

## Effect of CD40 and sCD40L on Renal Function and Survival in Patients With Renal Artery Stenosis

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**Abstract**—Activation of the CD40 receptor on the proximal tubular epithelium of the kidney results in fibrosis and inflammation in experimental models of kidney injury. Soluble CD40 ligand is released by activated platelets. The role of CD40-soluble CD40 ligand in patients with ischemic renal disease is unknown. Plasma levels of CD40 and soluble CD40 ligand were measured by enzyme-linked immunosorbent assay in a single center cohort of 60 patients with renal artery stenosis recruited from Salford Royal Hospital, Manchester, United Kingdom. A natural log transformation of CD40 and soluble CD40 ligand was performed to normalize the data. Estimated glomerular filtration rate was used as the primary indicator of renal function. By univariate analysis, low baseline levels of circulating CD40 ( $R^2=0.06$ ;  $P<0.05$ ) and baseline creatinine ( $R^2=0.08$ ;  $P=0.022$ ) were associated with loss of kidney function at 1-year follow-up, whereas soluble CD40 ligand was not ( $R^2=0.02$ ;  $P=ns$ ). In a multiple linear regression model, CD40 ( $P<0.02$ ) and baseline creatinine ( $P<0.01$ ) continued to be significantly associated with a decline in renal function (model  $R^2=0.17$ ;  $P<0.005$ ). Baseline CD40 levels were somewhat lower in patients who died during follow-up (survivors,  $7.3\pm 0.9$  pg/mL,  $n=48$  versus nonsurvivors,  $6.7\pm 1.0$  pg/mL,  $n=12$ ;  $P=0.06$ ). The CD40/soluble CD40 ligand signaling cascade may be a novel mechanism contributing to the development and progression of renal injury in patients with atherosclerotic renal artery stenosis. (*Hypertension*. 2013;61:894–900.)

**Key Words:** CD40 ■ renal artery stenosis ■ renal artery stenting ■ renal function ■ soluble CD40 ligand

There is considerable interest in the interaction of atherosclerosis and kidney injury. In some circumstances, a mediator of renal fibrosis and inflammation may be activation of the CD40 receptor on the renal proximal tubular epithelium. CD40 is a membrane glycoprotein that belongs to the tumor necrosis factor (TNF) receptor superfamily and is expressed on multiple cell lines, including B lymphocytes, macrophages and monocytes, dendritic cells, and endothelial cells.<sup>1</sup> The primary activator of CD40 is CD40 ligand that can be expressed and secreted in a soluble form (sCD40L) by activated platelets and is elevated in atherosclerosis.<sup>2</sup> CD40 in the kidney is upregulated after renal injury,<sup>3</sup> and activation of the receptor results in infiltration of inflammatory cells into the interstitium of the kidney through monocyte chemoattractant protein-1 (MCP-1) and intercellular adhesion molecule-1 (ICAM-1) expression<sup>4</sup> and increases plasminogen activator inhibitor-1 (PAI-1) and interstitial fibrosis.<sup>5–7</sup> Angiotensin II, which is increased during renal ischemia, increases transforming growth factor- $\beta$ , which in turn increases expression of CD40.<sup>7</sup> Finally, CD40 activation increases antigen-specific recognition and killing of tubular epithelial cells by cytotoxic CD8+ T cells.<sup>7</sup> Inhibition of CD40 significantly decreased the severity of renal injury in experimental chronic proteinuric renal disease.<sup>8</sup>

Although the role of CD40–sCD40L in cognate immunity is well established, there is also evidence that innate immunity, specifically macrophage activation, may play a role in renal injury.<sup>9</sup> Interestingly, in chronic kidney disease, circulating CD40 levels are elevated<sup>10,11</sup> and are associated with impaired immunity, presumably by binding circulating sCD40L and preventing its interaction with tissue-bound CD40.<sup>11</sup> Soluble CD40L levels do not seem to be elevated in end-stage renal disease, per se; however, the levels are elevated in end-stage renal disease patients with coronary artery disease or those who have atherothrombotic events.<sup>12,13</sup>

The interplay between circulating levels of CD40, sCD40L, and loss of kidney function over time is not clear. In a cohort of type 1 diabetics, sCD40L was elevated in patients who developed nephropathy but was not predictive of mortality, coronary vascular disease events, or later loss of kidney function.<sup>14</sup> It is conceivable that high levels of circulating CD40 can prevent sCD40L-dependent renal injury in chronic kidney disease. At this point, the role of CD40–sCD40L in patients with ischemic renal disease is unknown. In the current study, we sought to determine the relationship between CD40 and CD40L and progression

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of kidney disease in patients with known atherosclerotic renovascular disease.

