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Exploring the role of serum adiponectin and its holigomerization in fibrotic interstitial lung diseases: results from a cross-sectional study

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Abstract

Intestitial lung diseases (ILDs) include a group of inflammatory and fibrotic pulmonary disorders with different etiologies which in several patients might lead to a progressive reduction of respiratory capacities and chronic respiratory failure. Nowadays, biomarkers for predicting the ILD progression and response to therapies are lacking. Adiponectin, the most abundant peptide secreted by adipocytes, has emerged as a potential response biomarker in fibrotic progressive ILDs. The aim of this observational prospective single-center cross-sectional study is therefore to verify whether serum adiponectin levels were altered in patients with fibrotic ILDs (f-ILDs) and its correlation with clinical and pulmonary function data. Sixty-four f-ILDs patients – divided in three subgroups IPF, CTD-ILDs and other f-ILDs - and 45 healthy subjects were recruited. Serum adiponectin concentration were measured by enzyme-linked immunosorbent assay (ELISA). Pulmonary function tests and clinical data were systematically collected. The results showed that patients with f-ILDs have reduced circulating levels of serum adiponectin (12.5 [10.8–15.4] versus 19.3 [17.3–20.8] $p < 0.001$). No significant difference in adiponectin levels were observed in the different f-ILDs subgroups ($p = 0.619$). Adiponectin levels were not associated with progression of f-ILDs ($p = 0.745$). High molecular weight adiponectin isoform was highly reduced in patients with f-ILDs. In patients with CTD-ILDs – but not in other subgroups – adiponectin levels were associated with pulmonary function and GAP index. These resuls support a potential role of adiponectin as diagnostic and prognostic biomarker of f-ILDs.

Keywords Interstitial lung diseases, Idiopathic pulmonary fibrosis, Connective tissue diseases, Adypokines, Adiponectin

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Introduction

Interstitial lung diseases (ILDs) encompass a large family of non-neoplastic diffuse parenchymal lung diseases, of both unknown origin – idiopathic interstitial pneumonias (IIPs) – and of known causes characterized by varying degree of pathologic changes [1]. Altough idiopathic pulmonary fibrosis (IPF) represents the prototypical progressive fibrosing ILDs (PF-ILDs), other forms of ILDs, including those associated with connective tissue diseases (CTD-ILDs), fibrotic hypersensitivity pneumonitis (fHP) or fibrotic sarcoidosis, may present similar clinical and functional decline suggesting common biological mechanisms.

It is now well recognized that adipose tissue is not merely specialized in energy storage, mechanical protection, and thermal insulation. Adipocytes indeed are also capable of producing several adipokines involved in autocrine, paracrine, and endocrine communications [2]. Among others and characterized by anti-inflammatory, antifibrotic properties and vasoprotective effects, adiponectin is considered one of the main adipokines and it has recently gained growing interest due to its regulation in the development of various metabolic conditions as well as neoplastic and non-neoplastic lung disorders [3–8]. With respect to ILDs, recent evidences suggest that adiponectin may directly affecte the intensity of immune response, the damage to the extracellular matrix as well as tissue sensitivity to other endocrine stimuli [9]. Notably, in a recent phase II trial testing the safety of a novel oral lysophosphatidic acid receptor 1 antagonist – admilparant – adiponectin showed notable rapid and stable increase in the intervention arm possible reflecting a potential role as response biomarker [10]. Nonetheless, whether serum adiponectin levels correlates with functional impairment, radiological appearance as well as prognosis in patients with different ILDs has not been completely elucidated. Therefore, in an attempt to explore the potential involvement of adiponectin also in fibrotic ILDs (f-ILDs), and to support its potential role as novel biomarker, we analyzed serum adiponectin levels in a single center in a prospective observational cross-sectional study. Furthermore, we investigated whether adiponectin levels differed in different fibrotic ILDs. Finally, we investigated the potential association between adiponectin serum concentrations and functional parameters, radiological pattern and prognostic indices of f-ILDs.

