High Baseline Levels of Tumor Necrosis Factor Receptor 1 Are Associated With Progression of Kidney Disease in Indigenous Australians With Diabetes: The eGFR Follow-up Study

Diabetes Care 2018;41:739–747 | https://doi.org/10.2337/dc17-1919

Elizabeth L.M. Barr,[1,2] Federica Barzi,[1] Jaquelyne T. Hughes,[1,3] George Jerums,[4,5] Wendy E. Hoy,[6] Kerin O'Dea,[1,7] Graham R.D. Jones,[8,9] Paul D. Lawton,[1] Alex D.H. Brown,[10,11] Mark Thomas,[12] Elif I. Ekinci,[1,4,5] Ashim Sinha,[13] Alan Cass,[1] Richard J. MacIsaac,[5,14] and Louise J. Maple-Brown[1,3]

[1]Menzies School of Health Research, Darwin, Northern Territory, Australia
[2]Baker Heart and Diabetes Institute, Melbourne, Victoria, Australia
[3]Royal Darwin Hospital, Darwin, Northern Territory, Australia
[4]Department of Endocrinology, Austin Health, Melbourne, Victoria, Australia
[5]Department of Medicine, University of Melbourne, Melbourne, Victoria, Australia
[6]The University of Queensland, Brisbane, Queensland, Australia
[7]Nutrition and Population Health, University of South Australia, Adelaide, South Australia, Australia
[8]SydPath, St Vincent's Hospital Sydney, Sydney, New South Wales, Australia
[9]Faculty of Medicine, University of New South Wales, Sydney, New South Wales, Australia
[10]Aboriginal Health, Sansom Institute for Health Research, University of South Australia, Adelaide, South Australia, Australia
[11]Indigenous Health, South Australian Health and Medical Research Institute, Adelaide, South Australia, Australia
[12]Royal Perth Hospital, Perth, Western Australia, Australia
[13]Diabetes and Endocrinology, Cairns Base Hospital, Cairns, Queensland, Australia
[14]Department of Endocrinology and Diabetes, St Vincent's Hospital Melbourne, Melbourne, Victoria, Australia

Corresponding author: Elizabeth L.M. Barr, elizabeth.barr@menzies.edu.au.

Received 13 September 2017 and accepted 15 December 2017.

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc17-1919/-/DC1.

OBJECTIVE

To examine the association between soluble tumor necrosis factor receptor 1 (sTNFR1) levels and kidney disease progression in Indigenous Australians at high risk of kidney disease.

RESEARCH DESIGN AND METHODS

This longitudinal observational study examined participants aged ≥18 years recruited from >20 sites across diabetes and/or kidney function strata. Baseline measures included sTNFR1, serum creatinine, urine albumin-to-creatinine ratio (uACR), HbA_{1c}, C-reactive protein (CRP), waist-to-hip ratio, systolic blood pressure, and medical history. Linear regression was used to estimate annual change in estimated glomerular filtration rate (eGFR) for increasing sTNFR1, and Cox proportional hazards were used to estimate the hazard ratio (HR) and 95% CI for developing a combined renal outcome (first of a ≥30% decline in eGFR with a follow-up eGFR <60 mL/min/1.73 m^2, progression to renal replacement therapy, or renal death) for increasing sTNFR1.

RESULTS

Over a median of 3 years, participants with diabetes (n = 194) in the highest compared with the lowest quartile of sTNFR1 experienced significantly greater eGFR decline (−4.22 mL/min/1.73 m^2/year [95% CI −7.06 to −1.38]; P = 0.004), independent of baseline age, sex, eGFR, and uACR. The adjusted HR (95% CI) for participants with diabetes per doubling of sTNFR1 for the combined renal outcome (n = 32) was 3.8 (1.1–12.8; P = 0.03). No association between sTNFR1 and either renal outcome was observed for those without diabetes (n = 259).

CONCLUSIONS

sTNFR1 is associated with greater kidney disease progression independent of albuminuria and eGFR in Indigenous Australians with diabetes. Further research is required to assess whether TNFR1 operates independently of other metabolic factors associated with kidney disease progression.

Convincing evidence shows that inflammation is associated with chronic conditions, including diabetes mellitus (1) and cardiovascular disease (2). Inflammatory processes and prothrombotic biomarkers associated with the development of atherosclerosis in cardiovascular disease may also play an important role in the development of kidney disease (3). Tumor necrosis factor (TNF)-α is a proinflammatory cytokine generated by immune cells in the presence of inflammation. TNF-α is involved in cellular signaling, including apoptosis, by interacting with membrane receptors: soluble TNF receptor (sTNFR) 1 and sTNFR2. Activation of TNF pathways has been associated with kidney disease progression in populations with renal insufficiency (4,5). In individuals with type 2 diabetes, sTNFR1 and sTNFR2 levels have been correlated with renal structural changes such as area of mesangial volume fraction, interstitial volume fraction, percentage of glomerular endothelial cell fenestration, total filtration surface per glomerulus, and global glomerular sclerosis, indicating that inflammation may have a role in kidney damage (6,7).

Evidence for TNF pathways promoting kidney damage is supported by prospective studies of patients with type 1 diabetes (8–11) and patients with type 2 diabetes (12–16), in whom sTNFR1 is associated with a decline in kidney function independent of known risk factors for kidney disease such as albuminuria, HbA_{1c}, and hypertension. Thus inflammation may mediate diabetic kidney disease progression, rather than be a consequence of reduced kidney filtration, although evidence from interventional studies is required to confirm causality. Furthermore, evidence is inconsistent regarding the potential role of TNF pathways in kidney disease progression among the general population (17–21), and most studies have not accounted for potential confounding by albuminuria (17–20).

Indigenous Australians experience extremely high rates of diabetes (including intermediate hyperglycemia) and kidney disease compared with non-Indigenous Australians, and these conditions have serious consequences with regard to premature mortality, disability, quality of life, and socioeconomic disadvantage (22). Furthermore, Indigenous Australians have a higher prevalence of chronic inflammation than do non-Indigenous Australians (23). Therefore, it is important to improve our understanding of the impact of chronic inflammation on diabetes and kidney disease, as this may help to identify potential targets for intervention. The eGFR Study was designed to investigate the accuracy of estimated compared with directly measured glomerular filtration rate (GFR) (24,25). The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation without adjustment for ethnicity provides a reasonably unbiased and accurate assessment of GFR. Furthermore, longitudinal follow-up of the estimated GFR (eGFR) cohort has shown albuminuria measured at baseline to be the key predictor of eGFR decline and clinically based renal outcomes (26). However, elevated C-reactive protein (CRP) was also found to be significantly associated with kidney disease progression (26). In this context, we sought to explore further the association between chronic inflammation and kidney disease progression in Indigenous Australians. The aim of this study was to assess whether elevated sTNFR1 is a predictor of eGFR decline and clinically relevant renal outcomes, independent of albuminuria, CRP, HbA_{1c}, and hypertension, in those with and without diabetes.

