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Cystatin C is Associated with Inflammation but not Atherosclerosis in Systemic Lupus Erythematosus

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Abstract

Background—Even mild renal impairment is associated with increased atherosclerosis and cardiovascular mortality. Cystatin C, a novel measure of renal function, is more sensitive than conventional creatinine-based measures for the detection of subtle renal impairment. Increased cystatin concentrations are also associated with cardiovascular risk, independent of conventional measures of renal function. We examined the hypothesis that cystatin C is elevated in systemic lupus erythematosus (SLE) and is associated with coronary atherosclerosis.

Methods—We measured serum cystatin C, creatinine, TNF-α, IL-6, coronary artery calcium score (CACS), Framingham risk score (FRS), Modified Diet in Renal Disease estimated glomerular filtration rate (MDRD-eGFR) and other clinical parameters in 118 patients with SLE and 83 control subjects. The independent association between concentrations of cystatin C and SLE was evaluated using multivariable linear regression models, and the relationship between renal measures and coronary calcium was assessed with multivariable proportional odds logistic regression models.

Results—Cystatin C, but not other measures of renal function, was significantly higher in patients with SLE than controls (1.09[Interquartile range, IQR: 0.85–1.28]mg/L vs. 0.89 [IQR: 0.76–0.99]mg/L; P<0.001 after adjusting for age, race and sex and MDRD-eGFR). Cystatin C was significantly associated with SLICC (P=0.04), ESR (P<0.001), CRP (P=0.04), TNF-α (P=0.008) and IL-6 (P=0.01) after adjustment for age, race and sex. Cystatin C was not significantly correlated with coronary calcium score in SLE (rho=0.096, P= 0.31) and the association remained non-significant after adjustment for age, race, sex and Framingham risk score (P=0.99).

Conclusions—Cystatin C was higher in patients with SLE than control subjects even after adjustment for conventional measures of renal function. Cystatin C was significantly correlated with several markers of inflammation in SLE but was not associated with coronary atherosclerosis. Subtle renal dysfunction does not appear to be directly associated with accelerated atherosclerosis in SLE.

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Keywords

cystatin C; systemic lupus erythematosus; renal function; atherosclerosis; Inflammation

Introduction

Cystatin C is a reversible inhibitor of cysteine proteinases [1,2] that is produced by most cells. It is an excellent marker of glomerular filtration rate (GFR) because it is freely filtered at the glomerulus and then reabsorbed and catabolized in the proximal renal tubules. In contrast to serum creatinine concentrations, cystatin C is not affected by gender and muscle mass, and therefore provides a more accurate measure of renal function.[2] It is particularly useful for the detection of mild renal impairment, a frequent complication of SLE.[3]

In addition to its utility as a measure of renal function, cystatin C provides independent prognostic information about cardiovascular risk, even after renal function determined from serum creatinine concentrations is considered.[4–7] Coronary heart disease (CHD) has emerged as a major cause of morbidity and mortality in SLE.[8] Concordant with the increased risk of CHD, subclinical atherosclerosis is accelerated in SLE; however, traditional CHD risk factors, lupus disease activity, and corticosteroid therapy do not account for the increased prevalence of CHD and atherosclerosis in SLE.[9] Another factor that increases the risk of CHD substantially is renal impairment.[10] Even small decreases in renal function are associated with a marked increase in CHD risk.[11] Accordingly, subtle renal dysfunction that is not detected by altered serum creatinine concentrations may explain the accelerated atherosclerosis in patients with SLE.

Although SLE is associated with renal impairment, premature atherosclerosis and increased cardiovascular mortality, there is little information about their relationship to cystatin C. Thus, we examined the hypotheses that cystatin C concentrations are: 1) higher in patients with SLE than control subjects, independent of standard measures of glomerular filtration rate derived from serum creatinine concentrations; and 2) associated with coronary atherosclerosis independent of traditional cardiovascular risk factors in SLE.