## Methods

The study was conducted after approval from the institutional review board at the University of Toledo. The plasma samples and phenotypic data were obtained in collaboration with the department of vascular research at Salford Royal Hospital, Greater Manchester, United Kingdom, as indicated below.

### Patient Recruitment

Between 2007 and 2009, patients with radiologically determined (magnetic resonance or computed tomography angiography) atherosclerotic renovascular disease at Salford Royal Hospital (catchment population for renal disease 1.55 million) were approached for entry into a prospective study, which entailed assessment of phenotypic characteristics, medication usage, and previous revascularization status (either angioplasty with stenting or no revascularization). Patients provided full informed consent, and the study was approved by the local ethics committee (regional ethics committee reference number 07/Q1410/33). Patients were eligible for the study if they had any degree of atherosclerotic renovascular disease determined by radiology; the only exclusion criterion was for those patients unable to give informed consent. Patients were followed up via routine hospital clinic visits until either death or December 1, 2010. In the current study, only those 60 patients who provided an evaluable baseline plasma sample were included in this analysis.

### Blood Pressure

All blood pressure measurements were made by trained staff in accordance with trust protocol. An automated sphygmomanometer with an appropriately sized cuff was used, with all measurements made after at least 5 minutes of seated rest. Patients were requested not to consume caffeine, alcohol, or undertake vigorous exercise before clinic visits. A minimum of 2 readings were obtained, with an average of these results recorded.

### Blood Collection

Blood samples were obtained at the time of recruitment into the study, and at annual intervals for analysis of plasma biomarkers and creatinine. Peripheral venous blood was collected in lithium heparin plasma separator tubes, spun at 1000g for 15 minutes, and frozen at  $-75^{\circ}\text{C}$  until analysis. Creatinine measurements were performed using a Roche diagnostics analyzer (Integra 700) using an uncompensated modified Jaffe reaction. Estimated glomerular filtration rate (GFR), calculated from the modified Modification in Diet and Renal Disease equation, was used as the primary measure of renal function.<sup>15</sup>

### Measurement of CD40 and sCD40L

Plasma levels of CD40 and sCD40L were measured by enzyme-linked immunosorbent assay (Abcam Inc, Cambridge, MA [CD40]; and R&D Systems, Minneapolis, MN [sCD40L]) at the University of Toledo according to the manufacturer recommendations.<sup>16</sup> The enzyme-linked immunosorbent assay kits had intra-assay and inter-assay coefficients  $<10\%$  and  $<12\%$ , respectively. The average minimum detectible amount of sCD40L was 4.2 pg/mL and CD40 was  $<50$  pg/mL. Analyses were performed by personnel who were blinded to the clinical data.

### Statistical Analysis

Study data are presented as continuous (mean $\pm$ SD) and categorical data. Significance was defined as  $P<0.05$ . All analyses were performed in SAS (version 9.2) or R (version 2.10). The response variable was estimated GFR measured at baseline and at 1 year, and the change was calculated from baseline and expressed as percent change. A natural log transformation of CD40 and sCD40L was performed to normalize the data.

Univariate analysis of continuous predictor variables and the response variable were compared with Pearson correlation, 2-tailed  $t$  tests, and 1-way ANOVA, and for categorical data  $\chi^2$  with Fisher exact test. Regression analysis was used to estimate the percent effect (adjusted  $R^2$ ), the predictor variable contributed to the overall response. Significant univariate factors were selected to create a multivariate linear regression model with stepwise selection applied to obtain the optimized model. Interaction effects were also examined using the generalized linear model. Logistic regression was used to study survival, as well as the Kaplan–Meier estimator of the survival function.