RESEARCH DESIGN AND METHODS

Participants

Between 2007 and 2011, 654 Indigenous Australians aged $\geq$16 years took part in the eGFR Study. Participants were recruited from urban, rural, and remote centers in Australia where indigenous people experience high rates of end-stage kidney disease (24). Recruitment occurred across five predefined strata: *1*) "healthy" people without diabetes, chronic kidney disease (CKD), or albuminuria; *2*) participants with physician-diagnosed diabetes or albuminuria and eGFR >90 mL/min/1.73 m^2 (based on the four-variable MDRD equation); *3*) eGFR 60–90 mL/min/1.73 m^2; *4*) eGFR 30–59 mL/min/1.73 m^2; *5*) eGFR <15–29 mL/min/1.73 m^2. Participants with CKD and/or diabetes were volunteers from participating medical services, and "healthy" participants were volunteers from the community. Individuals were ineligible if they were identified as having rapidly changing kidney function, receiving dialysis, being pregnant or breastfeeding, or having an allergy or adverse reaction to iodine-based contrast media.

Of the 654 baseline participants, 619 were eligible to participate in a follow-up examination. Participants aged <18 years (n = 13), who withdrew consent (n = 7), or who had no baseline blood sample (n = 15) were not eligible (26). This analysis included 453 participants, excluding 166 participants who were *1*) lost to follow-up (n = 8); *2*) acutely unwell at follow-up (n = 1); *3*) examined <6 months after the baseline examination (n = 14); *4*) missing enzymatic creatinine measures at follow-up (n = 46); or *5*) missing baseline urine albumin-to-creatinine ratio (uACR) measurements (n = 30), missing sTNFR1 measurements (n = 50), and missing medical history of cardiovascular disease (n = 17). Baseline characteristics, except for measures of body composition, were largely comparable between those excluded from and those included in this analysis. Participants excluded from the analysis had a significantly lower BMI and narrower waist circumference (Supplementary Table 1). Participants provided informed consent, and the following ethics committees approved the study: the Human Research Ethics Committee of the joint Menzies School of Health Research–Northern Territory Department of Health, including the Aboriginal subcommittee; the Central Australian Human Research Ethics Committee; the Western Australian Aboriginal Health Information and Ethics Committee; the Royal Perth Measurements Hospital Ethics Committee; and the Cairns and Hinterland Health Services District Human Research Ethics Committee.

Measurements

Baseline and follow-up examinations involved the collection of nonfasting venous blood samples and review of pathology and clinical records (24,26). sTNFR1 levels were measured in serum samples stored at −80°C using a Human sTNFR1 EIA- BIO 94 kit obtained from EKF Diagnostics (Dublin, Ireland). The assay was undertaken using a 4.5-h solid-phase quantitative sandwich enzyme immunoassay. The test procedure is based on the sequential addition of sample, polyclonal anti–human sTNFR1 antibody-enzyme conjugate, and calorimetric substrate to microplate wells coated with anti–human sTNFR1 monoclonal antibody. The coefficients of variation for intra-assay/interassay precision (as assessed by the manufacturer) were 3.3% and 5.1%, respectively.

Accredited local laboratories provided baseline clinical data on HbA_{1c}, urine creatinine and albumin (to determine uACR), high-sensitivity CRP, HDL, and total cholesterol (24). Baseline anthropometric measurements of height, weight, and waist and hip circumferences were taken (24). Blood pressure was measured three times while the participants were seated, and the mean was calculated (Welch Allyn Medical Products, Skaneateles Falls, NY) (24). Medical records were reviewed to determine diabetes diagnosis and prescription of hydroxymethylglutaryl-CoA reductase inhibitor medicines (statins), antihypertensive medicines (primarily ACE inhibitors), and angiotensin II receptor antagonists (angiotensin receptor blockers) (27). Information regarding self-reported cigarette smoking status (current smoker, former smoker, and never smoker) was collected at baseline.

Outcomes

The follow-up time was the date between baseline and follow-up serum creatinine measurements (range 0.52–5.75 years). In 67% of participants, serum creatinine from thawed frozen sera (–80°C) was measured at baseline and follow-up by a single laboratory (Melbourne Pathology, Melbourne, Australia) using an isotope dilution mass spectrometry–aligned enzymatic method (Roche Diagnostics, Melbourne, Australia). For the remaining participants without a follow-up blood sample, serum creatinine was measured by laboratories at each recruitment site, all using isotope dilution mass spectrometry–aligned assays. CKD-EPI eGFR was calculated based on serum creatinine without correcting for African American ethnicity (25). Outcomes were *1*) the annual change in CKD-EPI eGFR ([CKD-EPI eGFR at follow-up − CKD-EPI eGFR at baseline]/follow-up period) and *2*) the incidence of a combined renal end point, which was the first of the following: an absolute 30% decline in eGFR (28,29) with a follow-up eGFR $<$60 mL/min/1.73 m^2, death from renal causes, or initiation of renal replacement therapy. All deaths occurring when eGFR declined to $<$15 mL/min/1.73 m^2 were defined as renal deaths. Participants were censored at the time the first end point was reached.

