Curr Diab Rep (2013) 13:560–566
DOI 10.1007/s11892-013-0385-9

Novel Biomarkers for the Progression of Diabetic Nephropathy: Soluble TNF Receptors

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Published online: 10 May 2013

Abstract Despite 2 decades of advances in therapy of diabetic patients, the prevalence of diabetic nephropathy among patients with diabetes has not decreased. However, large-scale multicenter studies have achieved great success in terms of the reduction of albuminuria, suggesting that albuminuria might not be an accurate surrogate marker for slowing the rate of renal function decline. It is important to be able to identify individuals at high risk for renal function decline, or ultimately, end-stage kidney disease (ESKD) and its associated cardiovascular disease (CVD). More sensitive early biomarkers, other than albuminuria and the estimated glomerular filtration rate (eGFR), should be required. Recently, serum concentrations of soluble tumor necrosis factor (TNF), receptor 1 (TNFR1), and TNFR2 have predicted future GFR loss and ESKD in patients of a wide variety of stages and both types of diabetes. Longitudinal interventional studies are needed to validate these biomarkers in a broad range of populations prior to implementation in routine diabetes management.

Keywords TNF-α · TNF receptor 1 (TNFR1) · TNF receptor 2 (TNFR2) · Inflammation · Biomarker · Chronic kidney disease (CKD) · Diabetes · Diabetic nephropathy

Introduction

Albuminuria is one of the first asymptomatic clinical manifestations of microvascular injury in diabetes. A growing body of evidence is accumulating that the presence of mild degrees of albuminuria is an increased risk of cardiovascular disease (CVD) [1–6]. Therefore, screening for quantification of albuminuria is recommended for all diabetic patients to identify individuals at risk of diabetic complications [7]. However, association of mild albuminuria with progressive renal disease has been highly challenged, except in patients of progression of albuminuria. Albuminuria also lacks specificity and sensitivity as a prognostic biomarker for progressive diabetic nephropathy (DN) [8, 9•], as DN is sometimes able to progress without an increase in albuminuria and even in the presence of normoalbuminuria [10, 11]. Furthermore, even in the current large-scale study of the BP-lowering arm of the Action in Diabetes and Vascular disease: preterAx and diamicroN-MR Controlled Evaluation (ADVANCE), diabetic patients with mild albuminuria but no decrease in glomerular filtration rate (GFR) did not have poor renal outcomes.

DN affects up to one third of all patients with diabetes [12, 13]. Based on the annual report of the US Renal Data System (USRDS) and the Japanese Society for Dialysis Therapy (JSDT), diabetes is a leading cause of end-stage kidney disease (ESKD) and accounts for nearly half of all incidence cases of ESKD [14]. The incidence of ESKD has flattened in USRD data as well as Canadian and UK data, recently, despite the trends towards start of dialysis at low creatinine level [15]. However, at the same time the prevalence of nephropathy among diabetic patients [13], or the cumulative risk of ESKD in patients with type 1 diabetes (T1D) and proteinuria has not changed much [16, 17]. Assuming that the prevalence of ESKD among diabetic patients is partly affected by the better life expectancy of patients with DN, we may be able to understand at least partly this discrepancy. Taken all together, this may reflect the success in retarding the progression of chronic kidney disease (CKD) with more aggressive control of blood pressure and use of drugs that block the renin-angiotensin-aldosterone system (RAAS) as well as improved glycemic control. The Diabetes Control and Complications Trial (DCCT), the UK prospective Diabetes Study (UKPDS) and the Kumamoto study demonstrated that a strict glucose control prevents the development/progression of albuminuria in patients with T1D and type 2 diabetes (T2D), respectively [18–20]. However, most studies have not been proven to

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prevent a decrease of GFR in randomized control trials [18–21]. This finding may partly come from the study or observation period. In fact, long-term follow- up studies for more than 10 to 20 years such as UKPDS [22] and DCCT-Epidemiology of Diabetes Interventions and Complications (EDIC) study [23•] intensive diabetes therapy to early diabetic patients were an excellent proof of prevention of the proportion of doubling their plasma creatinine or decrease in GFR. The use of RAAS inhibitors has dramatically increased over the last 2 decades. RAAS inhibitors postponed the onset of ESKD in both types of diabetic patients with proteinuria [24, 25], leading to changes in the standard therapy. Alternatively, RAAS inhibitors not only failed to prevent the development of microalbuminuria but also failed to diminish an early morphologic change in the kidneys in patients with T1D and normoalbuminuria [26].

