-1) was elevated only in patients with overt nephropathy [10]. In another study, only an elevated baseline plasma level of ICAM-1 was associated with the onset of microalbuminuria in type 1 diabetic patients [11]. In a study by Rubio-Guerra et al. [12], significantly higher levels of ICAM-1 and VCAM-1 were found in type 2 diabetic patients compared to control subjects. A significant correlation between VCAM-1 levels and 24-hour urinary albumin excretion was also found in this study [12].

In published clinical studies, only the association between adhesion molecules and proteinuria was shown. Further research is required to clarify the possible role of adhesion molecules in renal function loss among diabetic patients.

Chemokines

The recruitment of inflammatory cells from the circulation into renal tissue plays an important role in renal diseases, including in diabetic nephropathy. The interaction of chemokines and their receptors is the basis of this process. Experimental studies have demonstrated that MCP-1 mediated macrophage accumulation and activation is a critical mechanism in the development of early diabetic nephropathy [13].

In a study by Wada et al. [14] that included patients with type 2 diabetes, the urinary levels of MCP-1 were significantly elevated only in patients with nephrotic proteinuria. There were no differences in the urinary levels of MCP-1 in healthy subjects, patients with microalbuminuria and patients with proteinuria lower than nephrotic [14]. Similar results were found in a study by Mori et al. [15] where the urinary levels of MCP-1 were significantly elevated only in type 2 diabetic patients with macroalbuminuria compared to the levels in patients with normo- and microalbuminuria. In a study by Wolkow et al. [2], type 1 diabetic patients with normoalbuminuria and stable renal function (the reference group), patients with microalbuminuria and stable renal function (nondecliners) and patients with microalbuminuria and early progressive renal function decline (decliners) were included. The baseline urinary MCP-1 was significantly higher in patients with an early progressive kidney function decline compared to nondecliners and the reference group [2].

In summary, the number of serum and urinary markers of inflammation have been proposed as risk markers of the development and progression of renal disease in diabetic patients. Of these soluble forms of TNF- α receptors, both 1 and 2 seem to be the most promising.

Markers of Oxidative Stress

The generation of oxygen-free radicals and antioxidant defence mechanisms used to deactivate free radical toxicity is balanced in physiological conditions. Oxidative stress is also involved in increased cytokine production. A frequently used marker of oxidative stress is urinary 8-oxo-7,8-dihydro-2'-deoxyguanosine (8-oxodG) [16, 17]. Urinary 8-oxodG is directly related to the DNA oxidation ratio and effectiveness of DNA repair [16, 17]. Normoalbuminuric or microalbuminuric type 2 diabetic patients were included in a large Japanese study [18]. A 5-year follow-up revealed a significant progression of diabetic nephropathy (from normo- to microalbumin-

uria and from micro- to macroalbuminuria) in the patients with higher urinary 8-oxodG compared to patients with moderate or lower excretion of 8-oxodG [18]. In this study, the urinary 8-oxodG was the strongest predictor of nephropathy among several known risk factors for the development of nephropathy, that is, diabetes duration, HbA1c, and hypertension [18]. In another study that also included type 2 diabetic patients with or without nephropathy and healthy control subjects, different results were found [19]. Urinary 8-oxodG levels were higher in diabetic patients compared to control subjects but no statistical difference was found between diabetic patients with or without nephropathy [19].

The conflicting results of these clinical studies have not demonstrated that markers of oxidative stress offer additional prognostic information in diabetic patients compared to already established risk markers.

In summary, although markers of oxidative stress were elevated in diabetic patients compared with healthy controls, clinical studies have not clearly demonstrated that these markers offer additional information in relation to the development and progression of renal disease in diabetic patients.

Conclusions

Inflammation and oxidative stress are involved in complex processes in the development and progression of renal disease in diabetic patients. In recent years, some new promising markers of inflammation and oxidative stress have been identified. Unfortunately, at the moment, none of these biomarkers are ready for use in everyday clinical practice and further validation in large, multi-centre prospective studies with clearly defined outcomes (changes in albuminuria, changes in renal function or development of hard end points) is required. The ability to predict the development and progression of renal disease in diabetic patients may also be enhanced by a 'multi-marker approach' (using simultaneously multiple biomarkers). Unfortunately, there are only a few studies that include diabetic patients in which this strategy has been used [2, 20]. The results were promising but further studies are necessary.

Disclosure Statement

The authors declare no conflicts of interest.

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