Materials and methods

Subject's recruitment

In this cross-sectional prospective observational single-center study, 64 consecutive patients were enrolled at Interstital Lung and Rare Diseases Outpatient Clinic of the Vanvitelli Respiratory Diseases Clinic, Monaldi Hospital, Naples, Italy; forty-five age and matched healthy subjects were recruited from the CEINGE. Inclusion criteria were: (1) diagnosis of IPF, according to the 2018 ATS/ERS/JRS/ALAT [11] or any other fibrotic ILD; (2) age ≥ 40 years old; (3) ability to understand and sign a written informed consent form. Exclusion criteria included: (1) current diagnosis of asthma or chronic obstructive pulmonary disease (COPD) or any history of malignancy malignancy with exeption of non-melanoma skin cancer; (2) acute ILD exacerbation in the previous 3 months; (3) presence of BMI < 18.5 or ≥ 40.

Pulmonary functional tests, other measurements and prognostic indexes

Demographic and anthropometric patients' characteristics were systematically collected including gender, smoking history, and comorbidities along with radiological data. According to the f-ILD, patients were divided in three subgroups: IPF, CTD-ILDs, Other f-ILDs. Spirometry, body plethysmography and Single-breath DLco were performed in all patients according to the 2022 American Thoracic Society and European Respiratory Society (ATS/ERS) guidelines [12], using Vyntus BODY (Vyaire Medical), Germany. The following spirometric parameters were measured: FEV1, FEV1%, FVC, FVC% FEV1/FVC, TLC, TLC%, RV, RV%, DLco, DLco%. Patients were subjected to arterial blood gas analysis (ABG) for the evaluation of the following parameters: pH, partial pressure of oxygen (pO2), partial pressure of carbon dioxide (pCO2), bicarbonates (HCO3-) and lactates. 6-minute walking test was performed according the ATS guidelines [13]. For patients with f-ILD, the Gender-Age-Physiology (GAP) index [14] and Distance-Oxygen-GAP (DO-GAP) [15] prognostic indexes were calculated. A validated Italian version of The King's Brief Interstitial Lung Disease (K-BILD) to measure the health-related quality of life (HRQOL) questionnaire was administered [16, 17].

Adiponectin measurement

Blood samples were collected after a 12-hours overnight fasting period and centrifuged. Serum aliquots were immediately frozen. The concentration of total Acrp30 in serum was measured by enzyme-linked immunosorbent assay (ELISA) method using an in a house produced polyclonal antibody designed versus the human Acrp30 amino acid region (H2N-ETTTQGPGVLLPLPKG-COOH) as previously reported [18].

Western blotting analysis

Five micrograms of total serum proteins were treated and subjected to electrophoresis as previously described [7]. The blots were developed by ECL (Amersham Biosciences, Piscataway, NJ, USA) with the use of Kodak Bio-Max Light film and digitalized with a scanner (1.200 dpi)

and analyzed by densitometry with the ImageJ software. Each serum sample was tested two times in duplicate.

Ethics, consent to participate, and consent to publish

All patients and healthy subjects were informed about the nature of the study and agreed to participate by signing an informed consent form. All the procedures were in accordance with the ethical standards of the institutional and/or national research committee and with the Helsinki declaration. The study was approved by the Ethic Committee of the University of Campania, Naples, Italy, number 43607/2022 (22th November 2022). Data were treated anonymously and consent for publication was waived as no personal data have been showed.

Statistical analysis

Categorical or qualitative variables were expressed as absolute number and percentage, whereas continuous or quantitative variables were expressed as median and inter-quartile range (IQR) after testing with Shapiro Wilk for normal distribution. The Mann-Whitney test was used to analyze differences in serum levels of adiponectin in different groups. For univariate correlations, Pearson's or Spearman coefficient were used as appropriate. A ROC curve was provided to evaluate the performance of Adiponectin as diagnostic biomarker. A p-value < 0.05 was considered statistically significant.