Statistical Analysis

Study population characteristics were compared across quartiles of sTNFR1 using one-way ANOVA, the Kruskal-Wallis test, and the χ^2 test. Associations between sTNFR1 and continuous covariates were assessed with a Pearson correlation. After categorizing sTNFR1 into quartiles, analyses were then stratified by diabetes, which was defined as medical record report of diabetes or $HbA_{1c} \geq$48 mmol/mol ($\geq$6.5%). We examined plots of the relation of sTNFR1 concentration (natural logarithm) at baseline with eGFR decline. Associations of baseline sTNFR1 (as a continuous natural logarithmic variable and in quartiles) with annual eGFR decline (milliliters per minute per 1.73 m^2) were assessed with linear regression. Models were adjusted for baseline age, sex, CKD-EPI eGFR, and uACR and other clinically important covariates selected a priori, including HbA_{1c}, waist-to-hip ratio, systolic blood pressure, antihypertensive medicines, CRP, smoking status, and medical history of ischemic heart disease or myocardial infarction. Continuous risk factors were normally distributed except for sTNFR1, HbA_{1c}, CRP, and uACR, which were transformed by taking the natural logarithm. No evidence indicated multicollinearity between covariates for any of the fitted models (variance inflation factor $<$3 for all independent variables) (30). Interactions were assessed between sTNFR1 and baseline sex (P = 0.02), age ($<$45 vs. $\geq$45 years), ethnicity (Aboriginal vs. Aboriginal and/or Torres Strait Islander), waist-to-hip ratio ($<$0.95 vs. $\geq$0.95), albuminuria ($<$3, 3–30, or $\geq$30 mg/mmol), CKD-EPI eGFR status (eGFR $<$60, 60 to $<$90, or $\geq$90 mL/min/1.73 m^2), and diabetes after adjusting for baseline sex (except for the interaction with sex), age (except for the interaction with age), and uACR (except for the interaction with albuminuria). The proportion of the variance in eGFR decline explained by the models with and without sTNFR1 was assessed with the adjusted R^2 statistic, and these nested models were compared using log-likelihood ratio tests.

We also undertook three sensitivity analyses. First, participants taking statins (n = 119) were excluded, as previous studies have indicated that statins may have an anti-inflammatory effect (5). Second, we excluded participants who had a baseline CKD-EPI eGFR $<$30 mL/min/1.73 m^2 (n = 15) or who had a uACR $\geq$30 mg/mmol (n = 85) in order to assess the potential impact of reverse causality between low eGFR or albuminuria and sTNFR1 levels.

Cox proportional hazard models were used to assess the relation of sTNFR1 with a dichotomous renal end point. sTNFR1 was entered as a continuous variable because too few events occurred to model it in quartiles. Models were adjusted for baseline age, sex, CKD-EPI eGFR, and uACR. Proportional hazards assumptions were satisfied based on graphs of the log-log plots of the relative hazards by time and by scaled Schoenfeld residuals. The Harrell C-statistic was calculated to assess whether adding sTNFR1 to a multivariate model with baseline age, sex, CKD-EPI eGFR, and uACR improved model discrimination between participants who experienced and who did not experience the combined renal outcome. We used likelihood ratio tests to compare these models.

Analyses were performed in Stata version 14.1 (StataCorp, College Station, TX). P values $<$0.05 were considered statistically significant.

RESULTS

Table 1 shows that increasing sTNFR1 quartiles at baseline were significantly associated with older age and a generally poorer cardiometabolic risk factor profile. Correlations between sTNFR1 concentration and continuous covariates were weak, except for uACR and CKD-EPI eGFR (Supplementary Table 2).

The median follow-up was 3.0 years, and 43 participants experienced the combined renal outcome (2 renal deaths and 41 with an absolute 30% decline in eGFR with a follow-up eGFR $<$60 mL/min/1.73 m^2). For the outcome of eGFR decline, there was no evidence of an interaction between sTNFR1 and age, ethnicity, eGFR, albuminuria, or adiposity ($P > 0.05$). The association between a doubling of baseline TNFR1 and eGFR decline was greater in women than in men (−3.74 mL/min/1.73 m^2/year [95% CI −5.84 to −1.64] vs. −1.44 mL/min/1.73 m^2/year [95% CI −3.90 to 1.02]; P for interaction = 0.02). The median (interquartile range) eGFR decline according to increasing quartiles of sTNFR1 at baseline was −2.2 (−5.2 to −0.2), −2.3 (−4.5 to −0.2), −2.0 (−5.2 to −0.5), and −2.3 mL/min/1.73 m^2/year (−6.5 to −0.5) in those without diabetes (n = 259) and −1.2 (−3.3 to 1.1), −1.6 (−4.5 to −0.01), −1.4 (−3.6 to 1.2), and −4.8 mL/min/1.73 m^2/year (−8.7 to −2.3) in

Table 1—Characteristics of the eGFR Study population according to quartiles of sTNFR1

	Quartile 1 (n = 114)	Quartile 2 (n = 113)	Quartile 3 (n = 113)	Quartile 4 (n = 113)	Total (n = 453)	P value
Baseline characteristics						
sTNFR1 (pg/mL), range	465–1,285	1,286–1,617	1,618–2,130	2,131–11,637		
Age, years	41 ± 13	42 ± 14	46 ± 14	52 ± 13	45 ± 14	<0.001
Men	46 (40)	50 (44)	36 (32)	38 (34)	170 (38)	0.18
Currently smoking	57 (50)	48 (42)	39 (35)	36 (32)	180 (40)	0.15
Diabetes*	35 (31)	41 (36)	51 (45)	67 (59)	194 (43)	<0.001
CRP (mg/L)	5.0 (2.0, 7.6)	5.0 (3.0, 10.0)	8.0 (3.0, 14.0)	6.0 (3.8, 13.0)	6.0 (3.0, 11.0)	0.007
BMI (kg/m^2)	29.2 ± 6.9	30.2 ± 6.8	32.4 ± 7.0	30.9 ± 7.8	30.7 ± 7.2	0.008
Waist circumference (cm)	97.5 ± 15.6	100.5 ± 15.8	106.1 ± 16.0	104.9 ± 16.3	102.2 ± 16.3	<0.001
Blood pressure (mmHg)						
Systolic	114 ± 16	116 ± 15	119 ± 18	123 ± 19	118 ± 17	0.002
Diastolic	74 ± 11	74 ± 10	76 ± 11	76 ± 10	75 ± 10	0.23
Antihypertensive medicine	29 (25)	34 (30)	35 (31)	70 (62)	168 (37)	<0.001
HbA_{1c} (mmol/mol)	47 ± 18	47 ± 18	51 ± 21	55 ± 21	50 ± 20	0.006
HbA_{1c} (%)	6.5 ± 1.7	6.5 ± 1.6	6.9 ± 1.9	7.2 ± 1.9	6.8 ± 1.8	0.006
Total cholesterol (mmol/L)	5.1 ± 1.0	4.9 ± 1.0	4.7 ± 1.1	4.7 ± 1.1	4.8 ± 1.0	0.014
Statins	24 (21)	26 (23)	22 (19)	47 (42)	119 (26)	<0.001
HDL cholesterol (mmol/L)	1.1 ± 0.4	1.1 ± 0.4	1.1 ± 0.4	1.0 ± 0.3	1.1 ± 0.3	0.63
Triglycerides (mmol/L)	1.7 (1.2, 2.4)	1.8 (1.2, 2.4)	1.8 (1.2, 2.5)	2.0 (1.6, 2.6)	1.8 (1.3, 2.5)	0.079
Albumin-to-creatinine ratio (mg/mmol)	1.2 (0.6, 2.4)	1.4 (0.7, 3.9)	1.1 (0.6, 6.2)	28.1 (2.7, 140.1)	1.7 (0.7, 13.8)	<0.001
CKD-EPI eGFR (mL/min/1.73 m^2)†	104.7 ± 18.6	103.1 ± 17.0	97.6 ± 20.3	71.1 ± 31.3	94.1 ± 26.2	<0.001
Follow-up characteristics						
eGFR decline over follow-up (mL/min/1.73 m^2/year)	−2.53 ± 5.22	−1.99 ± 3.79	−2.28 ± 7.48	−5.12 ± 5.82	2.50 ± 1.12	<0.001
Combined renal outcome‡	4 (3.5)	1 (0.9)	4 (3.5)	34 (30)	43 (9.5)	<0.001

