Association of Soluble TNFR-1 Concentrations with Long-Term Decline in Kidney Function: The Multi-Ethnic Study of Atherosclerosis

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ABSTRACT

Background TNF receptor-1 (TNFR-1), which plays a causative role in endothelial cell dysfunction and inflammation, is expressed on the cell surface in glomerular and peritubular capillary endothelium of the kidneys. Higher soluble TNF receptor-1 (sTNFR-1) concentrations are associated with kidney disease progression among persons with established diabetic kidney disease. However, no studies have assessed sTNFR-1's role in long-term kidney function changes in a multiethnic population without cardiovascular disease at baseline.

Methods We tested associations between baseline sTNFR-1 concentrations and 10-year decline in eGFR (incident ≥40% decline and annual proportional decline) among 2548 participants in the Multi-Ethnic Study of Atherosclerosis (MESA), a prospective cohort study. Serum creatinine concentrations were determined at enrollment and study years 3, 5, and 10.

Results Mean age of participants was 61 years old, 53% were women, and mean baseline eGFR was 79 ml/min per 1.73 m^2. Serum sTNFR-1 was inversely associated with baseline eGFR. Over median follow-up of 9.3 years, 110 participants developed ≥40% decline in eGFR; each SD higher concentration of sTNFR1 was associated with higher risk of 40% eGFR decline (adjusted hazard ratio, 1.43; 95% confidence interval [95% CI], 1.16 to 1.77; $P<0.001$). The highest sTNFR-1 tertile was associated with adjusted annualized decline in eGFR of 1.94% (95% CI, 1.79 to 2.09). Associations persisted across subgroups defined by demographics, hypertension, diabetes, and baseline CKD status.

Conclusions Elevated serum sTNFR-1 concentrations are associated with faster declines in eGFR over the course of a decade in a multiethnic population, independent of previously known risk factors for kidney disease progression.

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Endothelial dysfunction and inflammatory processes contribute to multiple disease pathways, including the development of hypertension, diabetes, atherosclerosis, and kidney dysfunction. TNF receptor-1 (TNFR-1) is a cell surface receptor expressed in the glomerular and peritubular capillary endothelium of the kidneys that plays a causative role in the development of endothelial cell dysfunction and inflammation.[1] Binding of circulating TNFα to its receptor, TNFR-1, leads to intracellular caspase activation, cellular apoptosis, immune activation, and eventual shedding of TNFR-1 into a soluble form in the serum.[2,3] Among persons with established diabetes, serum soluble TNF receptor-1 (sTNFR-1) concentrations are

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associated with early glomerular structural lesions[4] and kidney disease progression.[5,6] However, no studies have assessed the potential effect of sTNFR-1 on long-term changes in kidney function decline among a multiethnic population without known cardiovascular disease.

Serum sTNFR-1 concentrations are also associated with micro- and macrovascular dysfunction, including arterial stiffness,[7] recurrent vascular events,[8] and intracerebral hemorrhage.[9] Previously, renal artery calcium (RAC) has been strongly associated with subclinical atherosclerosis and cardiovascular disease.[10] However, studies have been more mixed on the association of RAC with kidney function.[11,12] Thus, we sought to determine whether RAC scores mediate the association between sTNFR-1 and kidney function decline.

We evaluated serum sTNFR-1 concentrations among 2548 participants in the Multi-Ethnic Study of Atherosclerosis (MESA), a community-based prospective study of people free of known cardiovascular disease.[13,14] We determined associations of sTNFR-1 with 10-year changes in kidney function. We also investigated atherosclerotic renal artery disease as one potential mechanism linking sTNFR-1 concentrations and kidney function decline *via* measurement of RAC.

Significance Statement

TNF receptor-1 (TNFR-1), which plays a role in the development of endothelial cell dysfunction and inflammation, is expressed in the glomerular and peritubular capillary endothelium of the kidneys. Studies previously showed that serum levels of soluble TNF receptor-1 (sTNFR-1) are associated with kidney disease progression among persons with established kidney disease. In this study of a multiethnic population without cardiovascular disease at enrollment, elevated baseline sTNFR-1 concentrations were strongly associated with the development of a ≥40% decline in eGFR over a decade. This association persisted after adjustment for kidney disease–associated covariates and other inflammatory biomarkers, suggesting that a high concentration of sTNFR-1, independent of previously known risk factors for kidney disease progression, predicts kidney function decline in a multiethnic population with few comorbidities.