Methods

Study Subjects

We studied 118 patients with SLE and 83 control subjects participating in ongoing studies of cardiovascular risk.[9,12,13] The patients and control subjects were recruited from January 2000 to February 2008. The study was approved by the Vanderbilt University Institutional Review Board and all subjects gave written informed consent. Consecutive eligible patients, age>18 years, who met the classification criteria for SLE [14] and had disease duration >1 year, were enrolled. Controls did not meet the classification criteria for SLE or any other autoimmune disease and were frequency-matched for age, sex and race so that the two groups did not differ materially with regard to these variables. Detailed descriptions of the recruitment procedures and study design have been reported previously. [9,12,13] Patients and controls with a history of angina, myocardial infarction, stroke and dialysis were excluded from this study.

Clinical Assessment

Patients and controls were evaluated using a standardized clinical interview, physical examination, laboratory tests, and in patients, review of the medical record. A history of renal involvement was defined as having renal disease that met the ACR SLE classification criterion for renal involvement [14] at any time. Height and weight were measured and body

mass index (BMI) was calculated ask g/m^2. Blood pressure was recorded as the mean of two measurements obtained 5 minutes apart after participants had rested in a supine position for 10 minutes. Patients were classified into the following categories of immunosuppressive drug use: current use, and any use of an immunosuppressive drug, based on their exposure to azathioprine, mycophenolate mofetil, and cyclophosphamide.

Laboratory tests

Blood was collected after an overnight fast for the measurement of total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides and homocysteine. In patients with SLE, the erythrocyte sedimentation rate (Westergren), Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) and the Systemic Lupus Erythematosus International Collaborating Clinics Damage Index (SLICC) indices were measured.[15,16] Total hemolytic complement (CH50) and C-reactive protein (CRP) concentrations were measured in the hospital clinical laboratory. Before 2003, the laboratory did not use a high-sensitivity CRP assay, and low concentrations were reported as <3 mg/L. In 26 lupus patients with values <3 mg/L, CRP concentrations were measured using a Lincoplex Multiplex Immunoassay (Millipore). Serum concentrations of tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), were measured by Lincoplex Multiplex ELISA (Millipore). Serum cystatin C was measured by enzyme-linked immunosorbent assay according to the manufacturer's instructions (Biovendor, Candler, NC).

To estimate GFR from serum creatinine we used the MDRD (Modified Diet in Renal Disease) formula (eGFR) [17]:

$$MDRD{-}eGFR{=}186{\times}Serum\ Creatinine^{-1.154}{\times}Age^{-0.203}{\times}(1.210\ if\ black){\times}(0.742\ if\ female)$$

Coronary-artery calcification

Coronary calcium was measured by electron beam computed tomography (CT) scanning with an Imatron C-150 (GE/Imatron, South San Francisco, CA) scanner, except for 22 patients with SLE, in whom 64-row mulitdetector CT (Light-Speed VCT, General Electric) was used. The extent of coronary-artery calcification was calculated as described by Agatston et al [18] and the total calcium score calculated by a single experienced cardiologist who was unaware of the disease status.

Statistical Analysis

Descriptive statistics are presented as percentage (%) for categorical variables, and mean with standard deviation (mean±SD), or median with interquartile range (median [IQR]), according to the distribution of the continuous variables. Demographic and clinical factors were compared using a Wilcoxon's rank sum test or a Pearson chi-square test as appropriate.

The independent association between disease status and concentrations of cystatin C was assessed using multivariable linear regression models with cystatin C as the response variable and with age, race, and sex as covariates. Among patients with SLE, we first evaluated the association between measures of renal function (cystatin C, serum creatinine, MDRD-eGFR) and traditional cardiovascular risk factors, inflammation (ESR, CRP, CH50, TNF-α, IL-6), other clinical variables, and coronary artery calcium score. Wilcoxon's rank sum test or Spearman's rank correlation coefficients (rho) were used to assess the univariate relationships. The independent associations were examined by multivariable linear regression adjusting for age, race and sex as covariates.

