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Increased Serum Hepatocyte Growth Factor (HGF) Levels in Patients with Idiopathic Pulmonary Fibrosis (IPF) or Progressive Sarcoidosis

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Abstract

Background: Endogenous Hepatocyte Growth Factor (HGF) is required for self-repair of injured liver, kidneys and lungs. It also exerts a regenerative effect on epithelium. HGF can inhibit both the initiation and progression of lung fibrosis in Idiopathic Pulmonary Fibrosis (IPF). However available literature data on the role of HGF in sarcoidosis are scarce and conflicting. The aim of our study was to estimate and compare the serum concentrations of HGF both in patients with IPF and sarcoidosis and in healthy controls.

Material and methods: In 43 patients with sarcoidosis, 17 patients with IPF and 20 healthy controls serum HGF concentrations were measured using multiplex bead based sandwich immunoassay.

Results: In patients with IPF mean concentrations of HGF (1286.2 ± 238.3 pg/ml) were significantly higher than in controls (819.8 ± 61.0 pg/ml, $p<0.05$), but not significantly higher than in sarcoidosis patients (990.0 ± 52.2 pg/ml). In all patients with sarcoidosis the mean levels of HGF did not differ significantly from levels obtained in control group. However, the mean levels of HGF in 18 patients with progressive sarcoidosis (1260.7 ± 83.7 pg/ml) were significantly higher ($p<0.001$) than in 25 patients with non-active, stable sarcoidosis (802.7 ± 34.8 pg/ml) and controls ($p<0.05$).

Conclusion: The role of serum HGF as a potential biomarker in sarcoidosis needs further explorations to answer the question if increased HGF serum levels can predict deterioration of the disease or reflect lung epithelial injury by granulomatous inflammation.

Keywords: Hepatocyte Growth Factor (HGF); Sarcoidosis; Idiopathic Pulmonary Fibrosis (IPF)

Introduction

It has been 30 years since Hepatocyte Growth Factor (HGF) was first discovered as a mitogen of adult rat hepatocytes after partial hepatectomy [1]. HGF, a heat-labile protein, is a dimeric molecule with an alpha-subunit (69 kDa) and a beta-subunit (34 kDa) linked by a disulfide bond [2]. HGF is the product of mesenchymal cells (e.g. fibroblasts and macrophages), and stimulates epithelial cell proliferation, motility, morphogenesis, and angiogenesis in various organs via tyrosine phosphorylation of its receptor, c-Met. HGF is secreted as a single chain (pro-HGF) biologically inert precursor. In certain conditions (eg, tissue damage), pro-HGF is converted to its bioactive form, which is comprised of alpha- and beta- chains [3]. Endogenous HGF is required for self-repair of injured liver, kidneys, and lungs. It also exerts a protective effect on epithelial and non-epithelial organs via anti-apoptotic and anti-inflammatory signals [2,3].

Results from rodent studies demonstrated that HGF exerted an anti-fibrotic effect in bleomycin-induced lung injury [4], induced apoptosis in myofibroblasts, and suppressed vascular medial hyperplasia and matrix accumulation in advanced pulmonary hypertension [5]. Hence, HGF can inhibit the initiation and spread of lung fibrosis in some interstitial lung diseases, mainly in IPF [6].

The interstitial lung diseases include sarcoidosis and Idiopathic Pulmonary Fibrosis (IPF). In IPF, tissue damage and exuberant repair with abnormal wound-healing response severely disrupt the pulmonary architecture [6,7]. Among the lung architectural changes are loss of cells (alveolar epithelial and endothelial cells), persistent production of activated fibroblasts or myofibroblasts, and widespread changes in the extracellular matrix [6,7]. Features of sarcoidosis include noncaseating epithelioid cell granulomas and the amassing of CD4-T cells and macrophages at inflammation sites [8,9]. In sarcoidosis, immune and inflammatory cells produce various cytokines that can promote proliferation of fibroblasts and deposit matrix proteins, primarily fibronectin and collagen [9]. Dendritic cells, which function as antigen-presenting cells, possess a chief role in the immunology of sarcoidosis [10]. HGF, both in vivo and in vitro, can suppress dendritic cell function, e.g. antigen-presenting capacity, and thereby down-regulate antigen-induced Th1- and Th2-type immune responses [11].