METHODS

Study Population

The MESA is a multiethnic prospective cohort study designed to understand subclinical cardiovascular disease and its progression.[15,16] The MESA included a sample of the general population. The study recruited 6814 men and women who were between 45 and 84 years old, were free of clinically apparent cardiovascular disease, and self-identified as white, black, Hispanic, or Chinese American. Participants were recruited between July 2000 and August 2002 from six communities: Baltimore and Baltimore County, Maryland; Chicago, Illinois; Forsyth County, North Carolina; Los Angeles County, California; northern Manhattan and the Bronx, New York; and St. Paul, Minnesota. Follow-up visits were conducted in 2002–2004 (examination 2), 2004–2005 (examination 3), 2005–2007 (examination 4), and 2010–2012 (examination 5). Serum creatinine concentrations were measured at baseline and then again at visits 3–5. The institutional review boards at all participating centers approved the study, and all participants gave informed consent.

The MESA investigators measured serum sTNFR-1 concentrations among a race/ethnicity-balanced group of 2871 participants at baseline through the MESA Family Ancillary Study. We excluded four participants without a baseline serum creatinine measurement and 319 participants without follow-up creatinine measurements, leaving a final analytic sample of 2548.

Exposures

Participants fasted and avoided heavy exercise for 12 hours before venipuncture, and they were asked to avoid smoking the morning of their examination. All blood samples were processed according to a standard protocol and stored at −80°C until analyzed. Laboratory assay for sTNFR-1 was done at the University of Vermont (Burlington, VT).[17] Serum concentrations of sTNFR-1 were measured using an ultrasensitive ELISA assay (Quantikine Human sTNFR-I Immunoassay; R&D Systems, Minneapolis, MN). Analytical coefficients of variation were 5%. All measurements were made in duplicate, in random order, and in a blinded fashion.[18] Samples were collected between 2000 and 2002, and measurements were completed in 2008.

Outcomes

Serum creatinine concentrations in the MESA were calibrated to isotope dilution mass spectroscopy standards. GFR was estimated at each study visit using the 2009 Chronic Kidney Disease Epidemiology Collaboration equation on the basis of serum creatinine concentrations, age, race, and sex.[19] We recognize that cystatin C may be more precise than serum creatinine. However, due to difficulties with calibration of cystatin C values, particularly in the examination 5 visit, this measurement was not suitable for longitudinal analyses. We selected a primary outcome of a ≥40% decline in eGFR over follow-up, because this outcome is clinically and biologically significant, avoids the ambiguous interpretation of small differences in slopes of GFR decline, and is proposed by the National Kidney Foundation and the US Food and Drug Administration as a broadly accepted measure for kidney function decline.[20] We evaluated the continuous relative decline in GFR as a secondary outcome. Our inclusion criteria required participants to have a baseline eGFR and at least one follow-up measurement. Of the 2548 participants in our analytic population, 2469 (97%) returned for examinations 2 and 3, 2335 (92%) returned for examination 4, and 1862 (73%) returned for examination 5.

RAC

RAC measurements were completed among a random subsample of MESA participants who underwent electron beam or electrocardiogram-triggered computed tomography scanning

at visit 2 or 3.[12] Images were read centrally. Calcified foci were defined by three contiguous pixels with a density >130 Hounsfield units, and lesions were scored using the Agatston method. For this study, RAC measurements were available in a subset of 567 participants.

Other Study Data

MESA personnel ascertained medical and personal histories using standardized questionnaires and assessed medication use *via* the inventory method. MESA investigators defined diabetes by the use of a diabetes medication or a fasting blood glucose level ≥126 mg/dl. Urine was collected for albumin and creatinine, which were used to calculate the urinary albumin-to-creatinine ratio. BP was assessed using multiple measurements completed by trained staff. Hypertension was defined as self-reported treatment for hypertension, systolic BP ≥140 mm Hg, or diastolic BP ≥90 mm Hg.[21]

