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Circulating CTRP9 is Associated with Severity of Systemic Sclerosis-associated Interstitial Lung Disease

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Abstract

Objective: While interstitial lung disease (ILD) is the leading cause of morbidity and mortality in systemic sclerosis (SSc), there remains a paucity of predictive markers to assess disease progression. We previously demonstrated that adipose tissue metabolism and adipokine homeostasis is dysregulated in SSc. We sought to determine the association and predictive ability of the novel adipokine C1q/TNF-Related Protein 9 (CTRP9) for SSc-ILD.

Methods: We performed a retrospective longitudinal study utilizing the Northwestern Scleroderma Program Patient Registry and Biorepository. Serum levels of CTRP9 were measured in 110 SSc patients at baseline, and demographic, clinical and pulmonary function test data were collected in 12-month intervals to 48 months. Longitudinal trajectory of forced vital capacity percent predicted (FVC%) was used as a primary outcome measure. We utilized a mixed model to compare trajectories of lung function by CTRP9 groups and performed latent trajectory analysis to accommodate for heterogeneity.

Results: In cross-sectional analysis, elevated circulating CTRP9 was associated with significantly lower FVC% at baseline (72%±17 vs. 80%±18, p=0.02) and 48 months (68±19 vs. 84±18, p=0.001). In mixed model analysis, high CTRP9 was associated with worse lung function, but not with a different trajectory (p=0.23). In contrast, low CTRP9 identified patients with stability of lung disease with reasonable accuracy (sensitivity=73%). Latent trajectory analysis confirmed the association of lower CTRP9 with higher FVC%.

Conclusions: Higher circulating CTRP9 associated with worse pulmonary function while low CTRP9 identified patients with lung disease stability over time. These findings suggest that CTRP9 may be a potential biomarker in SSc-associated ILD.

Significance and Innovation

- This research addresses the urgent need to discover and validate novel biomarkers in systemic sclerosis (SSc)-associated ILD, the leading cause of disease-associated mortality.
- Significance lies in advancing knowledge of the association of adipokines with SSc, focusing on a novel and poorly understood adipokine called CTRP9 as a potential marker for SSc-associated ILD.
- Innovation lies in the focus on CTRP as a novel member of the adipokine family; additionally, the application of longitudinal data to a rare disease, allowing for latent trajectory analysis, is still lacking in the field.

Systemic sclerosis (SSc), characterized by diffuse fibrosis and vasculopathy, affects nearly every organ system and shows great variability in disease progression, response to therapy, and outcomes. While interstitial lung disease (ILD) is the leading cause of morbidity and mortality in SSc[1], its course is highly variable, ranging from nonprogressive fibrosis to rapid progression of end stage lung disease. There is currently a paucity of predictive biomarkers to assess disease progression of SSc-associated ILD (SSc-ILD), representing a significant unmet need in the field.

Work from our group has demonstrated that altered adipose tissue metabolism is a hallmark of SSc, and a potential pathogenic mechanism underlying fibrosis.[2] Furthermore, we showed that adipokines are associated with specific disease complications and may prove useful as biomarkers.[3] To date, the focus on adipokines in SSc has remained primarily on adiponectin, leptin and resistin.[4] A cross-sectional study showed that the novel adipokine, C1q/TNF-Related Protein 9 (CTRP9), was associated with pulmonary complications of SSc.[5]

Here we sought to investigate the association of CTRP9 and SSc-ILD in a retrospective longitudinal study utilizing the Northwestern Scleroderma Program Patient Registry and Biorepository. We hypothesized CTRP9 levels would be associated with, and have predictive value, for pulmonary function in SSc-associated ILD, namely that high CTRP9 would be associated with more severe lung disease. We found high CTRP9 was associated with worse pulmonary function while low CTRP9 identified disease stability over time.