Results

Adiponectin levels are reduced in fibrotic ILDs patients compared to controls

Study population characteristics are reported in Table 1. Briefly, f-ILD group included 64 patients with equal gender distribution (50% males). 50% had a diagnosis of CTD-ILD, 36% had a diagnosis IPF and 13% had a diagnosis of other f-ILDs (Supplementary Fig. 1). Among the CTD-ILDs, 74% were diagnosed as Systemic Sclerosis (SSc), 20% Rheumatoid Arthritis (RA) while 3% had mixed CTD and 3% Syogren's Syndrome (SS) (Supplementary Fig. 2). In the group of the f-ILD, out of 41 non-IPF patients, 19.5% had a progressive phenotype and were diagnosed with progressive pulmonary fibrosis (PPF) according to ATS/ERS/ALAT/JRS guidelines [19]. Twenty-seven patients (42.2%) were under antifibrotic drugs (Nintedanib or Pirfenidone, 32.8% and 9.4%, respectively). Fibrotic ILD patients generally had preserved lung volumes (median FVC 81.3% IQR [67-96.5] with a median DLCO 55.4% IQR [45.7–69.0]) and Stage I (54.7%) or II (40.6%) GAP index. Serum levels of total adiponectin levels were significantly different between f-ILD patients and control subjects ($p < 0.001$); in detail, f-ILD patients showed lower levels of total adiponectin compared to the control subjects (12.5 ug/mL [10.8–15.4] *versus* 19.3 ug/mL [17.3–20.8], $p < 0.001$) (Fig. 1). To verify whether adiponectin levels could be an independent discriminative value to predict f-ILD, we performed the ROC curve analysis; the results are reported in Fig. 2. In detail, when we compared controls to f-ILD patients, we observed that at an optimal cut-off point of 16.4 µg/mL corresponded a sensitivity of 84.4% and a specificity of 85.2%, Positive Predictive Value 80.8%, Negative Predictive Value 88.14% (AUC = 0.902, p = < 0.001).

3.2 *Adiponectin expression did not differ across different fibrotic ILDs, systemic autoimmune disorders, antifibrotic users neither between progressors and non-progressors.*

When we considered the three subgroups of patients (IPF, CTD-ILDs, other f-ILDs), we found no differences in adiponectin levels (Supplementary Fig. 3; $p = 0.619$). Similarly, no differences in adiponectin levels were found among different systemic autoimmune disorders (Supplementary Fig. 4; $p = 0.913$). We did not found any difference in adiponectin expression in patients under antifibrotics ($p = 0.557$). Furthermore, we divided the f-ILD population in progressors (IPF + PPF) *versus* non progressors; adiponectin levels did not correlate with the progression of the fibrotic disease (Supplementary Fig. 5; $p = 0.745$).

Adiponectin expression according HRCT pattern

To evaluate whether adiponectin serum levels were differentially expressed in patients with usual interstitial pneumonia (UIP) HRCT pattern compared to other radiological patterns we divided the study population (UIP versus non-UIP). The UIP group consists of 23 patients with IPF (65.7%), 4 patients with f-HP (11.4%), 4 patients with RA-ILD (11.4%), 2 patients with fibrotic sarcoidosis (5.7%), and 2 patients with SSc-ILD (5.7%). The non-UIP group consists mainly of patients with SSc-ILD (75.9%), and less prevalently RA-ILD (6.9%), iNSIP (6.9%), MCTD(3.4%), DIP (3.4%), and SS (3.4%). Patients with UIP pattern had numerical lower levels of serum adiponectin though non statistically significant [12.0 ug/mL [10.2–15.1] *versus* 13.1 ug/mL [12.0–16.0], $p = 0.076$) (Supplementary Fig. 6).

Adiponectin oligomeric state

Successively, we explored whether specific adiponectin oligomeric forms (HMW, MMW, LMW) were responsible for adiponectin downregulation in f-ILD patients compared to healthy controls (Fig. 3). Levels of HMW, the most biologically active oligomers, were lower in ILD patients than in controls with no differences accrs the ILD subgroups, suggesting that the adiponectin regulation represents a functional response of the adipose tissue to the pulmonary injuries established in ILD diseases. MMW and LMW oligomers were not differently modulated in the three groups of subjects (Fig. 3).