Statistical Analyses

We summarized baseline participant characteristics across tertiles of baseline serum sTNFR-1 concentrations with mean and SD for continuous variables and number and percentage for categorical variables. We graphically examined the univariate distribution of sTNFR, and we evaluated the cross-sectional association of sTNFR-1 with eGFR at baseline *via* linear regression. For the primary analysis, we used Cox regression to evaluate the association between baseline sTNFR-1 and incident ≥40% decline in eGFR over a median (interquartile range) of 9.3 (interquartile range, 8.5–9.7) years of follow-up in a series of nested models, which controlled for potential confounding factors: age, sex, race/ethnicity, education, site of enrollment, body mass index, hypertension, systolic BP, diabetes, urine albumin-to-creatinine ratio, baseline eGFR, IL-6, and high-sensitivity C-reactive protein (hsCRP) concentrations. We tested the proportional hazards assumption of the

Table 1. Baseline characteristics of cohort by tertiles of serum soluble TNF receptor-1 concentrations

Characteristic	Overall, *n*=2548	Tertile 1, *n*=851	Tertile 2, *n*=849	Tertile 3, *n*=848
Range sTNFR-1, pg/ml		<1160	1161–1420	>1420
Age, yr	61.0 (10.0)	57.0 (8.6)	60.4 (9.3)	65.7 (10.0)
Men, %	1192 (47)	353 (41)	414 (49)	425 (50)
Race/ethnicity, %				
White	666 (26)	190 (22)	217 (26)	259 (30)
Black	621 (24)	231 (27)	212 (25)	178 (21)
Chinese	629 (25)	266 (31)	191 (22)	172 (20)
Hispanic	635 (25)	165 (19)	229 (27)	241 (28)
BMI, kg/m^2	27.9 (5.5)	26.3 (4.7)	28.1 (5.3)	29.3 (5.9)
Education, %				
Less than high school	517 (20)	145 (17)	154 (18)	218 (26)
High school	461 (18)	140 (16)	169 (20)	152 (18)
College	1566 (62)	565 (67)	524 (62)	477 (56)
Family income <$25,000, %	855 (34)	230 (27)	280 (33)	345 (41)
Smoking status,%				
Never	1389 (54)	494 (58)	468 (55)	427 (50)
Former	816 (32)	248 (29)	260 (31)	308 (36)
Current	339 (13)	108 (13)	119 (14)	112 (13)
Diabetes status, %				
Normal	1865 (73)	662 (78)	632 (74)	571 (67)
Impaired fasting glucose	369 (14)	108 (13)	130 (15)	131 (15)
Untreated or treated diabetes	314 (13)	81 (9)	87 (10)	146 (17)
Baseline eGFR (CKD-EPI), ml/min per 1.73 m^2	79 (16)	87 (13)	80 (13)	70 (16)
Baseline eGFR (CKD-EPI) <60 ml/min per 1.73 m^2, %	289 (11)	10 (1)	40 (5)	239 (28)
Hypertension, %	1062 (42)	273 (32)	323 (38)	466 (55)
Medications, %				
Statins	354 (14)	94 (11)	113 (13)	147 (17)
RAAS inhibitors	421 (17)	86 (10)	127 (15)	208 (24)
Aspirin	421 (17)	92 (11)	154 (18)	175 (21)
NSAIDs	380 (15)	112 (13)	135 (16)	133 (16)
Inflammatory biomarkers				
hsCRP, median, mg/L	1.8 (0.8–4.0)	1.3 (0.6–3.0)	1.7 (0.8–4.0)	2.4 (1.1–5.5)
IL-6, median, pg/ml	1.1 (0.7–1.8)	0.9 (0.6–1.3)	1.1 (0.7–1.7)	1.5 (0.9–2.2)

Entries are mean (SD), *N* (%), or median (interquartile range) as appropriate. sTNFR-1, soluble TNF receptor-1; BMI, body mass index; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; RAAS, renin-angiotensin-aldosterone system; NSAID, nonsteroidal anti-inflammatory drug; hsCRP, high-sensitivity C-reactive protein; IL-6, interleukin-6.

Cox regression and found no violations; inspection of the Schoenfeld residuals likewise did not raise concerns.[22] We also estimated the annualized proportional decline in eGFR across strata of baseline sTNFR-1 concentrations using a linear mixed model approach with random intercepts to account for the within-person correlation occurring with repeated measurements; diagnostic inspection for the distribution of random effect variances revealed no gross departures from normality. Change in eGFR was computed on the basis of the slope across all visits. Finally, we evaluated the association of serum sTNFR-1 concentrations and RAC scores >0 *via* logistic regression, controlling for potential confounders.