We analyzed the association between each renal function measure and the outcome of coronary calcification using proportional odds logistic models [19,20] that adjusted for age, race, sex and Framingham risk score.

Cystatin C, creatinine, triglyceride, homocysteine, ESR, CRP, CH50, TNF-α and IL-6 were log-transformed to improve the fit of the regression models. Statistical analyses were performed using R version 2.10.0 (http://www.r-project.org). A two-sided significance level of 5% was required for consideration as statistical significant.

Results

Baseline Characteristics of Patients with SLE and Control Subjects

Characteristics of patients with SLE (n=118) and control subjects (n=83) are shown in Table 1. As we have reported previously in this cohort,[9,12,13] patients with SLE and control subjects were of similar age, race and sex and did not differ significantly as regards their history of smoking, the presence of diabetes, or Framingham Risk Score. Patients with SLE were more likely to be hypertensive, have a higher BMI, have a history of renal disease and have higher coronary calcium scores. Measures of homocysteine and inflammation such as TNF-α and IL-6 concentrations were all significantly higher in patients with SLE compared to control subjects (Table 1). In patients with SLE the median duration of disease was 5.5 years (IQR: 3–11), the median SLEDAI score was 4(0–6), SLICC was 0.44(0–1.46) and 45% had received an immunosuppressive drug.

Cystatin C concentrations were significantly higher in patients with SLE (1.09[IQR: 0.85–1.28]mg/L) than controls (0.89[IQR: 0.76–0.99]mg/L), (P<0.001). In contrast, serum creatinine concentrations (0.8[IQR: 0.7–0.9]mg/dl vs. 0.8[IQR: 0.7–0.9]mg/dl, P=0.73) and MDRD-eGFR (94.7[IQR: 78.2–109.7]ml/min/1.73m^2 vs. 92.2 [IQR: 82.8–110.1]ml/min/1.73m^2, P=0.66) did not differ significantly among patients and controls (Table 1, Figure 1). Cystatin C concentrations remained significantly higher in patients with SLE than controls after adjustment for age, race and sex (P<0.001), and also after additional adjustment for MDRD-eGFR (P<0.001).

Relationship between Measures of Renal Function

In patients with SLE, cystatin C concentrations were positively correlated with creatinine (rho=0.351, P<0.001), and negatively correlated with MDRD-eGFR (rho=−0.367, P<0.001). MDRD-eGFR and serum creatinine concentrations were negatively correlated (rho=−0.858, P<0.001). Serum creatinine concentrations were significantly higher in men than women (P=0.002); however, cystatin C (P=0.62) and MDRD-eGFR (P=0.87) did not differ significantly (Table 2) between the sexes. Cystatin C, creatinine and MDRD-eGFR were not significantly associated with smoking or current use of NSAIDS and COX2-inhibitors. All measures of renal function were associated with the presence of hypertension (cystatin C, P=0.006; creatinine, P=0.002 and MDRD-eGFR, P=0.01), and ever use of an immunosuppressive drug (cystatin C, P=0.04; creatinine, P=0.003 and MDRD-eGFR, P=0.05) after adjustment for age, race and sex (Table 2). Both cystatin C and creatinine, but not MDRD-eGFR, were associated with history of renal disease (cystatin C, P=0.04; creatinine, P=0.003 and MDRD-eGFR, P=0.09). Only cystatin C concentrations were significantly correlated with corticosteroid use (P=0.05) (Table 2).

Measures of Renal Function and Cardiovascular Risk Factors in SLE

Renal function, assessed by creatinine and MDRD-eGFR, decreased significantly with increasing age (creatinine rho=0.299, P<0.001 and MDRD-eGFR rho=−0.490, P<0.001). All measures of renal function were significantly associated with homocysteine concentrations,

even after adjustment for age, race and sex (cystatin C rho=0.291, P=0.001; creatinine rho=0.509, P<0.001 and MDRD-eGFR rho=−0.446, P<0.001) (Table 3).