Table 1 Study population characteristics

	Fibrotic ILDs (*n*. 64)	Controls (*n*. 45)	*p*-value
Gender (Male)	32 (50)	21 (46.7)	0.848
Age (ys)	70 [58.3–76]	62 [56–76]	0.248
Smoking Status			
Current	7 (11)		
Former	34 (53)		
Never	23 (36)		
BMI (kg/m2)	26.6 [24.1–30.5]	25.2 [24.2–26.8]	0.148
Waist circumference (cm)	90 [83–95]	90 [79–95]	0.681
Comorbidities			
Systemic Hypertension	37 (58)	.-	
Diabetes	10 (16)	.-	
Obesity	23 (36)	.-	
CAD	8 (12)	.	
Stroke	1 (1.2)	.	
Congestive Hearth Failure	2 (3)	.	
Atrial Fibrillation	3 (5)	.	
Chronic Kidney Disease	5 (8)	.	
Liver Disorders	3 (5)	.	
History of VTE	1 (2)	.	
Anxiety or Depression	11 (17.2)	.	
Allergy	7 (11)	.	
GERD	29 (45.3)	.	
ILD Group			
IPF	23 (36)		
CTD-ILDs	32 (50)		
Other fibrotic ILDs	9 (14)		
Immunomodulatory Agents			
Micofenolate mofetil	23 (36)		
Metothexate	3 (4.7)		
Azatioprine	2 (3.1)		
Tocilizumab	2 (3.1)		
Etanercept	1 (1.6)		
Abatacept	1 (1.6)		
Oral corticosteroids	4 (6.2)		
Non-IPF progressive pulmonary fibrosis	8/41 (19.5)		
Antifibrotic agents	27 (42.2)		
Nintedanib	21 (32.8)		
Pirfenidone	6 (9.4)		
Pulmonary function tests			
FEV1 (L)	2.10 [1.63–2.56]		
FEV1%	87.5 [72–102]		
FVC(L)	2.46 [1.90–3.16]		
FVC%	81.3 [67-96.5]		
FEV1/FVC%	83.8 [79.0-89.6]		
TLC (L)	4.12 [3.25–4.62]		
TLC%	71.6 [45.7–69.0]		
DLCO%	55.4 [45.7–69.0]		
FVC/DLCO	0.84 [0.79–0.90]		
K-BILD	69 [65.8–76.3]		
GAP Index	3 [2–4]		
GAP Stage			
I	35 (54.7)		
II	26 (40.6)		

Table 1 (continued)

	Fibrotic ILDs (*n.* 64)	Controls (*n.* 45)	*p*-value
III	3 (4.7)		
DO-GAP-Points	6 [3–14]		
DO-GAP-Grade			
1	29 (45.3)		
2	22 (34.4)		
3	13 (20.3)		
Adiponectin (ug/mL)	12.5 [10.8–15.4]	19.3 [17.3–20.8]	*< 0.001*

Data are presented as median [Interquartile range] or absolute number (%)