## Results

CD40 and sCD40L were measured in 60 patients with known renal artery stenosis (RAS). The characteristics of the study population in relation to percent change in estimated GFR at 1-year follow-up are displayed in the Table. The average percent change in GFR from baseline to 1-year follow-up was  $-7.8\pm 33.1$ . For survival analysis, the mean duration of follow-up was 469 days.

### CD40, sCD40L, and Baseline Characteristics

There were no baseline characteristics that were associated with CD40 in this cohort. Soluble CD40L was positively correlated with higher weight at baseline ( $R^2=13.4\%$ ; correlation coefficient=0.40;  $P<0.01$ ) and with men ( $5.5\pm 0.5$  versus  $5.0\pm 0.4$  pg/mL;  $P<0.01$ , Figure 1). Patients on statin therapy had lower levels of sCD40L compared with those who were not ( $5.2\pm 0.4$  versus  $5.5\pm 0.7$  pg/mL;  $P=0.06$ ). Aspirin did not significantly alter sCD40L levels. There was no correlation between levels of CD40 and sCD40L ( $R^2=2.2\%$ ;  $P=ns$ ).

### CD40, sCD40L, and Progression of Kidney Disease

By univariate analysis, CD40 was predictive of loss of renal function with low levels of circulating CD40 significantly associated with a greater loss of kidney function at follow-up ( $R^2=0.06$ ;  $P<0.05$ ; Figure 2). Other factors that were associated with loss of kidney function over the 1-year follow-up period included baseline creatinine ( $R^2=0.08$ ;  $P=0.022$ ). Revascularization with stenting was not associated with improvement of GFR ( $P=0.14$ ) in the 14 patients in which it was performed, on average, 92 days after baseline. A multivariate model was created to evaluate the overall contribution of CD40 to prediction of changes in renal function when other factors, such as baseline kidney function, were accounted for. Low CD40 levels continued to be significantly associated with a decline in renal function when revascularization was included in the multiple linear regression model ( $R^2=0.20$ ;  $P<0.01$ .) The relationship between baseline CD40 and change in renal function was not affected by baseline GFR or stent revascularization. Soluble CD40L was not predictive of changes in estimated GFR.

### CD40 and sCD40L and Survival

Next, we evaluated the role of CD40 and sCD40L on all-cause mortality in the cohort. We observed a trend toward lower levels of circulating CD40 in patients who died during follow-up (survivors,  $7.3\pm 0.9$  pg/mL versus nonsurvivors,  $6.7\pm 1.0$  pg/mL;  $P=0.06$ ; Figure 3). Soluble CD40L was not associated with mortality.

**Table. Association of Baseline Characteristics to Percent Change in eGFR at 1-Year Follow-Up in Patients With Renal Artery Stenosis**

Patient Characteristics	Mean±SD or n (%)	Percent Change eGFR Within Group (Mean±SD)	CC	P
Age±SD, y	70±10		-0.13	0.35
Sex				
Men	35 (58%)	1±31		0.09
Women	25 (42%)	-12±22		
Weight, kg	81±19		0.32	0.03
Systolic BP, mm Hg	154±30		-0.15	0.28
Diastolic BP, mm Hg	78±16		0.04	0.77
Laboratory values				
Serum creatinine, mg/dL	1.92±1.01		0.31	0.02
In sCD40L, pg/mL	5.28±0.52		0.17	0.24
In CD40, pg/mL	7.14±0.97		0.27	0.047
eGFR	40±19		-0.21	0.13
Proteinuria, 24 h, mg/mmol	622±940		-0.26	0.07
Risk factors, n (%)				
Hypertension				
Yes	11 (18%)	-12±25		0.34
No	49 (82%)	-2±29		
Angina				
Yes	18 (30%)	3±44		0.19
No	42 (70%)	-8±18		
Previous MI				
Yes	23 (38%)	-1.3±40.3		0.53
No	37 (62%)	-6±18		
Peripheral vascular disease				
Yes	15 (25%)	-11±15		0.40
No	45 (75%)	-3±31		
Cerebrovascular accident				
Yes	5 (8%)	-19±23		0.24
No	55 (92%)	-3±28		
Abdominal aortic aneurysm				
Yes	7 (12%)	12±51		0.09
No	53 (88%)	-7±23		
Diabetes mellitus				
Yes	16 (27%)	-12±24		0.26
No	44 (73%)	-2±29		
History/current smoking				
Yes	27 (52%)	-2±33		0.62
No	25 (48%)	-6±27		
Stent treatment				
Yes	14 (23%)	6±42		0.14
No	46 (77%)	-8±22		
Bilateral stenosis				
Yes	40 (67%)	-2±30		0.32
No	20 (33%)	-10±23		
Percent stenosis (%)	67±24		0.20	0.14
Medications, n (%)				
Aspirin				
Yes	39 (66%)	-6±33		0.68
No	20 (34%)	-2±18		