Cystatin C, creatinine and MDRD-eGFR were not significantly correlated with the Framingham risk score after adjustment for age, race and sex (cystatin C, P=0.25; creatinine, P=0.24 and MDRD-eGFR, P=0.41) (Table 3).

Association between Measures of Renal Function and Inflammatory Measures in SLE

Cystatin C was significantly correlated with SLICC (rho=0.231, P=0.04), ESR (rho=0.261, P<0.001), CRP (rho=0.180, P=0.04), TNF-α (rho=0.322, P=0.008) and IL-6 concentrations (rho=0.266, P=0.01) and the associations remained significant after adjustment for age, race and sex (Table 4). CH50 was not significantly correlated with cystatin C (rho=−0.085, P=0.421). Levels of serum creatinine and MDRD-eGFR were not significantly associated with measures of disease activity, damage, or inflammation in SLE.

Association between Measures of Renal Function and Coronary Calcium Score in SLE

Creatinine and MDRD-eGFR were correlated with coronary calcium score in SLE in univariate analyses (creatinine, rho=0.268, P=0.004, and MDRD-eGFR, rho=−0.259. P=0.005) (Table 3). After adjustment for age, race, sex and Framingham risk score there were no significant associations between any of the renal function measures (cystatin C, OR=0.73, 95% CI: 0.49 to 2.07, rho=0.096, P=0.99; creatinine, OR=1.25, 95% CI: 0.65 to 2.38, rho=0.268, P=0.51 and MDRD-eGFR, OR=0.73, 95% CI: 0.31 to 1.73, rho=0.259, P=0.48) and coronary calcium score (Table 3).

Discussion

The major new findings of this study are that concentrations of cystatin C were significantly higher in patients with SLE than control subjects and this difference remained significant after adjustment for age, race, sex and a conventional measure of renal function (MDRD-eGFR). Furthermore, cystatin C, but not other measures of renal function, were significantly correlated with inflammatory markers and disease activity in SLE.

Cystatin C is not affected by gender and muscle mass, and because its production rate is usually constant, its plasma concentration reflects GFR.[4] Cystatin C is more accurate than serum creatinine for the identification of mild renal impairment, and thus may allow early detection of renal disease in specific populations. Renal involvement -ranging from a mildly abnormal urine sediment to severe glomerulonephritis and renal failure is common in SLE.[3] However, little is known about cystatin C concentrations in SLE. In one study cystatin C was used as a measure of renal function to assess the effect of anti-CRP antibodies,[21] and a second study of 212 patients with various renal diseases, including 20 with SLE, found that cystatin C was reliable for the detection of subclinical renal dysfunction.[22]

We found that cystatin C concentrations were significantly higher in a group of patients with well-controlled SLE than controls, whereas conventional measures of renal function such as serum creatinine and MDRD-eGFR did not differ significantly. Furthermore, cystatin C concentrations remained significantly higher in SLE after adjustment for age, race and sex, and MDRD-eGFR. This suggests either that conventional measures of renal function perform poorly in patients with SLE who have mild disease activity, or that additional factors contribute to the elevated concentrations of cystatin C in SLE.

