Soluble TNF Receptors: A Biomarker for Diabetic Kidney Disease?

Matthew Farag1,4, Geetha Theverkalam1,4, Elif Ikinci1,3,4, George Jerums2,4 and Richard J MacIsaac1,4*

1Department of Endocrinology & Diabetes, St Vincent’s Hospital Melbourne
2Endocrine Centre, Austin Health, Australia
3Department of Endocrinology, Menzies School of Health Sciences, Australia
4Department of Medicine, University of Melbourne, Australia

Abstract

Diabetic Kidney Disease (DKD) is the leading cause of end-stage renal disease (ESRD) in the Western world. It is therefore imperative that patients with diabetes at the greatest risk for a progressive decline in renal function are accurately identified so that management of their risk factors for worsening renal function can be optimized. Current clinical risk markers such as albuminuria lack predictive accuracy for determining a patient’s risk for a progressive decline in glomerular filtration rate (GFR). Recent studies suggest that serum levels of soluble tissue necrosis factor (sTNF) receptors are linked to the progression of DKD and may have a stronger prognostic ability for the development of ESRD than albuminuria. However, the temporal relationship between changes in sTNF receptor levels and GFR, the mechanisms linking sTNF receptors with DKD and whether modulating sTNF receptor levels improves the prognosis of patients with DKD remains unknown. Here, we briefly review the evidence that suggests sTNF receptor levels are a promising biomarker for the progression of DKD.

ABBREVIATIONS

sTNF: soluble Tumour Necrosis Factor; DKD: Diabetic Kidney Disease; ESRD: End Stage Renal Disease; GFR: Glomerular Filtration Rate

INTRODUCTION

For people at risk of developing DKD, it is traditionally accepted that rising levels of albuminuria herald in a subsequent decline in GFR [1]. However, in recent times, worsening of albuminuria as a definitive predictor of DKD and declining GFR has been questioned. Spontaneous remission of microalbuminuria has been reported in >50% of patients with diabetes and the phenomenon of non-albuminuric renal insufficiency is now a well recognized manifestation of DKD [2]. This discordance between changes in renal function and albuminuria has resulted in a search for new markers that identify people with diabetes who are at risk of declining renal function independent of progressive increases in albuminuria.

Inflammation and the Pathophysiology of DKD

The pathophysiology of DKD is characterized by the activation of metabolic, haemodynamic and inflammatory pathways [3]. Recently attention has been focused on the role of the innate immune system and inflammatory pathways in the development of DKD. It is likely that pro-inflammatory cytokines secreted by renal cells or by macrophages infiltrating the kidney play an important role in the pathophysiology of DKD [4].

Tissue necrosis factor (TNF) α is a functional 26-kDa cell signalling protein involved in systemic inflammation and is one of the cytokines that make up the acute phase reaction. TNFα is a central pro-inflammatory cytokine that is generated in a wide variety of cells, including hematopoietic cells (monocytes, macrophages, and T cells), fat and endothelial cells. In patients with type 2 diabetes, urinary TNFα excretion is elevated and correlates with severity of renal disease in terms of both glomerular and tubulo-interstitial damage [5].

TNF exerts its biological actions via binding to two high affinity receptors with the type 1 receptor being implicated as the key mediator of TNF in the majority of cells. Recent studies have shown that the levels of the soluble form of the TNF receptors rather than TNF levels per se are powerful predictors of important clinical events in patients with DKD [6]. At present the exact role that sTNF receptors play in the development of DKD remains unknown. However, it is possible that sTNF receptors may bind to TNF in the circulation and hence reduce the biological effect...
of TNF. Alternatively, there is some experimental evidence to suggest that exposure of kidney cells to sTNF receptor exosomes in vitro increases tubular apoptosis [7].