We also performed subgroup analyses to explore whether the associations between serum sTNFR-1 concentrations and ≥40% incident eGFR decline were different between participants on the basis of age, sex, race/ethnicity, diabetes, hypertension, and baseline CKD status defined as an eGFR<60 ml/min per 1.73 m^2. Approximately 3% or fewer of analyzed participants were missing information on covariates, such as education and urine albumin-to-creatinine ratio; these subjects' values were multiply imputed using chained equations,[23] which were then combined using Rubin rules to account for the variability in the imputation procedure.[24] For all analyses, a two-tailed *P* value of <0.05 was taken as evidence of statistical significance. All statistical analyses were performed in R 3.4.0 (R Core Team 2015).

RESULTS

Demographics/Participant Characteristics

Among the 2548 participants in this ancillary study, the mean (SD) age was 61 (10) years old, 53% were women, and equal proportions were white, black, Chinese, or Hispanic (approximately 25%). The mean (SD) baseline eGFR was 79 (16) ml/min per 1.73 m^2, and 11% had an eGFR<60 ml/min per 1.73 m^2. The mean (SD) sTNFR-1 concentration was 1356 (406) pg/ml, and measurements were similar across different race/ethnic groups (Supplemental Figures 1 and 2). Participants in the highest sTNFR-1 tertile were more likely to be older, be men, be white, have hypertension, and be treated for diabetes, and they were far more likely to have a baseline eGFR <60 ml/min per 1.73 m^2 (Table 1).

Associations between sTNFR-1 and Baseline eGFR

Higher serum sTNFR-1 concentrations were associated with lower baseline eGFR (Table 2). After adjustment for baseline demographics, comorbidities, and urine albumin-to-creatinine ratio, participants in the highest tertile of sTNFR-1 had an average baseline eGFR that was 12.1 ml/min per 1.73 m^2 lower than that in the lowest tertile (95% confidence interval [95% CI], 10.8 to 13.5 lower). To account for the association of serum sTNFR-1 and baseline

Table 2. Cross-sectional association between serum soluble TNF receptor-1 tertiles and baseline eGFR

Serum sTNFR-1	Unadjusted		Baseline Demographics Adjusted[a]		Multivariable Adjusted[b]		Fully Adjusted[c]	
	Difference (95% CI), ml/min per 1.73 m^2	*P* Value	Difference (95% CI), ml/min per 1.73 m^2	*P* Value	Difference (95% CI), ml/min per 1.73 m^2	*P* Value	Difference (95% CI), ml/min per 1.73 m^2	*P* Value
Tertile 1	0 (Reference)	<0.001	0 (Reference)	<0.001	0 (Reference)	<0.001	0 (Reference)	<0.001
Tertile 2	−6.4 (−7.6 to −5.2)		−4.3 (−5.4 to −3.2)		−4.4 (−5.6 to −3.3)		−4.7 (−5.9 to −3.6)	
Tertile 3	−17.0 (−18.4 to −15.6)		−11.4 (−12.7 to −10.0)		−11.5 (−12.9 to −10.2)		−12.1 (−13.5 to −10.8)	

sTNFR-1, soluble TNF receptor-1; 95% CI, 95% confidence interval.
[a]Baseline demographics adjusted: age, age squared, sex, race/ethnicity, and site.
[b]Multivariable adjusted: baseline demographic covariates, education, body mass index, diabetes, hypertension, systolic BP, and urine albumin-to-creatinine ratio.
[c]Fully adjusted: multivariable covariates, IL-6, and high-sensitivity C-reactive protein.

kidney function, all subsequent longitudinal analyses adjusted for baseline eGFR and baseline albuminuria.

Associations between sTNFR-1 and Longitudinal Kidney Function Decline

Median follow-up was 9.3 years (interquartile range, 8.5–9.7 years); 72% of participants completed all four eGFR measurements, and 92% completed at least three. The primary outcome of a ≥40% decline in eGFR occurred in 110 participants. Higher serum sTNFR-1 concentrations were associated with a greater risk of a ≥40% decline in eGFR (multivariable adjusted hazard ratio, 1.51; 95% CI, 1.24 to 1.85 per SD increment in sTNFR-1 concentrations; $P<0.001$) (Table 3). The association between sTNFR-1 and ≥40% decline in eGFR seemed linear on the basis of multivariable splines (Figure 1). Participants in the highest sTNFR-1 tertile were approximately 94% more likely to develop the primary outcome than participants in the lowest tertile. Serum sTNFR-1 concentrations were also strongly associated with annualized proportional eGFR decline. In the multivariable adjusted models, the annualized proportional decline in eGFR for tertile 3 was 2.00% (95% CI, 1.85 to 2.15) compared with an annualized proportional decline in eGFR for tertile 1 of 1.45% (95% CI, 1.31 to 1.59; *P* value for interaction <0.001) (Table 4).