Data are number (percentage), mean ± SD, or median (25th, 75th percentile), unless otherwise indicated. *Diabetes was defined as HbA_{1c} ≥48 mmol/mol (≥6.5%) or physician diagnosis of diabetes. †CKD-EPI eGFR was calculated using the CKD-EPI eGFR equation based on serum creatinine without a correction for African American ethnicity. ‡Combined renal outcome was defined as the first of the following: an absolute 30% decline in eGFR with a follow-up eGFR <60 mL/min/1.73 m^2, death from renal causes, or initiation of renal replacement therapy.

those with diabetes (n = 194). Supplementary Fig. 1 shows that the relation between sTNFR1 concentration (logarithmic transformation) at baseline and eGFR decline was much greater among those with diabetes than those without diabetes at baseline. Given the different pattern of decline among those with and without diabetes, and the significant interaction between sTNFR1 level and diabetes status (P = 0.03), subsequent analyses were stratified by baseline diabetes status.

Table 2 shows the coefficients (reflecting the slope of eGFR decline) for sTNFR1 quartiles 2, 3, and 4 compared with quartile 1, stratified by baseline diabetes status. In those with diabetes, increasing baseline sTNFR1 was significantly associated with greater eGFR decline independent of baseline age, sex, CKD-EPI eGFR, and uACR. We found no relation between increasing sTNFR1 and greater eGFR decline among those without diabetes. Table 3 shows that the strong association between increasing sTNFR1 and eGFR decline in those with diabetes remained after additional adjustment for baseline waist-to-hip ratio, HbA_{1c}, systolic blood pressure, and antihypertension medicines or CRP. None of the other covariates were significantly associated with eGFR decline in these multivariate models (data not shown).

Among those with diabetes, a multivariate model that included baseline age, sex, smoking status, history of coronary heart disease, CKD-EPI eGFR, and uACR explained 12% of the variance in eGFR decline. When we included sTNFR1 as a continuous covariate in this multivariate model, the adjusted R^2 increased to 19% ($P < 0.001$).

A similar association between increasing sTNFR1 and eGFR decline was observed for those with diabetes when we excluded participants who had a baseline CKD-EPI eGFR <30 mL/min/1.73 m^2 (quartile 4 [Q4] vs. quartile 1 [Q1] of sTNFR1: −4.39 mL/min/1.73 m^2/year [95% CI −7.09 to −1.69]; $P < 0.002$) or when we excluded those with a uACR ≥30 mmol/L (Q4 vs. Q1 of sTNFR1: −3.62 mL/min/1.73 m^2/year [95% CI −6.07 to −1.16]; P = 0.004) or who were taking statins (Q4 vs. Q1 of sTNFR1: −3.88 mL/min/1.73 m^2/year [95% CI −7.85 to 0.10]; P = 0.06) after adjusting for baseline age, sex, CKD-EPI eGFR, and uACR.

We found no significant associations between baseline sTNFR1 levels and the risk for developing the combined renal outcome (n = 11) for those without diabetes (n = 259). For those with diabetes, the hazard ratio (HR) (95% CI) for the combined renal outcome (n = 32) associated with a doubling of baseline sTNFR1 level was 3.8 (1.1–12.8), adjusting for baseline age, sex, CKD-EPI eGFR, and uACR. However, further adjustment for CRP attenuated the association with sTNFR1 (HR 2.8 [95% CI 0.8–10.2]; P = 0.123) (Table 4). The C-statistic was 87% for a model that included baseline age, sex, CKD-EPI eGFR, and uACR; it increased to 88% (P = 0.03) when sTNFR1 was added.

CONCLUSIONS

This longitudinal observational study of a population at high risk of kidney disease is to our knowledge the first study to compare the association of serum concentration of sTNFR1 with renal progression in people with diabetes and people without diabetes after accounting for baseline albuminuria. It is important to note that our study provides information about a non-Europid population. With the exception

Table 2—eGFR decline according to quartiles of increasing baseline sTNFR1 stratified by diabetes at baseline

		sTNFR1 (pg/mL)		Model 1			Model 2			Model 3		
	Participants (*n*)	Median (25th, 75th percentile)	Range	β	95% CI	*P* value	β	95% CI	*P* value	β	95% CI	*P* value
No diabetes (*n* = 259)												
Q1	79	1,141 (1,039, 1,233)	465–1,285	Reference			Reference			Reference		
Q2	72	1,433 (1,341, 1,529)	1,286–1,615	0.99	−0.80 to 2.78	0.28	0.98	−0.79 to 2.74	0.28	1.02	−0.74 to 2.78	0.26
Q3	62	1,770 (1,691, 1,960)	1,616–2,130	0.67	−1.22 to 2.55	0.49	0.50	−1.37 to 2.36	0.60	0.43	−1.44 to 2.28	0.65
Q4	46	2,386 (2,271, 2,922)	2,131–11,637	−0.60	−2.67 to 1.47	0.57	−1.67	−3.84 to 0.50	0.13	−1.23	−3.50 to 1.04	0.29
sTNFR1*	—	—	—	−0.17	−2.06 to 1.71	0.86	−1.16	−3.19 to 0.87	0.26	−0.84	−2.90 to 1.21	0.42
Diabetes (*n* = 194)												
Q1	35	1,163 (1,002, 1,242)	773–1,282	Reference			Reference			Reference		
Q2	41	1,468 (1,379, 1,523)	1,283–1,617	−0.27	−2.96 to 2.42	0.84	−0.34	−3.02 to 2.34	0.80	−0.46	−3.06 to 2.14	0.73
Q3	51	1,829 (1,760, 1,959)	1,618–2,094	−0.67	−3.24 to 1.89	0.60	−0.90	−3.48 to 1.67	0.49	−0.92	−3.41 to 1.57	0.47
Q4	67	2,965 (2,481, 3,920)	2,095–9,264	−4.64	−7.12 to −2.15	<0.001	−5.61	−8.44 to −2.78	<0.001	−4.22	−7.06 to −1.38	0.004
sTNFR1*	—	—	—	−4.34	−6.19 to −2.49	<0.001	−6.78	−9.34 to −4.21	<0.001	−5.18	−7.82 to −2.54	<0.001