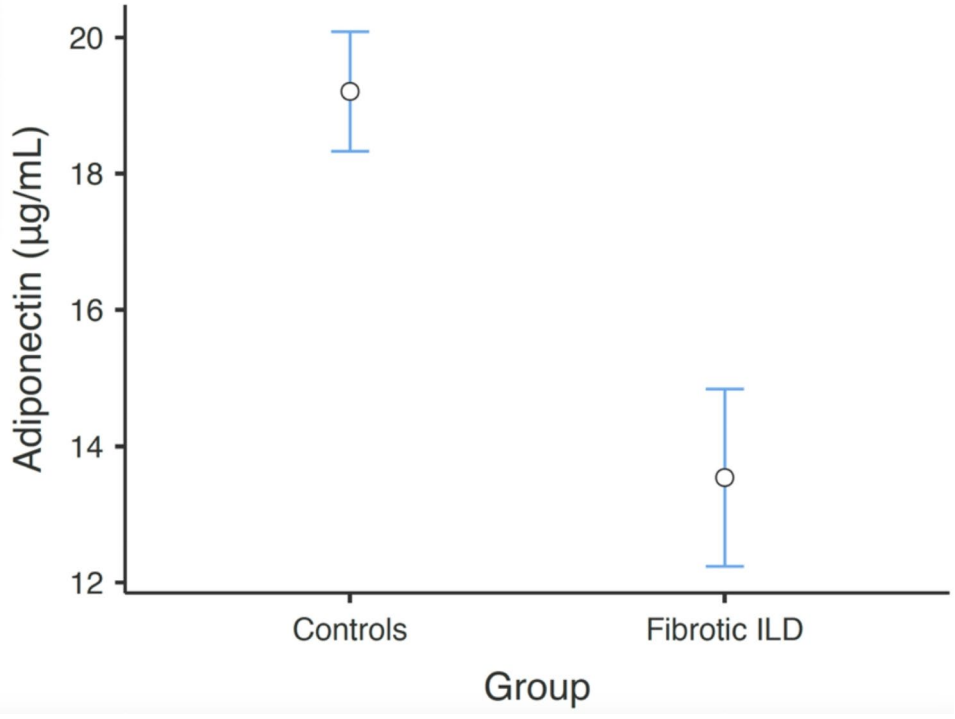

Fig. 1 Adiponectin is noticeably reduced in ILD patients compared to healthy controls (15 ug/mL [10.8–15.4] *versus* 19.3 ug/mL [17.3–20.8], $p < 0.001$)

Adiponectin is associated with functional parameters and prognostic indexes specifically only in CTD-ILDs subgroup

In the entire f-ILD population we failed to find any significant correlation between adiponectin and pulmonary function test parameters, K-BILD or prognostic indexes (Supplementary Tables 1–3). Therefore, we split the study population into the three subgroups according to fibrotic disorders. Interestingly, in the CTD-ILD subgroup, adiponectin was positively correlated with FVC% (ρ: 0.460, $p = 0.01$), DLCO% (ρ: 0.367, $p = 0.046$), TLC% (ρ:0.708, $p < 0.01$) and negatively correlated with GAP index (ρ: -0.476, $p = 0.011$) (Fig. 4).

Discussion

Little is known about the relationship among adiposity, the endocrine functions of adipose tissue and the pathogenesis of ILDs but an alteration in adipokines secretion has been suggested as possible mediators of the pro-inflammatory changes leading to interstitial lung abnormalities and fibrosis [9, 20]. In the present study focusing on adiponectin in f-ILDs, we found a strong reduction of this adipokine in serum levels in patients with ILD compared with a group of healthy controls matched for sex and age. ILDs include several subtypes which, despite being characterized by different etiologies, may share common pathogenetic pathways. In this regard, we found no differences in terms of serum adiponectin levels among the fibrotic groups in our cohort (IPF, CTD-ILDs, other f-ILDs). Furthermore, we found no correlation between adiponectin and clinical disease data in the entire population, suggesting that adiponectin may be considered a diagnostic tool but appears to be less useful as a marker for predicting disease severity and progression. In previous results of the literature, contrasting data have been reported. In SSc-ILD serum adiponectin levels were found to be decreased among subjects [21].