(Continued)

**Table. Continued**

Patient Characteristics	Mean±SD or n (%)	Percent Change eGFR Within Group (Mean±SD)	CC	P
ACE inhibitors				
Yes	30 (51%)	-5±33		0.90
No	29 (49%)	-4±23		
ARB				
Yes	16 (27%)	-13±21		0.18
No	43 (73%)	-1±30		
β-Blocker				
Yes	28 (47%)	-1±27		0.43
No	31 (53%)	-7±30		
Calcium				
Yes	28 (48%)	-4±29		0.99
No	31 (52%)	-4±27		
Diuretic				
Yes	32 (54%)	-1±34		0.30
No	27 (46%)	-9±18		
Statin				
Yes	45 (76%)	-4±31		0.91
No	14 (24%)	-5±16		
Renin inhibitor				
Yes	3 (5%)	16±34		0.19
No	56 (95%)	-6±28		

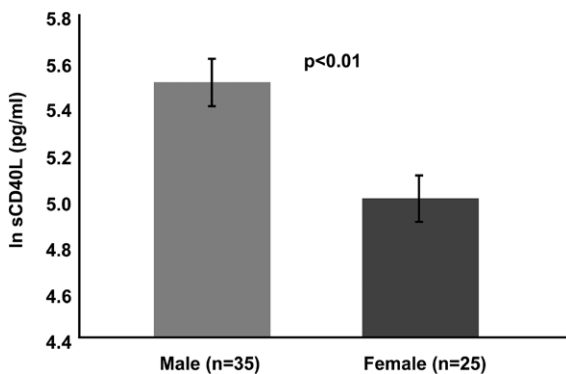
Values are mean±SD or number and percentage of patients. ACE indicates angiotensin converting enzyme; ARB, angiotensin II receptor blockers; BP, blood pressure; CC, correlation coefficient; eGFR, estimated glomerular filtration rate; MI, myocardial infarction; and sCD40L, soluble CD40 ligand.

**Discussion**

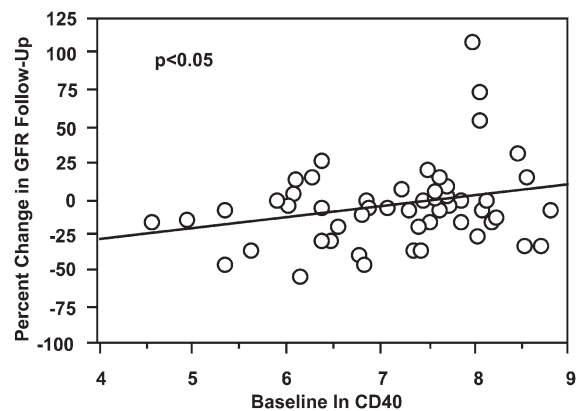
The adverse effect of ischemia on the kidney is well established experimentally, yet the role of atherosclerotic RAS in the genesis of renal dysfunction is controversial. Over 1 to 4 years, atherosclerotic stenoses may progress, although infrequently to occlusion.<sup>17-19</sup> In patients with significant (60%–99%) RAS, approximately one in four ipsilateral kidneys atrophy >1 cm.<sup>20,21</sup> However, several investigators have been unable to demonstrate a relationship between stenosis severity and renal function.<sup>22,23</sup> Clearly, there are factors other than percent stenosis that influence function. Some are intrinsic to RAS and may include the duration of the insult, atheroemboli, hypertensive nephrosclerosis of the contralateral kidney, activation of the renin–angiotensin system, and the effects of