The associations of sTNFR-1 concentrations with the primary outcome were statistically similar across strata defined by age, sex, race/ethnicity, diabetes, or hypertension (each *P* value for interaction >0.10) (Figure 2). Higher sTNFR-1 concentrations were associated with greater incident ≥40% decline in eGFR among participants with and without CKD on study enrollment (Supplement Table 1).

Serum sTNFR-1 Associations Adjusted for Inflammatory Biomarkers

We next sought to determine if the associations between sTNFR-1 and kidney outcomes were independent of other commonly measured circulating biomarkers that also reflect inflammation. Serum sTNFR-1 concentrations were minimally correlated with circulating concentrations of IL-6 ($r^2=0.35$) and hsCRP ($r^2=0.23$) (Supplement Table 2). In fully adjusted models, higher serum sTNFR-1 concentrations continued to be associated with a greater risk of a ≥40% decline in eGFR (adjusted hazard ratio, 1.43; 95% CI, 1.16 to 1.77 per SD increment in sTNFR-1 concentrations; $P<0.001$) (Table 3). In addition, the highest tertile of sTNR-1 continued to be associated with greater annualized proportional eGFR decline compared with the lowest tertile (*P* value for interaction <0.001) (Table 4). Finally, we tested whether sTNFR-1 concentrations were associated with kidney outcomes independent of markers of endothelial function, such as E-selectin and intercellular adhesion molecule 1. Because these markers were only measured in a minority of patients ($n=890$), we directly compared E-selectin and intercellular adhesion molecule 1 with sTNFR-1. After inclusion of all three markers, only sTNFR-1 concentrations were significantly associated with kidney disease progression (Supplement Tables 3 and 4).

Associations between sTNFR-1 and RAC

In the subset of 567 participants who had available RAC measurements, higher TNFR-1 concentrations were not associated with the presence of ostial or intrarenal calcium after adjustment (Table 5). This lack of association was seen in multivariable and fully adjusted models.

DISCUSSION

In a multiethnic cohort of individuals without cardiovascular disease, we found that higher serum sTNFR-1 concentrations were associated with increased risk of kidney function decline over a median follow-up period of 9.3 years. Our findings were consistent when decline in kidney function was defined using either incident ≥40% decline in eGFR or an annualized proportional decline in eGFR. These associations remained statistically significant even after adjustment for several confounding variables, including demographics, comorbidities, baseline eGFR, and albuminuria. In addition, sTNFR-1

Table 3. Association of serum soluble TNF receptor-1 concentration with incident 40% eGFR decline

Serum sTNFR-1	*N* at Risk	*N* Events	Unadjusted: Incident Rate per 1000 person-yr	Baseline Demographic Adjusted[a]		Multivariable Adjusted[b]		Fully Adjusted[c]	
				HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Tertile 1	851	19	2.6	1.0 (Reference)	<0.001	1.0 (Reference)	0.05	1.0 (Reference)	0.14
Tertile 2	849	24	3.3	1.11 (0.60 to 2.04)		1.14 (0.61 to 2.14)		1.03 (0.54 to 1.94)	
Tertile 3	848	67	10.1	2.66 (1.54 to 4.57)		1.94 (1.05 to 3.57)		1.64 (0.88 to 3.06)	
Per SD of sTNFR-1 (406 pg/ml)				1.70 (1.53 to 1.89)	<0.001	1.51 (1.24 to 1.85)	<0.001	1.43 (1.16 to 1.77)	<0.001

sTNFR-1, soluble TNF receptor-1; HR, hazard ratio; 95% CI, 95% confidence interval.
[a]Baseline demographics adjusted: age, age squared, sex, race/ethnicity, and site.
[b]Multivariable adjusted: baseline demographic covariates, education, body mass index, diabetes, hypertension, systolic BP, urine albumin-to-creatinine ratio, baseline eGFR, and baseline eGFR squared.
[c]Fully adjusted: multivariable covariates, IL-6, and high-sensitivity C-reactive protein.