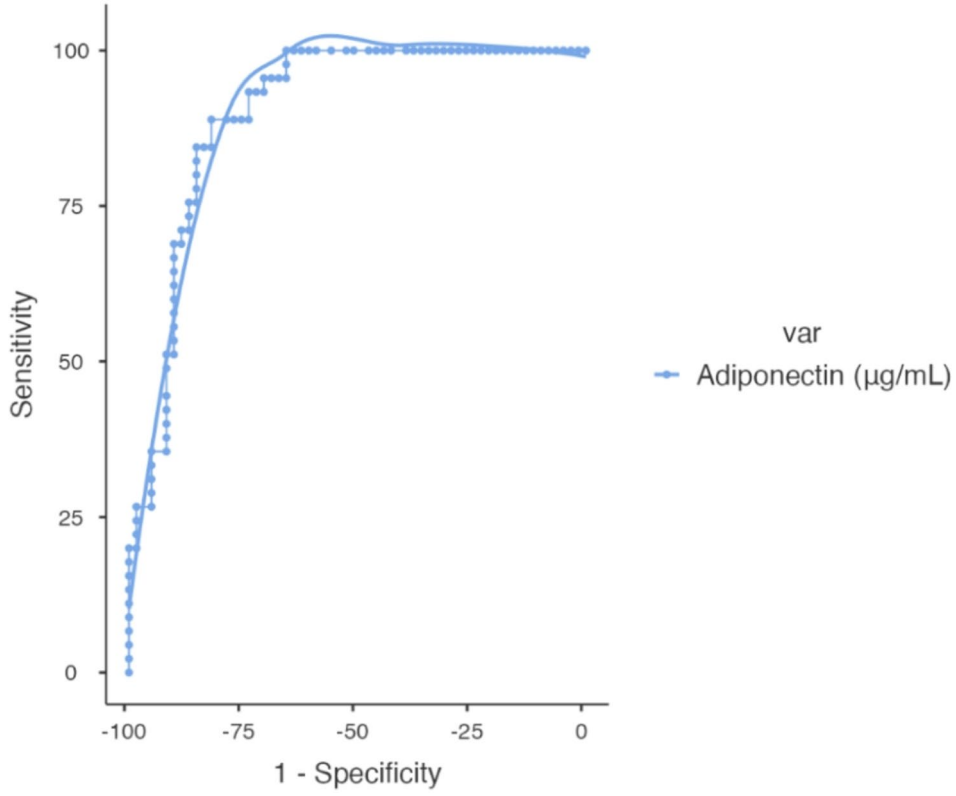

Fig. 2 ROC curve analysis for adiponectin in fibrotic-ILDs patients

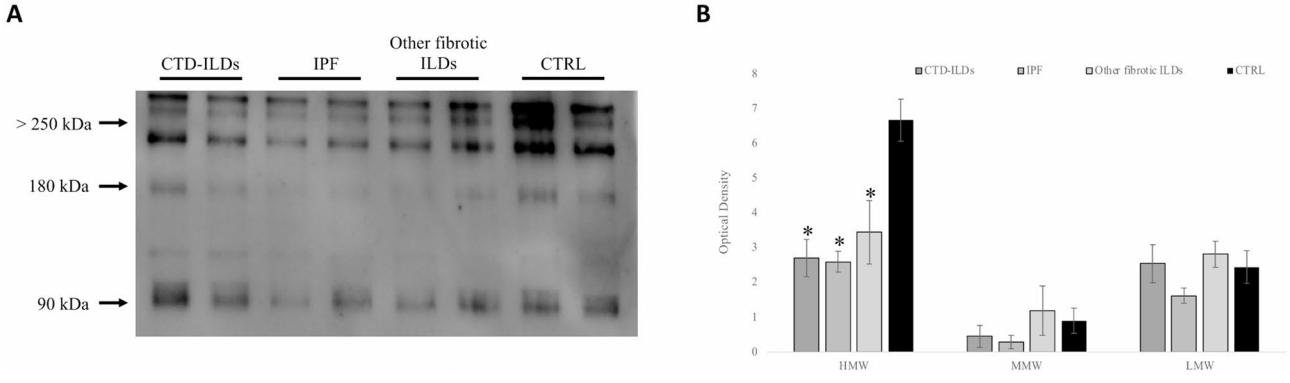

Fig. 3 Oligomeric distribution of adiponectin in the 4 studied populations: CTD-ILDs, IPF, other fibrotic ILDs, and controls. * $p < 0.05$, ** $p < 0.01$

Contrastingly, in another research investigating a broader panel of lipidic biomarkers the adiponectin and apelin levels were found higher in patients with IPF or sarcoidosis [9]. Therefore, these data are contrasting with our results documenting lower levels in patients with f-ILDs regardless the underlying disease. Likewise, interesting data emerged from other studies investigating BAL levels of adiponectin. Data from a study examining the role of lipidic biomarkers on BAL for discerning chronic hypersensitivity pneumonitis (HP) from IPF, the authors found lower levels of adiponectin, apolipoprotein A1, adipsin, apoliprotein C3 in the latter, reflecting differences in pathogenetic mechanisms [22]. Furthermore, our data suggests that adiponectin levels could be differently expressed in patients with UIP pattern when compared to other radiological patterns. UIP pattern is non specific for IPF and several other diseases might display pathology and radiological findings – including RA-ILD, f-HP, sarcoidosis, and others. We found only numernical difference and study was not powered to reach a statistically significant difference. This finding should be furthere explored as previous studies documented difference in prognosis in patients with UIP pattern (radiological or pathological) when compared to other fibrotic ILDs, irrespective from underlying disease [23, 24]. In our study population, we found any impact of antifibrotic