The finding that all measures of renal function were associated with hypertension and previous exposure to immunosuppressive drugs suggests that serum creatinine and MDRD-eGFR did identify patients in whom subtle renal impairment would be more likely to be

present. On the other hand, the finding that cystatin C concentrations, but not serum creatinine or MDRD-eGFR, were correlated with SLICC, ESR, CRP, TNF-α and IL-6, suggests that elevated cystatin C concentrations in SLE may be affected by inflammatory mechanisms. Unlike ESR, CRP is more likely to increase with infection rather than disease activity in SLE[23]. Thus ESR may be superior to CRP as a measure of disease activity in lupus. Our finding of a stronger association between cystatin C and ESR than CRP, therefore is of interest and concordant with the interpretation that cystatin C is influenced by inflammation in SLE. However, it is difficult to exclude the possibility that mild active inflammation is associated with subtle decreases in renal function. In a previous study of patients with rheumatoid arthritis, we also found a significant association between cystatin C and some measures of inflammation and disease activity such as DAS28 (Disease Activity Score 28-joint assessment), ESR and CRP, but not with IL-6 and TNF-α concentrations.[24] These findings suggest an association between cystatin C and inflammation.

Several other lines of evidence support an association between inflammation and cystatin C. In the Multi-Ethnic Study of Atherosclerosis (MESA) cystatin C was correlated with several inflammatory markers including CRP, IL-6, TNF-α soluble receptor 1, and intercellular adhesion molecule-1 across a broad range of renal function.[25] Similarly, in several other large population studies cystatin C was associated with some markers of inflammation.[26–29] This may reflect its immunomodulatory functions. Cystatin C plays an important role as an endogenous inhibitor of cysteine proteinases such as cathepsins and elastases. Also, cystatin C inhibits polymorphonuclear cell chemotaxis, O_2-release and phagocytosis,[1] and cystatin C knockout mice have an earlier onset and higher incidence of collagen-induced arthritis.[30]

The association between higher cystatin C concentrations and markers and mediators of inflammation in SLE raises several possibilities. For example, inflammation and impaired renal function (detected by higher cystatin concentrations) could co-exist but be causally unrelated; or inflammation could cause cystatin C concentrations to be elevated, either by affecting renal function, or through mechanisms related to the immunomodulatory functions of cystatin.[27,28] Further studies will be required to identify the contribution of these potential mechanisms. The relationship between cystatin C, inflammation and cardiovascular disease [29] is particularly relevant to SLE, because impaired renal function, common in SLE, is associated with increased cardiovascular risk in many populations. Cystatin C has been found to be a strong predictor of cardiovascular risk and mortality.[31,32] In the community-based longitudinal Cardiovascular Health Study involving 4637 participants 65 years of age or older, cystatin C was significantly associated with cardiovascular risk and mortality, whereas creatinine and MDRD-eGFR were not.[4] Cystatin C was also predictive of adverse cardiovascular outcomes in patients with acute coronary syndrome,[27,33] established coronary artery disease,[34,35] diabetes [36] and heart failure.[37,38] The increased cardiovascular risk associated with higher cystatin C concentrations could reflect the risk imparted by renal impairment.

There is substantial evidence for an association between renal impairment and atherosclerosis and cardiovascular risk. [39,40] Even mild to moderate renal impairment is strongly associated with cardiovascular morbidity and mortality, independent of the other risk factors.[41,42] Thus, cystatin C may serve as an early marker for increased cardiovascular risk resulting from subtle renal impairment, or perhaps could also participate directly in atherogenesis through its role in inflammatory processes.[42]

There is little information about the relationship between cystatin C and measures of coronary atherosclerosis. In the Multi-Ethnic Study of Atherosclerosis (MESA) study, cystatin C was not associated with cross-sectional severity of coronary artery calcification after adjustment for other risk factors in the population with mild to moderate kidney

dysfunction.[43] However, in another study angiographic presence of coronary artery disease was associated with higher cystatin C concentrations, independent of the other risk factors.[42] In our study, after adjustment for age, race, sex and Framingham Risk Score, there was no significant correlation between any measure of renal function and coronary artery calcification in patients with SLE.

The limitations of our study include the cross-sectional study design, a single measurement of cystatin C and inflammatory markers, and the lack of a gold standard measure of GFR such as the plasma clearance of ^{51}Cr-EDTA. Information about risk factors over time in a longitudinal study may be more informative. We did not measure the relationship between cystatin C and cardiovascular outcomes such as myocardial infarction. In addition, most of the SLE patients in the study had mild to moderate disease severity and activity, thus these findings may not apply to patients with more severe disease.