One may wonder why the number of affected DN patients has not decreased. The core of DN might be shifting from albuminuria to impaired GFR, according to the data of National Health and Nutrition Examination Surveys (NHANES) [13]. Albuminuria is eligible as a substitute clinical (surrogate) endpoint in most studies, though a growing body of evidence has demonstrated that a certain form of therapy has achieved success in terms of reducing albuminuria [27, 28]. However, there is a lack of data on GFR loss in these patients. Albuminuria/proteinuria might not always adequately identify individuals at risk for future GFR loss or ESKD in diabetes [9•, 29]. Alternatively, there is no guarantee that the slowing of GFR loss or even improved GFR by some treatment is accompanied by a decrease of proteinuria [26, 30–33]. Unfortunately, despite great interest and effort, no sensitive and specific prognostic biomarkers for progressive DN have been validated. Therefore, the discovery of a specific, reliable diagnostic and prognostic biomarker, other than albuminuria, is urgently needed and would be indispensable. This review focuses on the potential prognostic use of TNF receptors in patients with T1D and T2D.

Characteristics of TNFα, TNFR1, and TNFR2

Tumor necrosis factor α (TNFα) is a functional 26-kDa homotrimer type II transmembrane protein [34]. It is a central proinflammatory cytokine that is generated in a wide variety of cells, including hematopoietic cells (monocytes, macrophages, and T cells), fat and endothelial cells. Although TNFα is usually not present in normal kidneys [35], intrinsic renal cells, such as glomerular mesangial cells [36], and glomerular and tubular epithelial cells, produce TNFα after stimulation [37, 38]. At the same time, it has important immune-regulatory functions. Thus, TNFα may mediate both proinflammatory as well as immunosuppressive functions.

The biological activities of the TNFα signal are relayed by at least 2 functionally distinct cell surface receptors, termed TNF receptor 1 (TNFR1, TNFRSF1A, CD120a, p55) and receptor 2 (TNFR2, TNFRSF1B, CD120b, p75), on the target cells and induce expression of adhesion molecules, chemokines for leukocyte, and apoptosis in the susceptible cells [39, 40]. Both receptors belong to the TNFα receptor superfamily, a group of type I single transmembrane glycoproteins. TNFR1 and TNFR2 share only approximately 30 % homology in their extracellular domain and no homology in their intracellular domain. In contrast to TNFR1, TNFR2 has no death domain on its intracellular region, suggesting activation of different downstream transduction pathways. Although the exact roles of the receptors are not yet understood, TNFR1 modulates the immune response and apoptosis, whereas TNFR2 is one of the proinflammatory mediators in glomerulonephritis.

TNFR1 can be detected in almost all cell types [41], while TNFR2 is only located in oligodendrocytes [42], astrocytes [43], T cells [44], myocytes [45], thymocytes [46], endothelial cells [47], and human mesenchymal stem cells [48]. In healthy subjects, TNFR2 is usually not present in the kidneys, whereas TNFR1 is present in normal glomerular endothelium, where it is primarily localized within the Golgi apparatus [35].

TNFα and TNFR1 are shed from the cell surface by the TNFα converting enzyme (TACE) named a disintegrin and metalloprotease protein - 17 (ADAM-17), and are released into circulation as functional 17-kDa and 34-KDa soluble forms, respectively [49–51]. Full-length 55-kDa soluble TNFR1, which is the predominant form in human serum, is also recognized as the mechanism by exosome-like vesicles [52, 53]. It is not well known whether the same mechanisms apply to TNFR2 release and how this process is regulated.

In plasma, TNFα appears as free or bound to soluble TNFRs (TNFR1 and TNFR2). It has been suggested that soluble TNFRs represent a buffer system that may prolong the biological actions (a slow release reservoir) of TNFα [54, 55] or may function as decoys for TNFα [56]. Both receptors in the membrane-bound and soluble forms are active, and soluble receptors act as physiological attenuators of TNFα activity at high concentration, but low concentrations of soluble receptors enhance the effect of TNFα [57].