Data are milliliters per minute per 1.73 m^2 per year unless otherwise indicated. Model 1 was adjusted for baseline age and sex. Model 2 was adjusted for baseline age, sex, and CKD-EPI eGFR. Model 3 was adjusted for baseline age, sex, CKD-EPI eGFR, and uACR. CKD-EPI eGFR was calculated using the CKD-EPI eGFR equation based on serum creatinine without the correction for African American ethnicity. *sTNFR1 was transformed using the natural logarithm.

of one study of Native Americans (7), other studies of sTNFR1 and sTNFR2 in renal progression among participants with diabetes have been undertaken in predominantly Europid populations (8–14). We showed that over a median of 3 years' follow-up, greater sTNFR1 at baseline was significantly associated with both annual eGFR decline and risk of developing clinically important kidney disease outcomes in those with diabetes but not in those without diabetes. In those with diabetes, the relation of greater sTNFR1 with kidney disease progression was independent of baseline age, sex, CKD-EPI eGFR, albuminuria, CRP, hypertension, and adiposity. These findings suggest that the association between this inflammatory biomarker and kidney disease progression may be potentiated by hyperglycemia and related metabolic factors.

Previous studies have shown that sTNFR1 is significantly associated with kidney disease progression in participants with type 1 diabetes with (9,10) and without (8,11) proteinuria and in participants with type 2 diabetes (12–15). One study reported similar positive associations between TNF receptors and kidney disease progression irrespective of diabetes status (20), but associations for TNF receptors may have been overestimated because that study was unable to adjust for albuminuria. Our findings extend the results of these studies; we assessed the association between sTNFR1 and kidney disease progression in participants with and participants without diabetes after accounting for albuminuria, and we show that sTNFR1 is only associated with kidney disease progression in the presence of hyperglycemia. It is interesting that Skupien et al. (9) showed, in participants with type 1 diabetes and proteinuria, that the rate of eGFR loss associated with greater sTNFR2 (which is closely correlated with sTNFR1 [12]) increased with greater HbA_{1c}. Animal studies have demonstrated that macrophages produced many more inflammatory cytokines, including TNF, in diabetic rats compared with controls (31). These findings support our observation that the deleterious effects of sTNFR1 may be mediated by hyperglycemia.

We found no relation between sTNFR1 and kidney progression in those without diabetes. Findings from prospective studies of the general population are inconsistent (17–21). However, most studies

Table 3—eGFR decline according to quartiles of increasing baseline sTNFR1 (pg/mL) stratified by baseline diabetes and adjusting for known risk factors

		Model 1			Model 2			Model 3			Model 4		
sTNFR1	Participants (*n*)	β	95% CI	*P* value	β	95% CI	*P* value	β	95% CI	*P* value	β	95% CI	*P* value
No diabetes (*n* = 238)													
Q1	73	Reference			Reference			Reference			Reference		
Q2	69	1.04	−0.73 to 2.82	0.25	1.02	−0.74 to 2.79	0.25	1.07	−0.72 to 2.85	0.24	1.00	−0.78 to 2.72	0.27
Q3	56	1.34	−0.64 to 3.31	0.18	1.22	−0.70 to 3.14	0.21	1.36	−0.59 to 3.30	0.17	1.16	−0.80 to 3.13	0.24
Q4	40	−1.22	−3.58 to 1.14	0.31	−1.24	−3.59 to 1.11	0.30	−1.19	−3.57 to 1.18	0.32	−1.34	−3.72 to 1.04	0.27
sTNFR1*	—	−0.34	−2.63 to 1.95	0.77	−0.35	−2.61 to 1.91	0.76	−0.27	−2.55 to 2.00	0.81	−0.49	−2.79 to 1.80	0.68
Diabetes (*n* = 171)													
Q1	30	Reference			Reference			Reference			Reference		
Q2	39	−0.12	−2.98 to 2.72	0.93	−0.27	−3.13 to 2.59	0.85	−0.11	−2.95 to 2.74	0.94	−0.16	−3.00 to 2.68	0.91
Q3	43	−1.25	−4.04 to 1.54	0.38	−1.39	−4.17 to 1.38	0.32	−1.42	−4.19 to 1.36	0.32	−1.31	−4.08 to 1.46	0.35
Q4	59	−4.38	−7.50 to −1.25	0.006	−4.36	−7.50 to −1.22	0.007	−4.41	−7.54 to −1.28	0.006	−4.17	−7.32 to −1.00	0.01
sTNFR1*	—	−5.95	−8.90 to −3.01	<0.001	−5.70	−8.66 to −2.74	<0.001	−5.70	−8.64 to −2.75	<0.001	−5.53	−8.52 to −2.56	<0.001

Data are milliliters per minute per 1.73 m^2 per year unless otherwise indicated. Multivariate models are based on all participants without missing data (n = 409). All models were adjusted for baseline age, sex, CKD-EPI eGFR, uACR, history of ischemic heart disease or myocardial infarction, smoking (never, former, and current). Model 1 was also adjusted for waist-to-hip ratio, model 2 was also adjusted for the natural logarithm of HbA_{1c} (mmol/mol), model 3 was also adjusted for hypertension, and model 4 was also adjusted for CRP (natural logarithm). CKD-EPI eGFR was calculated using the CKD-EPI eGFR equation based on serum creatinine without correction for African American ethnicity. *sTNFR1 was transformed using the natural logarithm.

reporting a positive association between TNF pathways and kidney disease progression did not account for the possible confounding effects of kidney damage because albuminuria had not yet been measured (17–20). In addition, comparisons with these studies are difficult because the underlying risk of kidney disease and the prevalence of chronic inflammation are likely different. sTNFR1 levels were much higher in our study than in others. Therefore the association between sTNFR1 levels and kidney disease progression may not be as robust in individuals without diabetes compared with that in those with diabetes, but further examination of TNF pathways in kidney disease progression, independent of albuminuria, are warranted in those without diabetes, as our study had relatively short follow-up and may have been underpowered to detect a significant association.