Patient and Methods:

Study Population

We utilized the Northwestern Scleroderma Patient Registry and Biorepository, a resource of clinical data collected in a standardized prospective fashion for the purposes of research. The study was approved by the Northwestern University Institutional Review Board (STU00208417), and patients provided written informed consent. This study, part of a larger study examining circulating adipokines, included SSc patients who had sufficient serum for CTRP9 ELISA in duplicate, and sufficient longitudinal clinical data, including at least two modified Rodnan skin scores (MRSS), pulmonary function tests (PFT) and laboratory data subsequent to the baseline serum sample. Subjects without pulmonary function data within the designated follow up, or who died within one year of serum quantification were excluded from the study. All patients fulfilled the American College of Rheumatology/European League Against Rheumatism 2013 classification criteria.[6]

Determination of Adipokine Level

Serum samples were collected at baseline during a standard of care blood draw. Levels of CTRP9 were quantified by ELISA (Aviscera Bioscience) according to manufacturer's protocol. All samples were run in duplicate. Based on previous studies, a cutoff of $\geq$81.1ng/ml, representing 2 standard deviations above the mean, was used to define elevated CTRP9 and differentiate between high and low groups.[5]

Clinical Data

Clinical data were collected in a longitudinal retrospective fashion. For all patients, demographic, laboratory and pulmonary function test (PFT) data were obtained at the time of the baseline serum. For each individual, we examined pulmonary function test data in 12-month intervals up to 48 months after initial serum measurement. The primary outcome of interest was forced vital capacity percent predicted (FVC%), which is used as a surrogate for SSc-associated

ILD and has been shown to be a valid outcome measure for ILD patients.[7] Diffusing capacity of carbon monoxide percent predicted (DLCO%) was used as an additional outcome as it has been shown to be important in predicted extent of ILD.[8] As a secondary outcome, we measured serial serum monocyte level, which has been shown to be associated with severity of lung fibrosis and proposed as a biomarker in IPF.[9]

Statistical Analysis

Descriptive statistics summarized baseline demographic and clinical characteristics overall and by group (CTRP9 low vs high). Wilcoxon rank sum or chi-squared tests, as appropriate, compared these variables by group. Cross-sectional analyses compared both outcomes (FVC% and DLCO%) at baseline and 48 months between groups using two-sample t-tests. In a more comprehensive analysis, linear mixed effect models were used to examine associations between group and the trajectory of FVC% from baseline to 48 months. Specifically, fixed effects included group (low vs high), time, and the interaction. The interaction term assessed if the trajectory of FVC% was significantly different between groups. A random subject intercept and slope allowed for inclusion of repeated measures, while separating within-subject and between-subject variance components.

Additionally, recognizing the possible influence of other correlates on FVC%, multivariable analysis was performed adjusting for baseline covariates deemed significantly different between groups at an alpha level of 0.1. These included, disease duration, defined as the interval between first non-Raynaud's phenomenon SSc symptom and serum collection, and treatment status, defined as concurrent use of immunomodulatory agents at time of serum collection. A sensitivity analysis was considered re-classifying CTRP9 as detectable (CTRP>0) and non-detectable (CTRP=0). Disease stability was defined as subject specific decrease in

FVC% less than 3% in 48 months, based on subject specific trajectories estimate from the mixed model described above. Sensitivity and specificity of CTPR9 were reported, indicating the ability to accurately classifying individuals as disease stable.

In a complementary analysis, semiparametric group-based mixture models (SAS PROC TRAJ) were used to identify distinct clusters based on FVC%.[10,11] We considered models ranging from two to ten groups, with both linear and quadratic terms. Bayesian information criteria (BIC) was used to select the optimal number of groups and average posterior probabilities assessed goodness of fit. Models with group membership probabilities less than 5% were excluded from consideration. Similar analyses were employed for the secondary outcome, DLCO%. Additional secondary analyses considered associations between monocyte level and FVC% over time and between CTRP9 and monocyte level using linear mixed models as described previously. In all analyses, residual diagnostics assessed modeling assumptions. All analyses assumed a two-sided type one error rate of 0.05 and no formal adjustments were made for multiplicity, as analyses were meant to be exploratory in nature.

Results:

Stratification of CTRP9 Levels and Baseline Characteristics

The final cohort consisted of 61 patients with limited cutaneous (lcSSc) and 49 with diffuse cutaneous (dcSSc) SSc, with a mean disease duration was 9.7 (±8.5) years. The mean modified Rodnan skin score (MRSS) was 11.0 (±10.3) and FVC% predicted was 77.9 (±17.8). Demographic and clinical characteristics of the patients are shown in Table 1. Of the 110 patients, all had initial FVC% measurement, 89 had 12 months, 79 had 24 months, 74 had 36 months and 70 had 48 months follow up data. Utilizing a cutoff of ≥81.1ng/ml, 34 patients had elevated CTRP9 (31%) in baseline serum. There was no significant difference in age, smoking status, antibody profile or treatment status between the two groups. The median disease duration was shorter in the low CTRP9 group (7 vs. 11 years, p= 0.05).