In summary, we found that cystatin C concentrations were higher in SLE patients than control subjects independent of conventional measures of renal function. Cystatin C was associated with higher levels of several markers of inflammation but was not associated with coronary atherosclerosis. Subtle renal impairment does not appear to be directly associated with accelerated atherosclerosis in SLE.

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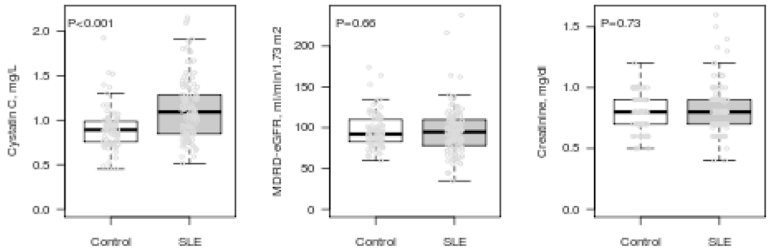

Figure 1. Concentrations of Cystatin C, Creatinine and MDRD-eGFR in Control Subjects and Patients with SLE

Distribution of serum cystatin C and creatinine concentrations and MDRD-eGFR in patients with SLE and control subjects. Data are presented as box plots, where the boxes represent the interquartile range (IQR), the lines within boxes represent the median, and the lines outside the boxes represent the lower quartile minus 1.5 times the IQR or the upper quartile plus 1.5 times the IQR. Cystatin C concentrations were significantly higher in patients with SLE than controls ($P<0.001$). Serum creatinine concentrations ($P=0.73$) and MDRD-eGFR ($P=0.66$) did not differ significantly among patients and controls.

Table 1

Baseline Characteristics of Control Subjects and Patients with Systemic Lupus Erythematosus

Variables[a]	Control (n=83)	SLE (n=118)	*P* value
Age, years	42 (30–49)	40 (30–48)	0.92
Sex, % female	86	92	0.12
Race, %white	72	71	0.86
BMI, kg/m2	25.3 (22.3–30.0)	27.8 (23.2–33.2)	0.04
Current smokers, %	18	23	0.41
Hypertension, %	18	42	<0.001
Diabetes, %	1	4	0.21
History of Renal Disease, %	-	21	-
Current immunosuppressive, %	-	25	-
Ever immunosuppressive, %	-	45	-
Systolic blood pressure, mmHg	114 (106–127)	115 (107–127)	0.79
Total cholesterol, mg/dl	180 (154–206)	167 (144–206)	0.17
HDL, mg/dl	47 (38–61)	49 (36–58)	0.82
LDL, mg/dl	108 (89–136)	97 (78–127)	0.04
Triglyceride, mg/dl	81 (62–108)	98 (73–147)	0.006
Framingham risk score	7.0 (−0.8–10.8)	5.0 (2.0–10.0)	0.88
SLEDAI	-	4 (0–6)	-
SLICC	-	0.44 (0–1.46)	-
ESR, mm/hr	-	18(8–34)	-
CRP, mg/L	-	4.0 (0.8–7.0)	-
CH50, U/ml	-	124.8 (78.0–221.6)	-
TNF-α, pg/ml	2.42 (1.81–3.02)	4.77 (3.01–7.92)	<0.001
IL-6, pg/ml	1.77 (0.87–4.73)	5.60 (2.17–23.36)	<0.001
Homocysteine, umoles/L	7.6 (6.6–8.9)	9.0 (7.3–11.0)	<0.001
Cystatin, mg/L	0.89 (0.76–0.99)	1.09 (0.85–1.28)	<0.001
Creatinine, mg/dl	0.8 (0.7–0.9)	0.8 (0.7–0.9)	0.73
MDRD-eGFR, ml/min/1.73 m^2	92.2 (82.8–110.1)	94.7 (78.2–109.7)	0.66
Coronary calcium score, Agatston units	3.71±27.36	35.0±156	0.003

Values are shown as mean ± SD, median and (IQR) or percent (%).