We recently demonstrated that albuminuria is a strong predictor of kidney disease progression (26). In the current analysis, we showed that greater concentrations of sTNFR1 remained significantly associated with eGFR decline and the combined renal outcome despite adjustment for uACR and exclusion of participants with macroalbuminuria at baseline. Our results agree with those of other prospective studies of participants with type 2 diabetes (12,15). In addition, we did not demonstrate any interaction effect between sTNFR1 and albuminuria in predicting eGFR decline. This concurs with other studies that reported associations between sTNFR1 and kidney disease progression irrespective of proteinuria status (8–10,12). Cross-sectional data from Native Americans with type 2 diabetes also showed that TNF receptors 1 and 2 were significantly correlated with early glomerular changes on kidney biopsy after adjusting for uACR (7). These findings provide further evidence that low-grade systemic inflammation, as represented by higher circulating levels of sTNFR1, may have a role in kidney function decline independent of the pathophysiological pathways associated with albuminuria.

Our study showed that the addition of sTNFR1 to a multivariate model including uACR and CKD-EPI eGFR resulted in the model explaining a greater variance in eGFR decline. However, we observed no clinically important improvements in model discrimination for the combined renal outcome among those with diabetes,

Table 4—Risk of combined renal outcome associated with sTNFR1

	sTNFR1 (pg/mL)					
	No diabetes (n = 259)			Diabetes (n = 194)		
	HR*	95% CI	P value	HR*	95% CI	P value
Model 1	2.9	0.7–12.0	0.15	13.7	6.4–29.0	<0.001
Model 2	0.2	0.03–1.1	0.07	5.6	1.7–18.9	0.01
Model 3	0.2	0.03–1.0	0.05	3.8	1.1–12.8	0.03

A total of 453 participants were included in the models. A total of 11 outcomes occurred in the group without diabetes and 32 outcomes occurred in the group with diabetes. Model 1 was adjusted for age and sex. Model 2 was adjusted for age, sex, and CKD-EPI eGFR. Model 3 was adjusted for age, sex, CKD-EPI eGFR, and uACR. CKD-EPI eGFR was calculated using the CKD-EPI eGFR equation based on serum creatinine without correcting for African American ethnicity. *The HR represents the risk of developing the combined renal outcome associated with a doubling of sTNFR1 (natural logarithm) at baseline.

and assessment of C-statistic changes was limited by the small number of outcomes in our study. Previous studies reported mixed results on whether inflammatory markers can improve model prediction or discrimination for renal outcomes (12,15,31). These contrasting findings might be explained by a different prevalence of chronic inflammation. Indigenous Australians have been reported to have a higher prevalence of chronic inflammation, as represented by higher CRP levels, than non-Indigenous Australians (23), and thus chronic inflammation may present as the more dominant feature in the pathogenesis of renal function decline in Indigenous Australians.

A previous analysis of our cohort showed that in the total study population, CRP was associated with the incidence of the combined renal outcome but not with eGFR decline (26). We now extend that previous analysis by evaluating the role of sTNFR1 in the progression of kidney disease. We found that in those with diabetes, higher sTNFR1 remained significantly associated with eGFR decline despite adjustment for CRP; for the combined renal outcome, however, adjustment for CRP attenuated the association for sTNFR1, rendering it nonsignificant. The stronger association of sTNFR1 with eGFR decline compared with that found for CRP suggests that sTNFR1 may be a more specific marker of earlier change in kidney function than CRP (a nonspecific inflammatory marker) in those with diabetes. Perhaps CRP elevates later in the disease process, reflecting its greater influence on the association between sTNFR1 and clinical renal outcomes. Nonetheless, some other studies (4,12)—but not all (5,21)—have reported sTNFRs to be most strongly associated with progression to end-stage kidney disease when compared with CRP.

Strengths of our study include longitudinal follow-up; measurement of CKD-EPI eGFR, which has been shown to provide a reasonably accurate and unbiased estimate of GFR in this Indigenous Australian study population (25); and recruitment of participants with different levels of albuminuria and at different stages of CKD from several sites across Australia. The following limitations should be considered. First, although study participants were selected from over 20 sites across Australia, data for this analysis were available for only 69% of the original baseline study population, and included participants had significantly greater adiposity than those who were excluded, which may have influenced the distribution of eGFR, limiting the generalizability of these findings. Second, confirmation of a causative role for sTNFR1 in renal disease progression is limited by our observational study design. Even though we found that the association between sTNFR1 and eGFR decline remained despite excluding participants with a low CKD-EPI eGFR at baseline, a potential influence of renal function per se on sTNFR1 levels remains a possible confounder in our study, as we adjusted for eGFR, not measured GFR. A previous analysis of our study population showed that, compared with measured GFR, CKD-EPI eGFR had greater bias in people with diabetes compared with those without diabetes (32). Third, even though we adjusted for baseline eGFR and uACR and found that the association between sTNFR1 and eGFR decline remained despite excluding participants with a low CKD-EPI eGFR or macroalbuminuria at baseline, our smaller sample size and relatively short follow-up period may have limited our ability to adjust fully for the confounding influence of these covariates. Fourth, other novel risk factors not measured in our study, including markers of bone mineralization (33), oxidative stress, and a procoagulant state, may also be important mechanisms in the deterioration of kidney function by triggering inflammation (16,34,35). Fifth, current sTNFR1 assays possibly measure biologically inactive fragments of sTNFR. Finally, this analysis relied on a single measure of sTNFR1 and other covariates, and thus the impact on our results of transiently low or high values of sTNFR1, which may occur during subclinical inflammatory episodes, could not be determined.

Blockage of the renin-angiotensin system has a significant impact on reducing renal disease outcomes and mortality in individuals with diabetes (36). However, new therapeutic strategies are urgently needed to slow and prevent the progression of renal disease and the subsequent development of cardiovascular disease (37). The results of this study and others suggest that therapeutic regimes that target chronic inflammation, and specifically sTNFR1, may be useful in the management of diabetic kidney disease. Some evidence has shown that hydroxymethylglutaryl-CoA inhibitors (statins) may reduce biomarkers of chronic inflammation, specifically CRP, in patients who receive renal dialysis (38). Medicines approved to treat rheumatoid arthritis and that target interleukin-6 could have a place in the management of kidney disease progression (39), and an anti-inflammatory role may even exist for antidiabetes agents (1). Thus further research is now warranted from clinical trials specifically designed to investigate whether a reduction in chronic inflammatory markers such as sTNFR1 can lead to improved renal outcomes. Studies of the effects of monoclonal antibodies on atherothrombosis are under way, but any benefits from inflammatory therapies will need to be weighed against the potential harms from reducing defense mechanisms that address infection and injury (2).