Cross-sectional associations between CTRP9 and Pulmonary Function

In cross-sectional analysis, FVC% was significantly lower in the high CTRP9 group compared to low CTRP9 group at both baseline (72%±17 vs. 80%±18, p= 0.02) and 48 months (68±19 vs. 84±18, p= 0.001) (Figure 1). Similar trends were observed for DLCO% predicted, with lower means in the high CTRP9 group at both baseline and 48 months.

CTRP9 and Pulmonary Function Trajectories

In the longitudinal analysis, elevated baseline CTRP9 was associated with significantly lower FVC% (9%, on average; p= 0.01). In longitudinal analysis, the trajectories of FVC% predicted were not significantly different by group (p= 0.229). Specifically, at the study midpoint (24 months), the estimated mean FVC% predicted in the elevated CTRP9 group was 72% ±3 compared to 83% ±2 in the low CTRP9 group (Figure 2A). Model results remained consistent after adjusting for disease duration, antibody profile, and treatment status. In particular, elevated CTRP9 was associated with significantly lower FVC% in adjusted models (10%, on average, p= 0.01) Again, similar trends were seen for DLCO% predicted with higher CTRP9 associated with significantly lower DLCO% predicted over time; however, the trajectories of DLCO% predicted over time were not significantly different (Figure 2B). In sensitivity analysis, CTRP9 groups were re-categorized as detectable (N=67) and undetectable (N=43). Similar trends were observed with lower mean FVC% predicted in the detectable CTRP9 group (p-value <0.01). The model estimates were similar after adjustment for disease duration and treatment status.

With emerging trends of the association between low CTRP9 and improved lung function compared to high CTRP9, we sought to examine the ability of CTRP9 levels to predict disease stability estimated from the mixed model described above. Disease stability was defined as a decrease in FVC% < 3% in 48 months based on the published definition of minimal clinically important differences for FVC% in SSc-ILD.[12] A low baseline CTRP9 demonstrated a sensitivity of 73% and a specificity of 45% for disease stability. When examined in conjunction with anti-centromere antibody (ACA) positivity, low CTRP9 demonstrated a sensitivity of 14% and specificity of 94% for stable disease.

Semiparametric group-based mixture models

Given the heterogeneity of SSc associated ILD, we performed latent trajectory analysis to better characterize subclasses of patients based on trajectories of FVC%. Group-based trajectory modeling separated individuals into 6 distinct linear trajectory clusters, with average posterior probabilities of >85%, demonstrating good fit (Figure 2D). Group 1 represented those with the most severe lung disease, with a mean baseline FVC% of 48% and significant downward trajectory. Mean serum CTRP9 of this group was 403 ng/ml. Group 3-6, which arguably represented adequate lung function with mean FVC% >75%, all had mean serum CTRP level of <81.1 ng/ml.

Correlation with Monocyte Levels

In light of a recent study demonstrating an association between circulating monocyte level and lung fibrosis, we examined the association of CTRP9 and serial monocyte levels over time. We observed a significant interaction between CTRP9 and time, indicating changes in monocyte level over time vary for high and low CTRP9 groups (p= 0.03). Specifically, high CTRP9 was associated with increasing monocyte counts over time, while low CTRP9 was associated with a decrease in monocytes, even after controlling for disease duration and treatment status (Figure 2C). Additionally, a significant association between monocyte levels and pulmonary function was observed, with higher monocyte levels associated with lower FVC% predicted (p= 0.02). Specifically, a one unit increase in monocyte level was associated with a 6.3 unit decrease in FVC%.

Discussion:

We demonstrate an association of serum CTRP9 levels and pulmonary function in SSc. Elevated CTRP9 was associated with more severe lung disease although did not predict the trajectory of lung function over time. In latent trajectory analysis, we found low CTRP9 was associated with preserved lung function. Additionally, a significant association between CTRP9 and monocyte levels was detected. These findings suggest a potential link between adipokine CTRP9 and SSc-ILD.