Association of Circulating Levels of Soluble TNF Receptors with GFR in Patients with and without Diabetes from Cross-Sectional Studies

A number of studies have documented significantly higher concentrations of inflammatory biomarkers in patients with diabetes and chronic kidney disease (CKD), and those levels

are closely correlated to the changes of GFR [58–61]. Even in a community-based setting, elevated inflammatory biomarkers have been shown to be associated with lower GFR and higher albuminuria [62–64]. In this review, the importance of promising biomarkers, soluble TNFR1, and TNFR2, relevant to kidney function, are in large part summarized and followed by a review of the available clinical data for the prediction of GFR loss in patients with diabetes as well as non-diabetic patients. In the beginning, most studies focused on understanding how abnormal levels of TNFRs are related to the severity of albuminuria. Several studies showed that circulating concentrations of TNFRs were elevated in comparison with healthy subjects, and higher concentrations of these biomarkers were associated with the elevated urinary albumin excretion [65–67]. Then, much of the attention on circulating TNFRs levels focused on the relationship with GFR from albuminuria [68–70, 71•]. Lin et al. [69] performed a cross-sectional study that showed for the first time the relationship between renal function and TNFR2 level in 732 patients with T2D. The TNFR2 level ($r = -0.39$, $P < 0.0001$) was inversely and significantly correlated with the GFR. In a multivariable logistic regression analysis, the highest quartile of TNFR2 levels had nearly an 8-fold increased odds of having CKD3 compared with those in the lowest quartile. Although this study is composed of a fairly large cohort, it is restricted to males. Furthermore, no information is available on albuminuria, another important renal function marker. Another cross-sectional study of 320 type 2 diabetic Chinese patients reported that composite TNFα score or individual molecule of TNF pathway markers (TNFα, TNFR1, and TNFR2) were associated with GFR independently of albuminuria [70]. One interesting fact about this study is that neither interleukin-6 (IL-6) nor C-reactive protein (CRP) showed any significant association with GFR, even with the exclusion of TNF pathway markers. At roughly the same time as the above article, Niewczas et al. [71•] examined serum inflammatory markers for association with GFR in patients with T1D and no proteinuria. Although limited by its cross-sectional study design, the 2nd Joslin Kidney study cohort is composed of a scientifically vetted, fairly large number of normo- ($n = 363$) and microalbuminuria ($n = 304$) diabetic patients. In addition, they measured multiple inflammatory markers [TNFα, TNFR1, TNFR2, interleukin-8 (IL-8), IFNγ inducible protein-10 (IP-10), monocytes chemoattractant protein-1 (MCP-1), intracellular and vascular adhesion molecules (ICAM-1, VCAM-1), FasL, Fas, interleukin-6 (IL-6), and CRP)]. Of special note is high correlativity ($r = 0.81$) between the levels of soluble TNFR1 and TNFR2, though both receptors promote different cellular responses. On the other hand, the 2 share the ability to induce the nuclear factor kappa B and apoptotic pathways. In any case, both TNFRs are strongly associated with renal function decline even after an adjustment for urinary albumin excretion.

Although most studies pay a great deal of attention to the relationship between circulating TNFRs and renal function, Idasiak-Piechocka et al. [72] measured urinary TNFR1 in patients with primary chronic glomerulonephritis (CGN) such as IgA nephropathy, mesangial proliferative glomerulonephritis, and focal segmental glomerulosclerosis. Levels of TNFR1 in patients with CGN were higher than those in healthy individuals. However, those levels did not differ among the 3 types of CGN. Multiple regression analysis revealed that urinary TNFR1, but not proteinuria, is independently associated with estimated creatinine clearance (eCCr). They speculate that the increased urinary TNFR1 is derived from the phenomenon of shedding the receptor from the membranes of glomerular cells activated by TNFα in response to the immunological response. It is hard to say whether urine is a better sample compared with serum, and whether this result applies to patients with diabetes at this moment, because they did not measure serum TNFR1 in this study.