In conclusion, our study showed that elevated serum concentration of sTNFR1 is associated with a greater decline in eGFR that seems to be independent of common clinical risk factors for kidney disease, including albuminuria, in Indigenous Australians with diabetes. Similar associations were not observed among

those without diabetes. While these findings suggest a role of the TNF system in renal disease progression in a population that experiences high rates of kidney disease and chronic inflammation, further research is warranted to explore whether the modulation of sTNFR1 in an interventional study prevents renal disease progression in these patients.

Acknowledgments. The authors gratefully acknowledge the support of the eGFR Study participants, study staff, and partner organizations. The authors thank Dr. Kevin Warr (Royal Perth Hospital, Perth, Australia) and Dr. William Majoni (Royal Darwin Hospital, Darwin, Australia) for facilitating participant recruitment and follow-up at the sites of their employing organization, and Loyla Leysley (Menzies School of Health Research, Darwin, Australia), Sian Graham (Menzies School of Health Research), Mary Ward (Menzies School of Health Research and Community Elder, Thursday Island, Australia), and Joseph Fitz (Menzies School of Health Research) for assisting with follow-up in their communities. The authors also thank Melbourne Pathology for providing technical support in the enzymatic creatinine analysis, Roche Diagnostics for supplying the enzymatic creatinine reagent kit for the baseline study, and EKD Diagnostics for their assistance in helping to source the sTNFR1 assay kits.

Funding. The eGFR Study was funded by the National Health and Medical Research Council (NHMRC; project grants 545202 and 1021460), with additional support from SVHA Inclusive Health Innovation Fund, Kidney Health Australia, NHMRC (program grant 631947), the Colonial Foundation, Diabetes Australia Research Trust, Rebecca L. Cooper Foundation, and SeaSwift Thursday Island. E.L.M.B. was supported by an NHMRC Training Research Fellowship (APP10 16612) and a National Heart Foundation of Australia post-doctoral fellowship (1012914). F.B. was supported by an NHMRC program grant (631947). J.T.H. was supported by an NHMRC fellowship (1092576) and Royal Australasian College of Physicians Jacquot Research Establishment Award. W.E.H. directs the NHMRC-funded Centre for Research Excellence in Chronic Kidney Disease (1079502). P.D.L. was supported by an NHMRC scholarship (1038721), a Royal Australasian College of Physicians Jacquot Research Establishment Award, and an NHMRC Early Career Fellowship (1120640). A.D.H.B. was supported by a Viertel Senior Medical Research Fellowship from the Sylvia and Charles Viertel Charitable Foundation. E.I.E. was supported by an NHMRC Early Career Fellowship (the Health Professional Research Fellowship, part time, 1054312), a Viertel Clinical Investigatorship, the Royal Australasian College of Physicians JDRF Research Establishment Fellowship, and project funding from the Sir Edward "Weary" Dunlop Medical Research Foundation. R.J.M. was supported by an Australian Diabetes Society-Servier Diabetes Research Fellowship and the Rebecca L. Cooper Foundation. L.J.M.-B. was supported by an NHMRC fellowship (605837) and an NHMRC practitioner fellowship (1078477).

The views expressed in this publication are those of the authors and do not reflect the views of the NHMRC. The funding bodies had no role in the study design; in the collection, analysis, or interpretation of data; in the writing of the manuscript; or in the decision to submit the manuscript for publication.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. E.L.M.B. drafted the manuscript and analyzed and interpreted the data. F.B. analyzed and interpreted the data and revised the manuscript. J.T.H. conceived and designed the study, collected and interpreted the data, and revised the manuscript. G.J., W.E.H., K.O., G.R.D.J., P.D.L., A.D.H.B., A.S., A.C., and R.J.M. conceived and designed the study, interpreted the data, and revised the manuscript. M.T. and E.I.E. interpreted the data and revised the manuscript. L.J.M.-B. conceived the work; led all aspects of the conduct of the study, including data collection; analyzed and interpreted the data; and drafted the manuscript. All authors approved the final version. E.L.M.B. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Prior Presentation. This study was presented in abstract form as "The Association Between Soluble Tumour Necrosis Factor Receptor 1 (sTNFR1) and the Progression of Kidney Disease in Indigenous Australians: The eGFR Follow-up Study" at the Australian and New Zealand Society of Nephrology 53rd Annual Scientific Meeting, Darwin, Australia, 4–6 September 2017.