Previous work demonstrated adipokines are dysregulated in SSc.[4] Given their immunomodulatory roles, there is growing interest in adipokines in SSc. Adiponectin, the best studied adipokine, has been shown to have antifibrotic effects through regulation of fibroblasts and is downregulated in SSc.[3] Leptin, another well studied adipokine, has proinflammatory effects through activation of monocytes and macrophages to release various cytokines.[13] These, along with resistin, visfatin and other more novel molecules are increasingly being implicated in SSc pathogenesis and related complications. While emerging data demonstrate adipokines are expressed in the lungs of SSc patients,[14] there has been limited work regarding adipokines and SSc-ILD.

CTRP9 is a novel adipokine and has yet to be largely studied in the SSc population. It belongs to the CTRP family, paralogs of adiponectin, with CTRP9 sharing the greatest structural similarity to adiponectin.[15] CTRP9, which is primarily expressed in adipose tissue, has been shown to have a protective role in improving insulin sensitivity, promoting lipid metabolism and attenuating cardiovascular disease.[16] Interestingly, CTRP9 serum levels are found to be upregulated in various disease models including newly diagnosed Type II diabetes, vessel atherosclerosis, and cardiac hypertrophy and heart failure.[17] Our findings concur with previous studies given CTRP9 appears elevated in SSc-ILD. While the mechanism of CTRP9 upregulation has yet to be explained, elevated levels of CTRP9 may represent an innate anti-fibrotic defense mechanism to compensate for progressive ILD.

Despite being the leading cause of morbidity and mortality in SSc, SSc-ILD remains an elusive complication with limited disease markers and interventions. In a recent large multicenter study, Scott et al. demonstrated increased monocyte count was associated with worse outcomes in ILD patients including both shortened survival and disease progression.[9] The results from this study demonstrate the association between monocyte levels and worsened pulmonary function, as previously reported. Furthermore, we found elevated CTRP9 was associated with increased monocyte level over time. The association with elevated monocytes, which are known to contribute to the pathogenesis of lung fibrosis,[18] further implicates CTRP9 in SSc-ILD.

These results demonstrate a clear link between serum CTRP9 and severity of SSc-associated ILD. Low baseline CTRP9 level appeared to predict less severe disease, and preservation of lung function over time particularly in ACA-positive patients, suggesting that low CTRP9 is a potential marker of disease stability. We did not demonstrate elevated CTRP9's ability to predict disease progression. This could be explained by the nature of retrospective data, sample size, and heterogeneity of the cohort, especially with regards to the baseline disease duration and treatment status of the samples. Development and progression of ILD in SSc is often early with a steep progression early on in disease. Since the cohort disease duration at baseline was 9 years, it is possible that a majority of patients were at the plateau of their lung disease. Future prospective studies could examine CTRP9's prognostic value at time of SSc diagnosis. Furthermore, we plan to perform future studies examining CTRP9 gene variants in SSc and examine if CTRP9 gene expression is altered in SSc-ILD.

There were both strengths and limitations to this study. We were able to apply longitudinal data to a relatively large and well characterized cohort of SSc patients. Current studies regarding adipokines as biomarkers have been largely cross-sectional studies, limiting their ability to assess prognostic significance. Given this was a single center study, the association of CTRP9 and SSc-ILD will need to be validated in independent SSc cohorts. Furthermore, as a retrospective observational cohort, our participants were heterogeneous in both treatment regimens and status of existing ILD. While we attempted to control for these variables utilizing multivariable models, residual confounding cannot be excluded.

In conclusion, variations in circulating CTRP9 in patients with SSc-ILD were associated with lung function. Elevated CTRP9 was associated with worse pulmonary function while low CTRP9 was associated with better lung function. Furthermore, we found that CTRP9 levels correlated with circulating monocyte numbers and established a clear trend between baseline CTRP9 and progression of SSc-ILD over time. Taken together, these findings support a novel role for CTRP9 as a prognostic biomarker, and potentially a therapeutic target for SSc-associated lung disease.