[a]Wilcoxon's rank sum test was used for comparing continuous variables, and percentages were compared using Pearson chi-square test.

BMI= Body Mass Index; HDL= High-Density Lipoprotein; LDL= Low-Density Lipoprotein; NA= not applicable; SLEDAI= Systemic Lupus Erythematosus Disease Activity Index; SLICC=Systemic Lupus Erythematosus International Collaborating Clinics Damage Index; ESR=Erythrocyte Sedimentation Rate; CRP=C-Reactive Protein; CH50=Total Hemolytic Complement; TNF-α = Tumor Necrosis Factor-α; IL-6=Interleukin-6; MDRD-eGFR= The MDRD (Modified Diet in Renal Disease) formula estimated GFR

Table 2

Association between Measures of Renal Function and Categorical Clinical Characteristics in Patients with SLE.

Variable	N	Cystatin C (mg/L)	*P* value[a]	Adjusted *P* value[b]	Creatinine (mg/dl)	*P* value[a]	Adjusted *P* value[b]	MDRD-eGFR (ml/min/1.73 m^2)	*P* value[a]	Adjusted *P* value[b]
Gender										
Male	9	0.94 (0.85–1.40)	0.62	-	0.9 (0.9–1.0)	0.002	-	94 (87–106)	0.87	-
Female	109	1.11 (0.85–1.28)			0.8 (0.7–0.9)			95 (78–110)		
Current Smoking										
Yes	27	1.12 (0.90–1.36)	0.66	0.62	0.8 (0.7–1.0)	0.53	0.37	95 (86–104)	0.96	0.33
No	91	1.09 (0.85–1.28)			0.8 (0.7–0.9)			95 (78–112)		
Hypertension										
Yes	49	1.22 (1.02–1.40)	0.005	0.006	0.9 (0.7–1.0)	<0.001	0.002	84 (72–98)	0.002	0.01
No	69	1.01 (0.84–1.23)			0.7 (0.7–0.9)			99 (86–113)		
Renal Disease History										
Yes	25	1.13 (0.88–1.66)	0.11	0.04	0.9 (0.7–1.1)	0.04	0.003	92 (72–118)	0.69	0.09
No	93	1.05 (0.85–1.25)			0.8 (0.7–0.9)			95 (83–105)		
Current Immunosuppressive Drug										
Yes	29	1.12 (0.93–1.65)	0.15	0.07	0.9 (0.7–1.0)	0.04	0.24	88 (75–108)	0.27	0.71
No	89	1.07 (0.84–1.27)			0.8 (0.7–0.9)			96 (84–112)		
Ever Immunosuppressive Drug										
Yes	53	1.12 (0.88–1.40)	0.15	0.04	0.9 (0.7–1.0)	<0.001	0.003	86 (75–109)	0.11	0.05
No	65	1.05 (0.84–1.25)			0.7 (0.7–0.8)			95 (82–110)		
Current corticosteroid										
Yes	64	1.15 (0.91–1.38)	0.04	0.05	0.8 (0.7–0.9)	0.02	0.12	87 (75–111)	0.15	0.46
No	54	1.01 (0.85–1.24)			0.7 (0.7–0.8)			96 (86–108)		
NSAIDS/COX2-inhibitor										
Yes	44	1.04 (0.85–1.26)	0.57	0.58	0.8 (0.7–0.9)	0.41	0.58	87 (82–98)	0.15	0.33
No	74	1.12 (0.85–1.35)			0.8 (0.7–0.9)			96 (76–113)		

Values are the median (Interquartile range)

MDRD-eGFR= The MDRD (Modified Diet in Renal Disease) formula estimated GFR, NSAIDS= Non-steroidal anti-inflammatory drugs

[a] Spearman's correlation coefficient test

[b] Multivariable linear regression was used for adjustment of age, race and sex.