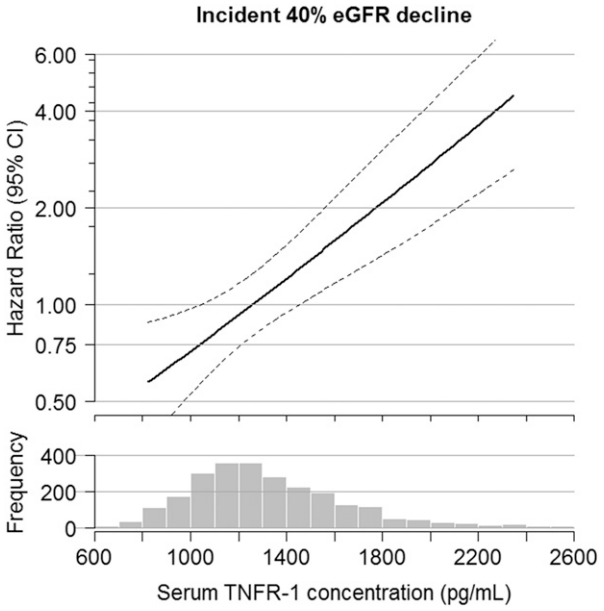

Figure 1. The adjusted association of serum soluble TNF receptor-1 (sTNFR-1) concentrations with ≥40% eGFR decline was linear. The smooth spline estimates the hazard ratio of ≥40% eGFR decline among Multi-Ethnic Study of Atherosclerosis participants according to baseline serum sTNFR-1 concentrations. Analyses are adjusted for age, age squared, and sex. Dotted lines represent 95% confidence intervals (95% CIs). Below the spline is the histogram of the distribution of sTNFR-1 to indicate the range of the data. TNFR-1, TNF receptor-1.

was a predictor of kidney prognosis independent of available measures of inflammation, such as hsCRP and IL-6. Finally, the association of sTNFR-1 with kidney function decline was similar across multiple *a priori* subgroups, including diabetes, CKD, and hypertension. Thus, a high concentration of circulating sTNFR-1 is a strong predictor for kidney function decline that is independent of previously known risk factors for kidney disease progression.

sTNFR-1 is the circulating version of the membrane-bound receptor, which is essential for TNFα signaling *via* NF-κB, a signaling cascade that results in both inflammation and endothelial dysfunction.[25] Prior studies have shown that sTNFR-1 concentrations are associated with AKI in critically ill populations, such as patients with acute respiratory distress syndrome[26] and patients with septic shock.[27] In patients with diabetes, elevated sTNFR-1 concentrations have been associated with CKD progression and development of ESRD.[6,28] However, it is unknown whether sTNFR-1 concentrations are associated with kidney function decline in a population without cardiovascular disease and low prevalence of diabetes. In this context, this study leverages the MESA's longitudinal follow-up to suggest that serum sTNFR-1 concentrations may be important before the development of kidney decline, regardless of baseline kidney function. These findings are consistent with animal studies[29,30] and provide biologic plausibility that markers of endothelial dysfunction and inflammation are linked to the development of kidney function decline and CKD.

The exact mechanism by which higher sTNFR-1 concentrations could lead to kidney function decline is not entirely clear. Previous literature has suggested that higher sTNFR-1 concentrations are associated with macrovascular disease.[31] Although RAC scans were available among only a subset of participants in our study, the robust absence of association with sTNFR-1 suggests that macrovascular atherosclerotic disease is potentially unlikely to be a major mechanism to explain the greater decline in kidney function over time. It is possible that elevated concentrations of sTNFR-1 contribute directly to microvascular kidney injury and progressive kidney function decline.[1] Interestingly, previously studied markers of inflammation in the MESA were minimally correlated with sTNFR-1 concentrations, suggesting that sTNFR-1 may represent a unique biologic pathway leading to kidney function decline.