**sTNF Receptors and Renal Outcomes in Patients with DKD**

The relationship of 12 serum markers of inflammation and apoptosis to GFR has been examined at the Joslin Diabetes Center, USA, in a cross-sectional analysis of subjects with type 1 diabetes [8]. Only the levels of sTNF receptors and Fas (which binds the Fas ligand and results in an apoptotic response) were associated with GFR in a multivariate analysis. Interestingly, variation in the concentration of the sTNF receptors had a much stronger impact on GFR than clinical covariates such as age and albumin excretion.

Subsequent studies, again including those from the Joslin Diabetes Center, have demonstrated the prognostic significance of baseline sTNF receptor levels in subjects with type 1 and type 2 diabetes in terms of renal outcomes. In a study involving subjects with type 2 diabetes, baseline levels of sTNF receptors, especially for the type 1 receptor, independently predicted progression to ESRD over 12 years [9]. This association was stronger in subjects with proteinuria than in those without proteinuria and was independent of other markers of the TNF-inflammatory pathway, markers of endothelial dysfunction and markers of systemic inflammation such as IL-6 and CRP. A recent study has also confirmed that levels of sTNF type 1 receptors are independently associated with the cumulative incidence of ESRD. This study was performed in patients with type 1 diabetes and overt nephropathy who were participating in the Finnish Diabetic Nephropathy (Finn Dianne) study [10].

Another study from the Joslin Diabetes Center but in subjects with type 1 diabetes with normo- or microalbuminuria and without any evidence of hypo-filtration at baseline has highlighted the potential for sTNF receptor levels to predict declines in GFR before ESRD is reached [11]. In that study, the cumulative incidence for reaching stage 3 CKD (GFR < 60 ml/min/1.73m²) for subjects with the highest sTNF type 2 receptor quartile was 60% after 12 years compared with only 5%-19% for the remaining quartiles. In Cox proportional hazards analysis, subjects with sTNF type 2 receptor values in the highest quartile were threefold more likely to experience an early decline in renal function than subjects in the other quartiles (hazard ratio, 3.0; 95% CI 1.7-5.5). In this study, risk of progression to stage 3 CKD associated with high sTNF type 1 receptor levels was slightly less than that associated with high sTNF type 2 receptor levels.

The relationship between elevated sTNF receptor levels and GFR loss appears to be most prominent in patients with poor glycaemic control. A further study from the Joslin Diabetes Centre has shown that in patients with type 1 diabetes and proteinuria with poor glycaemic control (HbA1c > 10.1% or 87 mmol/mol), the difference in the rate of GFR loss between the first and fourth quartiles of sTNF receptor levels was 5.4 ml/min/1.73m²/year, whereas it was only 1.9 in those with better glycaemic control (HbA1c <7.9% or 63 mmol/mol) [12].

**sTNFR1 and Mortality in DKD patients**

Studies from the Joslin Diabetes Centre have implicated levels of sTNF receptors as predictors of all-cause mortality in patients with type 2 diabetes. In one study, serum levels of fibroblast growth factor (FGF)-23 were found to be an important modulator of sTNF receptors as predictors of all-cause mortality in patients with type 2 diabetes. In a study involving subjects with type 1 diabetes and overt nephropathy (Finn Dianne cohort) [10].