Association of Circulating Levels of Soluble TNF Receptors with GFR in Patients with and without Diabetes from Prospective Study

To date, multiple studies have shown that several inflammatory biomarkers, including TNFRs, might predict renal function decline because CKD or diabetes may constitute a chronic inflammatory state. A post hoc analysis of data from a cholesterol and recurrent events (CARE) study showed that high concentrations of circulating TNFR2 and CRP were observed to be associated with the faster progression of GFR loss [73]. Interestingly, this study also demonstrated that pravastatin therapy has a salutary influence on GFR loss in at least some CKD patients. However, all patients in that study were limited to those who had CKD (GFR<60 mL/min/1.73 m^2) and coronary disease at baseline with the cause of renal disease unknown. In another prospective population based study, TNFR2 and IL-6, but not CRP, were positively associated with an increased risk of incident CKD in patients who were CKD-free at baseline [74]. Both investigations included less than 15 % and 9 % diabetic patients, respectively. On the other hand, Lin et al. [75] showed that women with T2D who were followed for 11 years showed a significant association between TNFR2 and a future GFR loss of more than 25 %. Unlike the CARE study, this study did not observe for CRP [73]. It is currently recognized that CKD and diabetes are independent risk factors for cardiovascular morbidity and mortality. The increased cardiovascular risk in those patients may also be at least partially mediated through chronic inflammation. Multiple prospective studies showed that increased levels of both TNFR2 and CRP were strongly associated with the risk of coronary events in patients with and without diabetes [68, 76]. However, after adjustment for

TNFR2 and classical cardiovascular risk factors, CRP was not significantly associated with a risk for coronary heart disease (CHD) in diabetic women, suggesting that CRP may entirely be explained by TNFR2. Although recent guidelines recommend the use of CRP as a cardiovascular risk-stratification tool, the relationship between CRP and GFR loss seems subtle. Interestingly, a comparable result was observed in a study for patients with rheumatoid arthritis in which TNFα is considered to be directly implicated in the pathogenesis of this disease [77].

Very recently, serum concentrations of TNF pathway markers such as TNFR1 or TNFR2 were shown to be excellent predictors of progressive kidney disease in patients with a wide variety of stages and both types of diabetes [78••, 79••]. Type 1 diabetic patients with normo- or microalbuminuria and with TNFR2 levels in the highest quartile had a 55 % cumulative incidence of reaching stage 3 CKD compared with less than a 15 % incidence for patients with TNFR2 levels in the lower 3 quartiles after 12 years of follow-up (Fig. 1). While type 2 diabetic patients with proteinuria and with TNFR1 levels in the highest quartile had a nearly 80 % cumulative incidence of progressing to ESKD after 12 years of follow-up, the rate was less than 20 % in those with TNFR1 levels in the lowest 3 quartiles (Fig. 2). Similar results were observed in each study with both TNFR isoforms, but the TNFR2 levels were a bit more predictive in patients with T1D and TNFR1 levels in patients with T2D. Total TNFα levels also tended to predict progressive nephropathy but were a much weaker predictor than TNFRs levels. On the other hand, ESKD was not associated with high concentrations of other inflammatory biomarkers such as ICAM-1, VCAM-1, IL-6, and CRP. Moreover, concentrations of TNFRs also predicted cardiovascular and all-cause mortality, but these effects were smaller than those observed in ESKD.

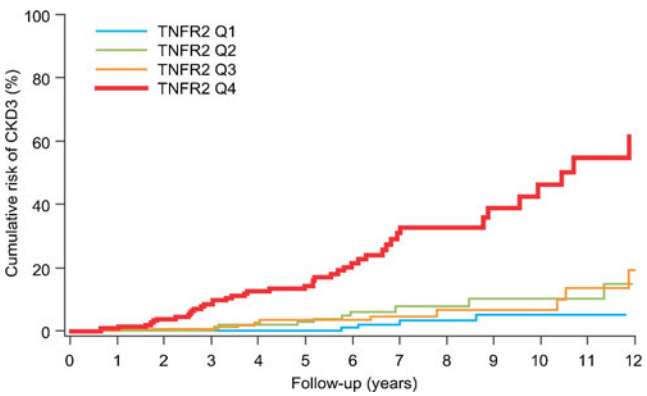

Fig. 1 Cumulative risk for CKD≥3 in patients with T1D during 12 years of follow-up according to quartile (Q1-Q4) of circulating TNFR2 at baseline. (With permission from: Gohda T, Niewczas MA, Ficociello LH, Walker WH, Skupien J, Rosetti F, et al. Circulating TNF receptors 1 and 2 predict stage 3 CKD in type 1 diabetes. J Am Soc Nephrol. 2012;23:516–24) [78••]