To our knowledge, this is the first study to determine the longitudinal association of serum sTNFR-1 concentrations with kidney function decline in a multiethnic cardiovascular-free population. One previous longitudinal study found that serum sTNFR-2 concentrations were associated with kidney function decline.[32] However, this study was completed in a predominantly white population (98% white), and analyses were not adjusted for baseline kidney function or baseline

Table 4. Association of baseline serum soluble TNF receptor-1 concentration with annualized proportional eGFR decline

Serum sTNFR-1	Unadjusted		Baseline Demographic Adjusted[a]		Multivariable Adjusted[b]		Fully Adjusted[c]	
	Annualized Proportional Decline (95% CI), %	*P* Value[d]	Annualized Proportional Decline (95% CI), %	*P* Value[d]	Annualized Proportional Decline (95% CI), %	*P* Value[d]	Annualized Proportional Decline (95% CI), %	*P* Value[d]
Tertile 1	1.32 (1.21 to 1.44)	<0.001	1.45 (1.31 to 1.59)	<0.001	1.45 (1.31 to 1.59)	<0.001	1.47 (1.33 to 1.62)	<0.001
Tertile 2	1.52 (1.40 to 1.64)		1.56 (1.43 to 1.69)		1.59 (1.45 to 1.72)		1.58 (1.44 to 1.71)	
Tertile 3	2.10 (1.98 to 2.23)		2.05 (1.90 to 2.20)		2.00 (1.85 to 2.15)		1.94 (1.79 to 2.09)	

sTNFR-1, soluble TNF receptor-1; 95% CI, 95% confidence interval.
[a]Baseline demographics adjusted: age, age squared, sex, race/ethnicity, and site.
[b]Multivariable adjusted: baseline demographic covariates, education, body mass index, diabetes, hypertension, systolic BP, urine albumin-to-creatinine ratio, baseline eGFR, and baseline eGFR squared.
[c]Fully adjusted: multivariable covariates, IL-6, and high-sensitivity C-reactive protein.
[d]*P* value for interaction.

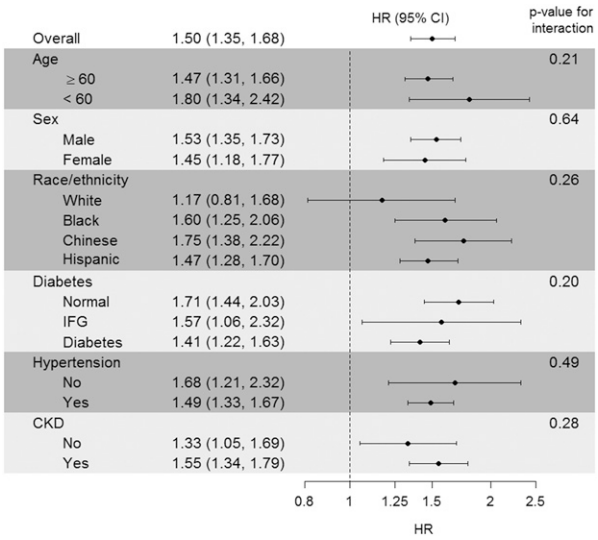

Figure 2. Forest plot demonstrates consistent associations of serum soluble TNFR receptor-1 (sTNFR-1) concentrations with ≥40% eGFR decline (estimates are per SD of sTNFR-1). Hazard ratio (HR) estimates are adjusted for age, age squared, sex, race/ethnicity, site, education, body mass index, diabetes, and hypertension. 95% CI, 95% confidence interval; IFG, impaired fasting glucose.

albuminuria. Thus, our findings extend the strong association of serum sTNFR-1 and sTNFR-2 concentrations with kidney progression in participants with established kidney disease[6] and now show the role of sTNFR-1 and kidney function decline in a multiethnic population.

Some limitations of this study deserve mention. First, serum sTNFR-1 concentrations were only measured at study baseline. Despite this fact, we showed that a single measurement of sTNFR-1 could identify the risk of kidney function decline, independent of classic risk factors. Second, we did not have measurements on sTNFR-2, another circulating TNFR that binds TNFα. However, multiple studies have shown high correlation ($r^2 \geq 0.90$) between sTNFR-1 and sTNFR-2, and thus, additional measurement of sTNFR-2 is unlikely to significantly change our findings.[6,33] Third, we only evaluated serum sTNFR-1 concentrations and did not evaluate TNFα. However, previous studies did not find an association between TNFα and kidney disease progression.[6] Fourth, it is unknown if sTNFR-1 is partly filtered by the kidney and if elevated levels may be a marker of decreased renal filtration. To account for this, we adjusted all longitudinal analyses for baseline eGFR and baseline albuminuria; our longitudinal associations suggest that there is a direct association leading from sTNFR1 to progressive eGFR loss.