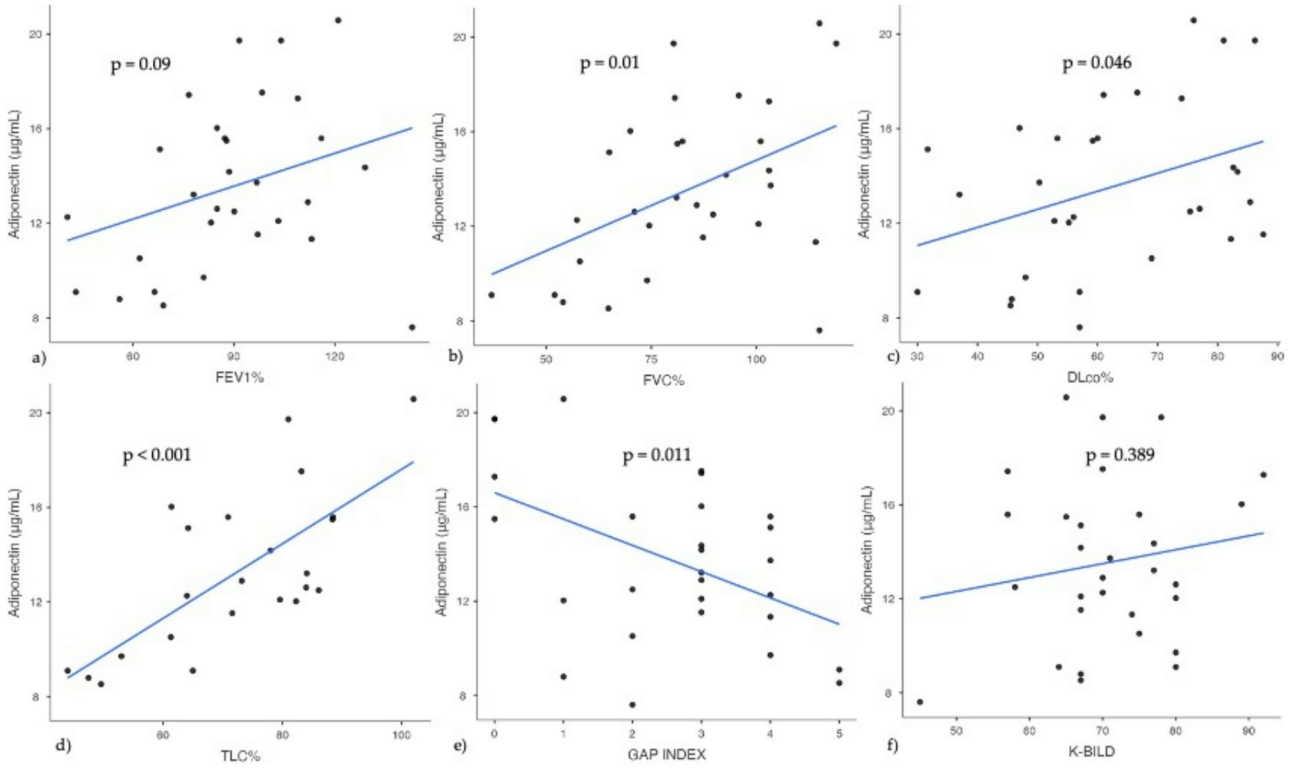

Fig. 4 Adiponectin levels showed no correlation with FEV1% (**a**) or K-BILD scores (**f**). In contrast, significant positive correlations were observed between adiponectin and FVC% (**b**), DLCO% (**c**), and TLC% (**d**). A significant negative correlation was found between adiponectin and the GAP Index (**e**)

in serum adiponectin; however, lack of longitudinal and subsequential evaluation of adiponectin represents a significant study limitation. Likewise, based on the cross-sectional study design we did not extrapolated data on immune-modulatory agents as the potential biases associated with previous treatments or the interference of different agents in combination therapies should be preplanned in further studies.