References

1. Kothari V, Galdo JA, Mathews ST. Hypoglycemic agents and potential anti-inflammatory activity. J Inflamm Res 2016;9:27–38
2. Koenig W. High-sensitivity C-reactive protein and atherosclerotic disease: from improved risk prediction to risk-guided therapy. Int J Cardiol 2013;168:5126–5134
3. Diamond JR. Analogous pathobiologic mechanisms in glomerulosclerosis and atherosclerosis. Kidney Int Suppl 1991;31:S29–S34
4. Amdur RL, Feldman HI, Gupta J, et al.; CRIC Study Investigators. Inflammation and progression of CKD: the CRIC Study. Clin J Am Soc Nephrol 2016;11:1546–1556
5. Tonelli M, Sacks F, Pfeffer M, Jhangri GS, Curhan G; Cholesterol and Recurrent Events (CARE) Trial Investigators. Biomarkers of inflammation and progression of chronic kidney disease. Kidney Int 2005;68:237–245
6. Fernández-Real JM, Vendrell J, García I, Ricart W, Vallès M. Structural damage in diabetic nephropathy is associated with TNF-α system activity. Acta Diabetol 2012;49:301–305
7. Pavkov ME, Weil EJ, Fufaa GD, et al. Tumor necrosis factor receptors 1 and 2 are associated with early glomerular lesions in type 2 diabetes. Kidney Int 2016;89:226–234
8. Gohda T, Niewczas MA, Ficociello LH, et al. Circulating TNF receptors 1 and 2 predict stage 3 CKD in type 1 diabetes. J Am Soc Nephrol 2012;23:516–524
9. Skupien J, Warram JH, Niewczas MA, et al. Synergism between circulating tumor necrosis factor receptor 2 and HbA_{1c} in determining renal decline during 5-18 years of follow-up in patients with type 1 diabetes and proteinuria. Diabetes Care 2014;37:2601–2608
10. Forsblom C, Moran J, Harjutsalo V, et al.; FinnDiane Study Group. Added value of soluble tumor necrosis factor-α receptor 1 as a biomarker of ESRD risk in patients with type 1 diabetes. Diabetes Care 2014;37:2334–2342
11. Krolewski AS, Niewczas MA, Skupien J, et al. Early progressive renal decline precedes the onset of microalbuminuria and its progression to macroalbuminuria. Diabetes Care 2014;37:226–234
12. Niewczas MA, Gohda T, Skupien J, et al. Circulating TNF receptors 1 and 2 predict ESRD in type 2 diabetes. J Am Soc Nephrol 2012;23:507–515
13. Lee JE, Gohda T, Walker WH, et al. Risk of ESRD and all cause mortality in type 2 diabetes according to circulating levels of FGF-23 and TNFR1. PLoS One 2013;8:e58007
14. Saulnier PJ, Gand E, Ragot S, et al.; SURDIAGENE Study Group. Association of serum concentration of TNFR1 with all-cause mortality in patients with type 2 diabetes and chronic kidney disease: follow-up of the SURDIAGENE Cohort. Diabetes Care 2014;37:1425–1431
15. Pavkov ME, Nelson RG, Knowler WC, Cheng Y, Krolewski AS, Niewczas MA. Elevation of circulating TNF receptors 1 and 2 increases the risk of end-stage renal disease in American Indians with type 2 diabetes. Kidney Int 2015;87:812–819
16. Coca SG, Nadkarni GN, Huang Y, et al. Plasma biomarkers and kidney function decline in early and established diabetic kidney disease. J Am Soc Nephrol 2017;28:2786–2793
17. Shankar A, Sun L, Klein BE, et al. Markers of inflammation predict the long-term risk of developing chronic kidney disease: a population-based cohort study. Kidney Int 2011;80:1231–1238
18. Medenwald D, Girndt M, Loppnow H, et al. Inflammation and renal function after a four-year follow-up in subjects with unimpaired glomerular filtration rate: results from the observational, population-based CARLA cohort. PLoS One 2014;9:e108427
19. Carlsson AC, Nordquist L, Larsson TE, et al. Soluble tumor necrosis factor receptor 1 is associated with glomerular filtration rate progression and incidence of chronic kidney disease in two community-based cohorts of elderly individuals. Cardiorenal Med 2015;5:278–288
20. Liu G, Deng Y, Sun L, et al. Elevated plasma tumor necrosis factor-α receptor 2 and resistin are associated with increased incidence of kidney function decline in Chinese adults. Endocrine 2016;52:541–549
21. Schei J, Stefansson VT, Eriksen BO, et al. Association of TNF Receptor 2 and CRP with GFR decline in the general nondiabetic population. Clin J Am Soc Nephrol 2017;12:624–634
22. Australian Institute of Health and Welfare. *Chronic Kidney Disease in Aboriginal and Torres Strait Islander People 2011*. Cat. no. PHE 151. Canberra, AIHW, 2011
23. Hodge AM, Maple-Brown L, Cunningham J, et al. Abdominal obesity and other risk factors largely explain the high CRP in Indigenous Australians relative to the general population, but not gender differences: a cross-sectional study. BMC Public Health 2010;10:700
24. Maple-Brown LJ, Lawton PD, Hughes JT, et al. Study protocol–accurate assessment of kidney function in Indigenous Australians: aims and methods of the eGFR Study. BMC Public Health 2010;10:80
25. Maple-Brown LJ, Hughes JT, Lawton PD, et al. Accurate assessment of kidney function in

Indigenous Australians: the estimated GFR study. Am J Kidney Dis 2012;60:680–682
26. Maple-Brown LJ, Hughes JT, Ritte R, et al. Progression of kidney disease in Indigenous Australians: the eGFR Follow-up Study. Clin J Am Soc Nephrol 2016;11:993–1004
27. Hughes JT, Maple-Brown LJ, Thomas M, et al. Cross-sectional associations of albuminuria among Aboriginal and Torres Strait Islander adults: the eGFR Study. Nephrology (Carlton) 2018;23:37–45
28. Coresh J, Turin TC, Matsushita K, et al. Decline in estimated glomerular filtration rate and subsequent risk of end-stage renal disease and mortality. JAMA 2014;311:2518–2531
29. Rebholz CM, Grams ME, Matsushita K, Selvin E, Coresh J. Change in novel filtration markers and risk of ESRD. Am J Kidney Dis 2015;66:47–54
30. Glantz S, Slinker B. *Primer of Applied Regression and Analysis of Variance*. New York, McGraw-Hill, 1990
31. Hasegawa G, Nakano K, Sawada M, et al. Possible role of tumor necrosis factor and interleukin-1 in the development of diabetic nephropathy. Kidney Int 1991;40:1007–1012
32. Maple-Brown LJ, Ekinci EI, Hughes JT, et al.; investigators of the eGFR Study. Performance of formulas for estimating glomerular filtration rate in Indigenous Australians with and without type 2 diabetes: the eGFR Study. Diabet Med 2014;31:829–838
33. Agarwal R, Duffin KL, Laska DA, Voelker JR, Breyer MD, Mitchell PG. A prospective study of multiple protein biomarkers to predict progression in diabetic chronic kidney disease. Nephrol Dial Transplant 2014;29:2293–2302
34. Cachofeiro V, Goicochea M, de Vinuesa SG, Oubiña P, Lahera V, Luño J. Oxidative stress and inflammation, a link between chronic kidney disease and cardiovascular disease. Kidney Int Suppl 2008;74:S4–S9
35. Macisaac RJ, Ekinci EI, Jerums G. Markers of and risk factors for the development and progression of diabetic kidney disease. Am J Kidney Dis 2014;63(Suppl. 2):S39–S62
36. Wu HY, Huang JW, Lin HJ, et al. Comparative effectiveness of renin-angiotensin system blockers and other antihypertensive drugs in patients with diabetes: systematic review and bayesian network meta-analysis. BMJ 2013;347:f6008
37. Formentini I, Bobadilla M, Haefliger C, et al. Current drug development challenges in chronic kidney disease (CKD)–identification of individualized determinants of renal progression and premature cardiovascular disease (CVD). Nephrol Dial Transplant 2012;27(Suppl. 3):iii81–iii88
38. Deng J, Wu Q, Liao Y, Huo D, Yang Z. Effect of statins on chronic inflammation and nutrition status in renal dialysis patients: a systematic review and meta-analysis. Nephrology (Carlton) 2012;17:545–551
39. Elewa U, Sanchez-Niño MD, Martin-Cleary C, Fernandez-Fernandez B, Egido J, Ortiz A. Cardiovascular risk biomarkers in CKD: the inflammation link and the road less traveled. Int Urol Nephrol 2012;44:1731–1744