Our study has several strengths. First, the MESA is a large multiethnic study with over 2500 participants with sTNFR-1 measured in a reference laboratory. Second, the MESA had validated measures of kidney function, including eGFR and albuminuria. Third, individuals within the MESA were free of cardiovascular disease and had a low prevalence of CKD or diabetes. This allowed study of associations between sTNFR-1 and kidney function decline in a general sample of the population with minimal comorbidities. Fourth, all longitudinal analyses of kidney function decline were adjusted for measures of baseline eGFR, albuminuria, and circulating markers of inflammation. Fifth, RAC scores were available on a random subset of participants to begin to understand the mechanism of sTNFR-1 with kidney function decline.

Table 5. Associations between serum soluble TNF receptor-1 concentrations and renal artery calcium greater than zero

Renal Artery Calcium	*N* at Risk	*N* Events	Unadjusted		Multivariable Adjusted[a]		Fully Adjusted[b]	
			OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Ostiarenal artery calcium >0								
Tertile 1	179	26	1.0 (Reference)	0.05	1.0 (Reference)	0.87	1.0 (Reference)	0.95
Tertile 2	186	34	1.02 (0.95 to 1.10)		1.00 (0.93 to 1.09)		1.00 (0.92 to 1.08)	
Tertile 3	215	74	1.09 (1.02 to 1.18)		1.02 (0.94 to 1.12)		1.01 (0.93 to 1.10)	
Per SD of sTNFR-1 (406 pg/ml)			1.05 (1.02 to 1.09)	0.004	1.03 (0.98 to 1.08)	0.29	1.02 (0.97 to 1.07)	0.42
Intrarenal artery calcium >0								
Tertile 1	202	21	1.0 (Reference)	0.08	1.0 (Reference)	0.83	1.0 (Reference)	0.95
Tertile 2	223	24	1.01 (0.96 to 1.07)		1.00 (0.95 to 1.06)		0.99 (0.94 to 1.05)	
Tertile 3	239	49	1.07 (1.01 to 1.13)		1.02 (0.96 to 1.08)		1.00 (0.94 to 1.06)	
Per SD of sTNFR-1 (406 pg/ml)			1.04 (1.01 to 1.07)	0.003	1.02 (0.99 to 1.06)	0.25	1.01 (0.98 to 1.05)	0.50
Total renal artery calcium >0								
Tertile 1	175	37	1.0 (Reference)	0.04	1.0 (Reference)	0.85	1.0 (Reference)	0.93
Tertile 2	184	40	1.02 (0.95 to 1.10)		1.00 (0.92 to 1.09)		0.99 (0.91 to 1.07)	
Tertile 3	208	80	1.10 (1.02 to 1.19)		1.02 (0.93 to 1.12)		1.00 (0.92 to 1.10)	
Per SD of sTNFR-1 (406 pg/ml)			1.06 (1.02 to 1.10)	0.002	1.03 (0.98 to 1.08)	0.25	1.02 (0.97 to 1.07)	0.42

OR, odds ratio; 95% CI, 95% confidence interval; sTNFR-1, soluble TNF receptor-1.

[a]Multivariable adjusted: age, age squared, sex, race/ethnicity, site, education, body mass index, diabetes, hypertension, systolic BP, urine albumin-to-creatinine ratio, baseline eGFR, and baseline eGFR squared.

[b]Fully adjusted: age, age squared, sex, race/ethnicity, site, education, body mass index, diabetes, hypertension, systolic BP, urine albumin-to-creatinine ratio, baseline eGFR, baseline eGFR squared, IL-6, and high-sensitivity C-reactive protein.

In conclusion, elevated serum sTNFR-1 concentrations are associated with increased risk of kidney function decline in a multiethnic population, independent of other known markers of inflammation, such as hsCRP and IL-6. Interestingly, sTNFR-1 concentrations were not associated with RAC, potentially suggesting that sTNFR-1 influences kidney outcomes irrespective of macrovascular renal artery disease. Further studies are warranted to evaluate the mechanistic role of sTNFR-1 and subsequent kidney function decline.

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DISCLOSURES

None.

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