---

**Table 1: Summary of clinical studies linking sTNF receptor levels to DKD outcomes in patients with diabetes.**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>References</th>
<th>Study Population</th>
<th>Key Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss of GFR</td>
<td>[12]</td>
<td>349 type 1 diabetic patients with proteinuria.</td>
<td>In patients with poor glycaemic control (HbA1c &gt; 10.1% or 87 mmol/mol), the difference in the rate of GFR loss between the first and fourth quartiles of sTNF receptor levels was 5.4 ml/min/1.73m²/year, whereas it was only 1.9 in those with better glycaemic control (HbA1c &lt;7.9% or 63 mmol/mol).</td>
</tr>
<tr>
<td></td>
<td>[8]</td>
<td>363 patients with type 1 diabetes and normoalbuminuria and 304 with microalbuminuria.</td>
<td>Levels of sTNF receptors were associated with GFR loss in a multivariate analysis.</td>
</tr>
<tr>
<td>Stage 3 CKD (&lt;60ml/min/1.73m²)</td>
<td>[11]</td>
<td>Two cohorts comprising 628 patients with type 1 diabetes, normal renal function and no proteinuria.</td>
<td>The cumulative incidence for reaching stage 3 CKD (GFR &lt; 60 ml/min/1.73m²) for subjects with the highest sTNF receptor quartile was 60% after 12 years compared with only 5%-19% for the remaining quartiles.</td>
</tr>
<tr>
<td>ESRD</td>
<td>[10]</td>
<td>429 patients with type 1 diabetes and overt nephropathy (Finn Dianne cohort study).</td>
<td>Levels of sTNF type 1 receptors were independently associated with the cumulative incidence of ESRD.</td>
</tr>
<tr>
<td></td>
<td>[15]</td>
<td>193 American Indians with type 2 diabetes.</td>
<td>The hazard ratio for ESRD was 1.6 (95% CI 1.1-2.2) for increases in sTNF receptor type 1 levels (per interquartile range).</td>
</tr>
<tr>
<td></td>
<td>[9]</td>
<td>410 patients with type 2 diabetes.</td>
<td>Baseline levels of sTNF receptors independently predicted progression to ESRD over 12 years in those with and without proteinuria.</td>
</tr>
<tr>
<td>All Cause Mortality</td>
<td>[14]</td>
<td>522 patients with type 2 diabetes and DKD (SURDIAGENE cohort).</td>
<td>Level of sTNF receptors were a strong prognostic indicator of all-cause mortality.</td>
</tr>
</tbody>
</table>

**Abbreviations:** ESRD: End Stage Renal Disease; sTNF: soluble Tumour Necrosis Factor; DKD: Diabetic Kidney Disease.
of the relationship between sTNF receptor levels and mortality [13]. In a multivariate analysis that included plasma levels of sTNF receptor and FGF-23 levels together, the relationship between sTNF receptor levels and all-cause mortality was no longer significant.

In 522 patients from the SURDIAGENE (Survie, Diabete de type 2 et Genetique) study from France, the level of sTNF type 1 receptors has also been shown to be a strong prognostic indicator of all-cause mortality in patients with type 2 diabetes with proteinuria and reduced GFR [14]. In a multivariate analysis, adjusting for age, diabetes duration, HbA1c, albuminuria and GFR, the relationship between increased sTNF receptor levels and all-cause mortality remained significant. Furthermore, measuring sTNF receptor levels appeared to increase risk prediction over and above existing risk factors. The integrated discrimination improvement index was statistically significant when sTNF receptor levels were added to the UK Prospective Diabetes Study outcome equation for death in patients with type 2 diabetes.

**CONCLUSION**

ARE sTNF Receptor Levels as a Biomarker for DKD?

Table 1 summarizes recent major studies that have implicated sTNF receptor levels as predictors of renal events and all cause mortality in subjects with diabetes. An ideal biomarker should be safe and easy to measure. Measurement of sTNF receptors appears to fulfill this criterion as a commercially accessible ELISA kit is available. This enables an assay of sTNF receptor type 1 levels in routinely collected blood samples. Furthermore, the relationship between sTNF receptor levels and renal events in patients with DKD appears to be consistent across both gender and ethnicity. Recently concentrations of sTNF receptors have been shown to be associated with an increased risk of ESRD in American Indians with type 2 diabetes, even after accounting for traditional risk factors [15]. Further studies are still needed to replicate this finding in other ethnic populations.

Another important characteristic of an ideal biomarker is that it is modifiable with treatment and that changes in the biomarker prevent the progression of an underlying disease process. So far the temporal relationship between sTNF receptor levels and changes in GFR has not been well characterized. In addition, a specific modifier for sTNF receptor levels has yet to be identified and developed.

Ultimately, the usefulness of using sTNF receptor levels to predict the onset of DKD remains to be determined. Thus far, measurement of sTNF receptor levels appears to provide an independent and robust predictor of DKD progression. However, its role as an early biomarker for DKD remains to be established.

**REFERENCES**