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Table 1. Clinical Characteristics of SSc patients

Demographic/Clinical	**Overall** (n=110)	**Low CTRP9** (n=76)	**High CTRP9** (n=34)	**P-value**
Age (years)	53.5 ± 4.5	54.0 ± 4	51.0 ± 6	0.19
Sex (%)				
Female	85 (77.3)	61 (80.3)	24 (70.6)	0.33
Male	25 (22.7)	15 (19.7)	10 (29.4)	
BMI (kg/m2)	26.1 ± 5.6	26.1 ± 5.6	26.13 ± 5.5	0.98
Race (%)				
Caucasian	84 (76.4)	55 (72.4)	29 (85.3)	0.48
African American	15 (13.6)	12 (15.8)	3 (8.8)	
Asian	2 (1.8)	1 (1.3)	1 (2.9)	
Hispanic	8 (7.3)	7 (9.2)	1 (2.9)	
Other	1 (0.9)	1 (1.3)	0 (0.0)	
Smoking Status (%)				
No	69 (62.7)	51 (67.1)	18 (52.9)	0.15
Former/Current	38 (34.6)	23 (30.3)	15 (44.1)	
Disease Duration (years)	9.0 ± 5	7.0 ± 6.5	11.0 ± 5	0.05
Antibodies (%)				
Triple Negative	26 (23.6)	21 (27.6)	5 (14.7)	0.35
Centromere	10 (9.1)	8 (10.5)	2 (5.9)	
Topoisomerase	25 (22.7)	15 (19.7)	10 (29.4)	
RNA poly	18 (16.4)	13 (17.1)	5 (14.7)	
Other	30 (27.3)	18 (23.7)	12 (35.3)	
Treatment (%)				
No	82 (74.6)	53 (69.7)	29 (85.3)	0.08
Yes	28 (25.4)	23 (30.3)	5 (14.7)	
FVC%				
Baseline	77.9 ± 17.87	80.46 ± 17.7	72.12 ± 17.23	0.02
DLCO%				
Baseline	59.98 ± 18.57	61.99 ± 19.21	55.50 ± 16.46	0.09
MRSS				
Baseline	7.0 (4.0, 19.0)	7.5 (4.0, 21.0)	7.0 (5.0, 16.0)	0.71

Figure 1.

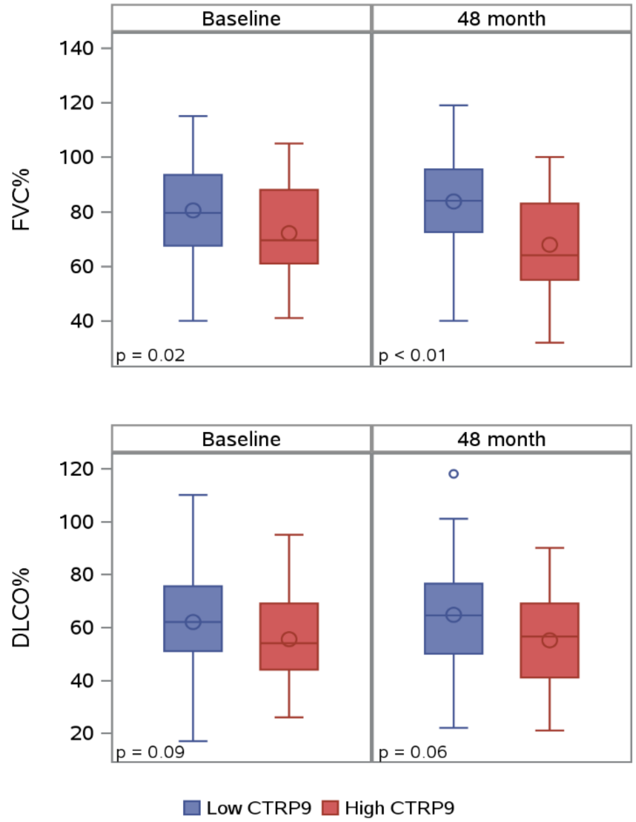

Figure 1. Association of serum CTRP9 levels in systemic sclerosis with SSc related interstitial lung disease. Top. Comparison of FVC% between groups at baseline (left) and 48 months (right). Bottom. Comparison of DLCO% between groups at baseline (left) and 48 months (right).