Regarding the functional parameters and the prognostic indexes, we found a significant positive correlation between adiponectin and FVC% ($p = 0.011$), DLCO% ($p = 0.046$) and TLC% ($p = 0.011$), while a negative correlation with GAP Index ($p = 0.011$) in patients with CTD-ILDs.

CTD-ILDs are typically defined by evidence of sustained, high-level lung inflammation, thought to be due to persistent immune activation. Interestingly, in these diseases the aberrant activation of inflammatory mediators appear relevant for the onset and maintenance of fibroproliferative phenomena. The molecular mechanisms driving inflammation and fibrosis in ILDs may differ depending on the disease subtype, but our data suggest that in patients belonging to the CTD-ILD subtype, adiponectin appears to be a molecule involved in disease severity, probably due to its known anti-inflammatory properties. It has in fact been demonstrated that the anti-inflammatory effects mediated by adiponectin are due to the activation of PPARγ, a key mediator involved in the fibrotic process [25, 26]. On the other hand, adiponectin-deficient mice are characterized by the spontaneous development of pulmonary endothelial activation, increased perivascular infiltration of immune cells, and increased pulmonary arterial pressure, suggesting that adiponectin expression is closely related to those pulmonary pathological processes crucial for ILDs.

To our knowledge, very few data are available about adiponectin relationship with disease severity and progression index. In line with our data, D'alessandro et al. 2020 analyzed adiponectin levels in both bronchoalveolar lavage (BAL) and serum from IPF patients at diagnosis [27]. The authors suggest that serum adiponectin levels are a useful indicator in predicting the prognosis of IPF, as they are inversely correlated with both BMI (r = -0.43, $p = 0.03$) and diffuse carbon monoxide in the lungs (DLco) percentages (r=-0.4, $p = 0.05$) [27]. Furthermore, in patients with IPF, they found a direct correlation between adiponectin levels and eosinophils in the BAL, the latter representing a negative prognostic factor in IPF ($r = 0.6$; $p = 0.019$) [27].

Our study has several limitations: a relatively low number of patients in each subgroup which limited some a profounder inferential analysis. Additionally, although we selected healthy controls BMI and age matched with patients, the presence of difference inflammatory

mediators and medications affect adiponectin levels might weaken our findings. Lastly, adding analyses on more adipokines could be useful to better define whether the regulatory mechanism observed in our study involves the endocrine function of adipose tissue; in this regard we must emphatise that adiponectin is the only adipokine expressed uniquely by adipose tissue.

In conclusion, our data further confirmed the functional crosstalk between adipose tissue and lung highlighting the specific regulation of adiponectin in f-ILDs; we can suggest that studies in larger cohorts and therefore its potential use as a diagnostic marker in this group of patients despite further of patients will clarify the potential use of adiponectin as a diagnostic tool in ILD patients. The biological role of adiponectin remains to be clarified, but the specific relationship of adiponectin with clinical parameters in CTD-ILD strongly suggests that the loss of adiponectin action on the lung epithelium influences the inflammatory and immune mechanisms underlying the onset and progression of ILD. From this perspective, it is plausible to believe that targeting adiponectin modulation in patients with f-ILDs deserves to be studied as a therapeutic target in both preclinical and clinical settings. Recently, an in vitro study by Nemeth et al. demonstrated that adiponectin-signaling via CDH13 and p38MAPKγ activation suppresses profibrotic activation of fibroblasts in the lung [28]. The down regulation of adiponectin levels we found in PF might result in a loss of suppression toward fibroblasts. Further studies deepening the possibility of targeting adiponectin may clarify wheter adiponectin reprenset a valuable marker for PF and/or pro vide therapeutic benefits in pulmonary fibrosis.

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Competing interests
The authors declare no competing interests.

Disclosures
The patients have no conflict of interest to declare with the present study. All Authors have read and approved the final version of the manuscript.

Clinical trial number
Not applicable.

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