Table 3

Association between Measures of Renal Function and Cardiovascular Risk factors in Patients with SLE.

Factor	Cystatin C			Creatinine			MDRD-eGFR		
	Rho (ρ)	*P* value[a]	Adjusted *P* value[b,c]	Rho (ρ)	*P* value[a]	Adjusted *P* value[b]	Rho (ρ)	*P* value[a]	Adjusted *P* value[b]
Age	0.080	0.40	-	0.299	<0.001	-	−0.490	<0.001	-
BMI	0.148	0.11	0.13	−0.001	0.99	0.36	0.072	0.44	0.12
Systolic Blood Pressure	0.091	0.33	0.35	0.195	0.04	0.08	−0.087	0.35	0.08
Diastolic Blood Pressure	−0.05	0.60	0.61	0.170	0.07	0.06	−0.105	0.26	0.03
HDL Cholesterol	−0.133	0.15	0.29	0.074	0.48	0.17	−0.190	0.04	0.27
LDL Cholesterol	−0.022	0.81	0.54	0.051	0.58	0.90	0.016	0.86	0.65
Homocysteine	0.291	0.001	0.001	0.509	<0.001	<0.001	−0.446	<0.001	<0.001
Framingham Score	0.141	0.13	0.25	0.339	<0.001	0.24	−0.448	<0.001	0.41
Coronary Calcium Score[c]	0.096	0.31	0.99	0.268	0.004	0.51	−0.259	0.005	0.48

[a] Spearman's correlation coefficient test.

[b] Multivariable linear regression was used for adjustment of age, race and sex.

[c] Proportional odds logistic regression was used for adjustment of age, race, sex and Framingham Risk Score

MDRD-eGFR= The MDRD (Modified Diet in Renal Disease) formula estimated GFR

BMI=Body Mass Index; HDL=High-Density Lipoprotein; LDL=Low-Density Lipoprotein

Table 4

Association between Measures of Renal Function and Inflammation in Patients with SLE.

Factor	Cystatin C			Creatinine			MDRD-eGFR		
	Rho (ρ)	*P* value[a]	Adjusted *P* value[b]	Rho (ρ)	*P* value[a]	Adjusted *P* value[b]	Rho (ρ)	*P* value[a]	Adjusted *P* value[b]
Disease duration	−0.056	0.55	0.61	0.181	0.05	0.19	−0.222	0.02	0.28
SLEDAI	0.136	0.14	0.07	−0.034	0.72	0.38	0.059	0.52	0.07
SLICC	0.231	0.01	0.04	0.080	0.39	0.08	−0.109	0.24	0.53
ESR	0.261	0.004	<0.001	0.008	0.94	0.96	0.085	0.36	0.54
CRP	0.180	0.05	0.04	0.027	0.77	0.92	−0.049	0.60	0.44
CH50	−0.085	0.32	0.42	−0.043	0.67	0.86	0.052	0.56	0.78
TNF-α	0.322	0.001	0.008	0.040	0.64	0.84	−0.002	0.98	0.53
IL-6	0.266	0.008	0.01	−0.010	0.99	0.77	0.023	0.82	0.95

[a]Spearman's correlation coefficient test.

[b]Multivariable linear regression was used for adjustment of age, race and sex.

MDRD-eGFR= The MDRD (Modified Diet in Renal Disease) formula estimated GFR

SLEDAI=Systemic Lupus Erythematosus Disease Activity Index; SLICC=Systemic Lupus Erythematosus International Collaborating Clinics Damage Index; ESR=Erythrocyte Sedimentation Rate; CRP=C-Reactive Protein; CH50=Total Hemolytic Complement; TNF-α=Tumor Necrosis Factor-α; IL-6=Interleukin-6