the stenosis (including lesion length, minimal lumen diameter, etc) on renal blood flow and intrarenal pressure.<sup>24-26</sup> Other factors may include coexisting essential hypertension, diabetes mellitus, medications, generalized atherosclerosis progression, and aging.<sup>24-26</sup> Ischemia reperfusion injury is also a major contributor to renal failure in RAS and renal transplantation characterized by an increase in reactive oxygen species and infiltration of inflammatory cells, leading to endothelial cell damage within the kidney.<sup>27,28</sup>

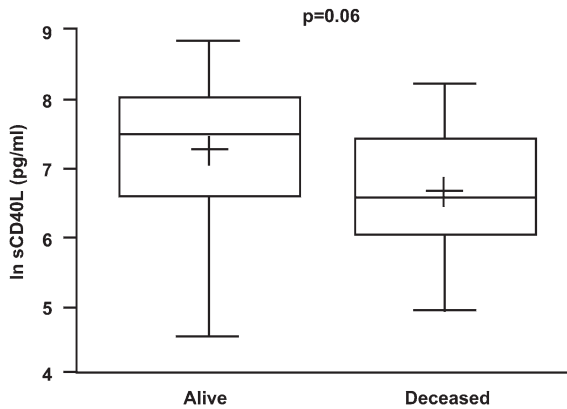
Experimentally, some research has ascribed a role of the renin–angiotensin system in ischemic nephropathy. Angiotensin II induces efferent arteriolar constriction that



**Figure 1.** Baseline sCD40L (log scale) levels in men and women.  $P<0.01$



**Figure 2.** Relationship between baseline CD40 (log scale) and percent change in estimated glomerular filtration rate (GFR) from baseline to 1-year follow-up,  $R^2=0.06$ ,  $P<0.05$ .



**Figure 3.** Baseline CD40 (log scale) and survival in patients with atherosclerotic renal artery stenosis,  $P=0.06$ .

aids in the maintenance of GFR. In 1983, Hricik et al<sup>29</sup> described renal failure secondary to angiotensin converting enzyme inhibition with bilateral RAS. Reversal of the angiotensin II-mediated efferent arteriolar vasoconstriction by angiotensin converting enzyme inhibition decreases glomerular filtration pressure and GFR. Importantly, severe chronic hypoperfusion may be accompanied by renal atrophy, although normal kidneys remain viable with blood flows and pressures below that required for glomerular filtration,<sup>30</sup> because <10% of oxygen delivery is required for kidney metabolism. Gobe et al<sup>31</sup> found that both necrosis and apoptosis contributed to tubular injury. Finally, chronic kidney disease can be the result of severe global ischemia, but nephrosclerosis also occurs in a nonstenotic kidney, perhaps mediated by hypertension, a vasculotoxic effect of renin,<sup>32,33</sup> or by angiotensin II through its interaction with endothelin-1, platelet-derived growth factor, and transforming growth factor- $\beta$ ,<sup>34</sup> and by other potential factors, such as atheroembolization.

In patients with atherosclerotic renal disease, a combination of vascular sclerosis, interstitial fibrosis, inflammatory cell infiltration, atubular glomeruli, and focal or global glomerulosclerosis is seen when biopsy of the affected kidney is performed.<sup>35</sup> Although some of these changes are seen in animal models of experimentally induced RAS, Meyrier commented “this mixture (of changes) cannot be reproduced in animal models.”<sup>24</sup> Acute and chronic tubular changes are typical of experimental renal ischemia, but the human experience also includes strong components of fibrosis and inflammatory cell infiltration, facts not accounted for when clinicians assume that a “blocked artery causes decreased renal blood flow.”<sup>24</sup> This discrepancy typifies the differences between younger patients with fibromuscular dysplasia that develop hypertension without loss of renal function, and older subjects with atherosclerotic stenoses who oftentimes develop renal dysfunction that may be disproportionate to the degree of stenosis.