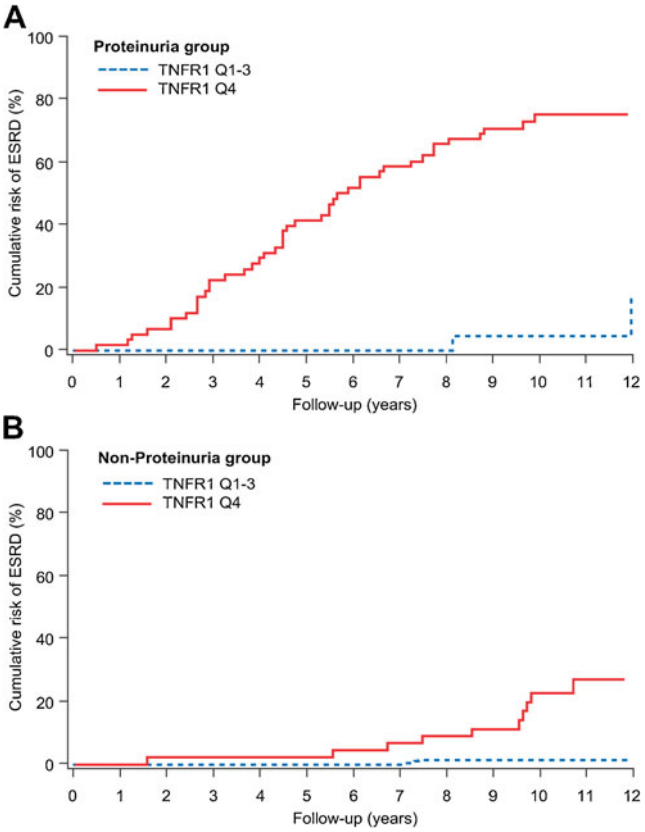

Fig. 2 A and B, Cumulative risk for ESKD in patients with T2D during 12 years of follow-up according to quartile (Q1-Q4) of circulating TNFR1 at baseline. (With permission from Niewczas MA, Gohda T, Skupien J, Smiles AM, Walker WH, Rosetti F, et al. Circulating TNF receptors 1 and 2 predict ESRD in type 2 diabetes. J Am Soc Nephrol. 2012;23:507–15) [79••]

Conclusions

Because of the complexities of the multiple pathophysiological processes in DN, it is difficult to accurately identify diabetic patients at high risk of developing progressive nephropathy that will likely lead to ESKD. No one is able to easily distinguish those at high risk of GFR loss (early decliner) from stable renal function (nondecliner) if the baseline GFR is similar and new-onset microalbuminuria occurs around the same time. Although albuminuria still remains an important biomarker, particular attention should be paid to hard renal outcomes such as ESKD or renal function decline in order to search for an ideal and validated biomarker. In this regard, TNFRs have the greatest promise in diabetic patients as a biomarker for renal function decline. Of particular note is that only a single measurement of the concentration of TNFR1 or TNFR2 is able to predict progression to CKD3 in patients with T1D who have normal renal function at baseline, and also progression to ESKD in both proteinuric and non-proteinuric patients with T2D. These associations are independent of circulating free or total TNFα and also of

conventional relevant clinical covariates such as age, HbA1c, urinary albumin excretion rate, baseline GFR, blood pressure, and treatment with RAAS inhibitors.

We should examine these biomarkers prospectively in large, multicenter, and multi-ethnic groups over an extended follow-up period before the transition into clinical practice. Also, methodologically well-designed interventional studies should examine whether TNFRs are not only markers but also have causal risk factors that may provide further information that could lead to novel treatment options. Novel biomarker should be independent of conventional risk factors. We believe there is no doubt that TNFRs are biomarkers, which are generally applicable to above, but new areas of research such as proteomics and metabolomics may be helpful in the identification of new biomarkers, unraveling existing pathologic pathways, and facilitating the more rapid development of novel and effective therapies.

Acknowledgement My heartfelt appreciation goes to Dr. Andrzej Krolewski (Joslin Diabetes Center, MA) whose idea and leadership made enormous contribution to this work.

Conflict of Interest Tomohito Gohda declares that he has no conflict of interest. Yasuhiko Tomino declares that he has no conflict of interest.

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- • Of importance
- •• Of outstanding importance

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