Figure 2.

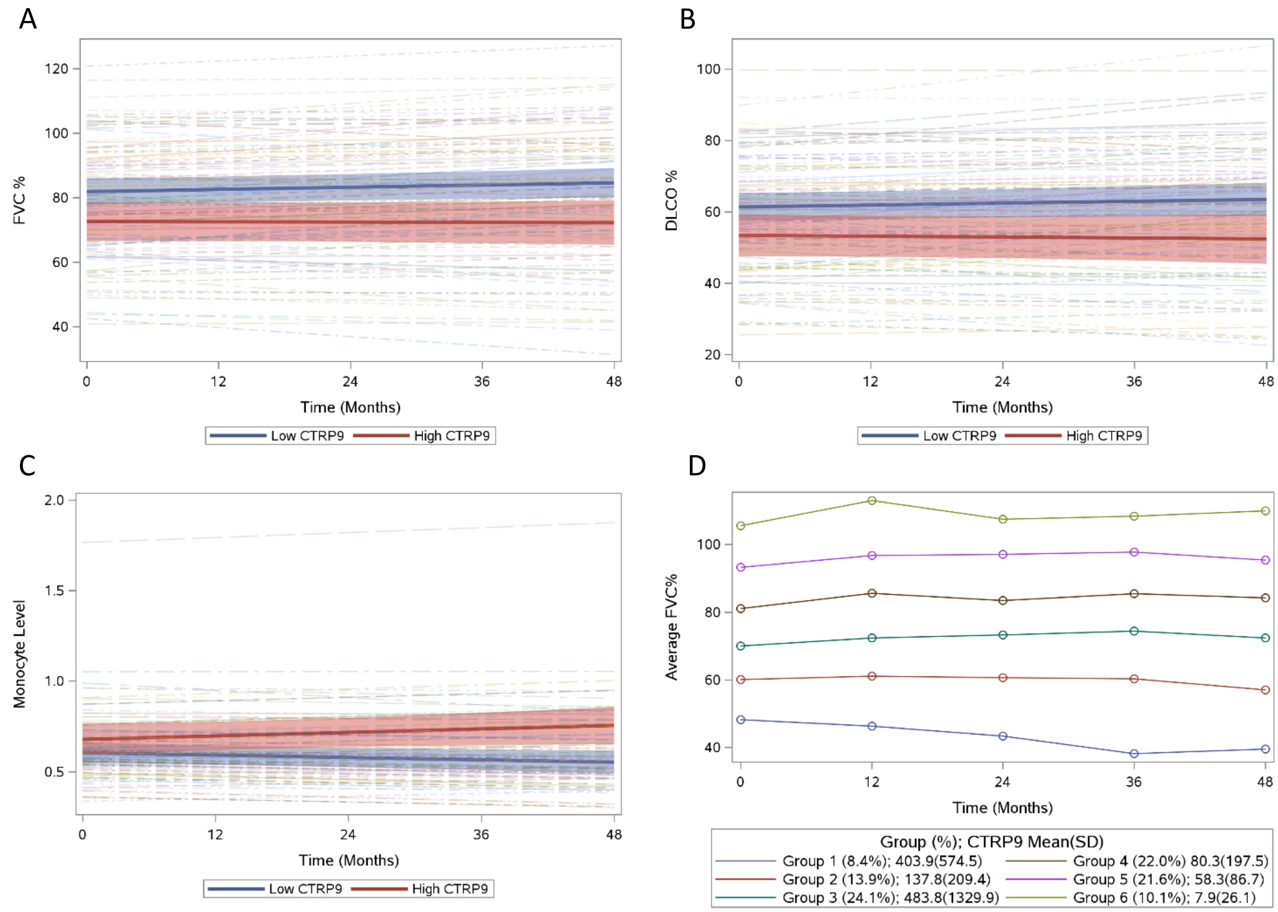

Figure 2. Observed trajectories of FVC% and DLCO% by CTRP9. The dashed multicolor lines represent each subject's predicted slope. The model estimates an average trajectory. A) FVC% over time by CTRP9 level B) DLCO% over time by CTRP9 level C) Serum monocyte level trajectories by CTRP9 level D) Latent trajectory analysis demonstrating six different groups.