The interaction of CD40 with sCD40L is particularly attractive as a mediator of renal dysfunction in atherosclerotic RAS because it is known that CD40 is upregulated in the injured kidney,<sup>3,9</sup> that it leads to fibrosis and inflammation within the kidney,<sup>4,6,7,36</sup> and its activator (sCD40L) is primarily derived from activated platelets.<sup>2,37</sup> In this context, we

sought to determine in the current study whether circulating levels of CD40 and sCD40L were related to loss of kidney function and overall survival. Recently we have found that sCD40L is increased in patients with atherosclerotic RAS, although this seemed to be attributable to atherosclerosis, per se, not to the presence of RAS.<sup>16</sup> However, a stenosis of the renal artery may be a powerful inducer of local platelet activation and aggregation, leading to shedding of sCD40L downstream. Importantly, we have also observed that inhibition of platelet activation with a platelet glycoprotein IIb/IIIa inhibitor both improved kidney function and acutely lowered sCD40L at the time of renal artery stenting.<sup>16,38</sup> In this regard, CD40-sCD40L is an attractive candidate that links atherosclerosis, thrombosis, and inflammation with acute and chronic kidney injury.

In the current study, we observed a modest inverse relationship between CD40 and progression of chronic kidney disease, which is consistent with previous observations in renal disease subjects, suggesting that circulating CD40 may inhibit activation of receptor-bound CD40 and at higher levels induces anergy.<sup>11</sup> Importantly, after accounting for other important covariates, such as baseline kidney function and revascularization, CD40 continued to be an important predictor of changes in renal function in the multivariate model. The current data support the hypothesis that the CD40-sCD40L interaction may be a factor in the development and progression of chronic kidney disease in patients with atherosclerotic RAS. However, because of the small sample of subjects and the relatively modest relationships observed, further work is necessary to confirm or refute this idea. Interestingly, sCD40L levels were significantly higher in men than in women within this cohort. In women, elevated baseline levels of sCD40L have been reported to be associated with an increased risk of developing cardiovascular events.<sup>39</sup> The majority of patients were on statin therapy (75%) at baseline and had lower levels of sCD40L compared with those who were not. Statin use has been shown to significantly decrease sCD40L levels in patients with coronary artery disease.<sup>40,41</sup> Although aspirin has been shown to suppress sCD40L levels in patients with chronic heart failure,<sup>42</sup> we did not see an effect of aspirin use in the current cohort. Previously, we have shown that aggressive antiplatelet therapy using a GPIIb/IIIa inhibitor drastically decreased sCD40L levels in patients with atherosclerotic RAS.<sup>16</sup>

If CD40 and sCD40L are causative in the development of ischemic nephropathy, then several important consequences may need to be considered. First, it sheds light on how atherosclerotic stenoses in the renal artery may lead to renal dysfunction and why the relationship between stenosis severity and kidney function is weak. Second, it also has the potential to explain why patients undergoing renal artery stent procedures often lose kidney function, despite angiographically successful procedures, and provides a biological understanding of how platelet inhibition can prevent renal injury during renal artery stenting. Finally, it may serve as a new target for medical interventions to prevent the progression of chronic kidney disease and a mechanism to identify patients that are at particular risk for worsening renal dysfunction.

## Perspectives

The current study found that low levels of CD40 are associated with loss of kidney function in patients with atherosclerotic RAS. The CD40–sCD40L signaling cascade provides a potential mechanistic rationale for the linkage among atherothrombosis, RAS, and loss of kidney function.

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## Disclosures

None.

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## Novelty and Significance

### What Is New?

- We report that low levels of circulating CD40 are associated with a decline in renal function at 1-year follow-up in patients with atherosclerotic renal artery stenosis.

### What Is Relevant?

- The role of CD40 and sCD40L in the development of renal injury in patients with ischemic renal disease is not known. Our study suggests that

the CD40–sCD40L interaction may be an important factor in the development and progression of kidney disease in patients with atherosclerotic renal artery stenosis.

### Summary

The CD40–sCD40L signaling cascade provides a potential mechanistic rationale for the linkage among atherothrombosis, renal artery stenosis, and loss of kidney function.

## Effect of CD40 and sCD40L on Renal Function and Survival in Patients With Renal Artery Stenosis

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