Yet available literature data on the role of HGF in sarcoidosis are scarce and conflicting [12-14]. Some studies indicated increased production and BAL fluid concentrations of HGF [12-14] and suggested it had a protective anti-fibrotic effect [14], but other authors [13] questioned the role of HGF as a potential biomarker in sarcoidosis. Therefore, we sought to estimate and compare the serum concentrations of HGF in patients with IPF and sarcoidosis and in healthy controls.

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Material and Methods

Forty three non-smoking patients with sarcoidosis and 17 patients with IPF were enrolled in the study. Patient recruitment with blood serum collection had been completed in 14 months – February 2012 till March 2013. Sarcoidosis was histologically proven according to ATS criteria [8] (i.e. by demonstration of noncaseating granulomas in tissue samples obtained by transbronchial lung biopsy, lymph node scale biopsy, mediastinoscopy, or bronchial biopsy). Only patients with clinical stages I - III were included into the study. Sarcoidosis stage I is featured by hilar lymph nodes enlargement, stage II by concomitant hilar lymphadenopathy and pulmonary infiltrates, whereas in stage III on chest X-ray only pulmonary infiltrates are visible.

Eleven patients had stage I, 20 patients had stage II, and 12 patients had stage III disease [8]. Among patients with sarcoidosis, 18 subjects had progressive disease, i.e. progressive lymphadenopathy or interstitial infiltrates with or without deterioration of pulmonary function tests (at least FVC or FEV_1 decline above 10% during 3 month period before study enrollment). None of the patients with sarcoidosis had Löffgren syndrome.

Seventeen patients with IPF were diagnosed according to ATS criteria [7] (using the HRCT and/or lung biopsy). The mean disease duration since diagnosis was 3.5 years (0.5-6 years) for sarcoidosis and 1.2 year (0.5-3 years) for IPF. No study participant was taking oral corticosteroids or immunosuppressive drugs at the time of study enrollment. None of the patients or controls suffered from chronic liver or kidney disease; all participants were free from infections for at least three months before blood sample collection.

All patients were routinely controlled in out-patient clinic at the Department of Pneumonology and Tuberculosis, Medical University of Silesia and underwent radiological and spirometric examinations. Spirometry was performed using PULM -Test 1000 spirometer (Krakow, Poland) according to ATS/ERS criteria [15] and the results were expressed as percent of predicted values [16]. Twenty healthy non-smoking volunteers matched for sex, age, and BMI to sarcoid group served as controls.

All subjects provided written informed consent and the study was approved by local ethical committee.

Serum levels of Hepatocyte Growth Factor (HGF) were measured in duplicate (the mean value from 2 measurements was derived) using commercially available multiplex bead-based sandwich immunoassay kits (Human Angiogenesis 9-Plex Panel, Bio-Rad Laboratories) [17].

All assays were performed according to manufacturer's instructions. The system allowed simultaneous identification of 9 different molecules in a 96-well filter plate. We used 9 different sets of fluorescent dyed beads with capture monoclonal antibodies specific for each molecule to be analyzed. The appropriate molecule standards (50 µl/well) and samples diluted (50 µl/well) in plasma diluents were added to a 96-well filter plate and incubated for 30 min at room temperature. After 3 washes, premixed streptavidin/phycoerythrin was added to each well and incubated for 10 min followed by 3 additional washes. Beads were resuspended with 125 µl of assay buffer, and the molecule reaction mixture was quantified via the Bio-Plex protein array reader. Data analysis was performed using the Bio-Plex Manager software version 4.1.1. (Bio-Rad Laboratories). Values with a coefficient of variation over 12% were discarded before final data analysis. The concentration (pg/mL) of different analytes in the plasma samples were identified using standard curves from multiplex assays. The minimum level of detection for HGF was 3.08 pg/mL.

Statistical analysis was conducted using Statistica 6.0 software (StatSoft Inc., Tulsa, OK). Normal data distribution was assessed using Shapiro-Wilk test. Homogeneity of variance was evaluated using Levene's test. Comparisons between the study groups were performed using the ANOVA, Mann-Whitney or Kruskal-Wallis test, if the distribution of data was abnormal. Correlations were analyzed by Spearman's test. All results were statistically significant if $p<0.05$.

Results

Demographic data, spirometric parameters and HGF concentrations in IPF and sarcoid patients are presented in Tables 1 and 2.

Examined IPF patients were significantly older and had significantly lower values of spirometric parameters (i.e. FEV1 and FVC) than patients with sarcoidosis. The highest concentrations of HGF were noticed in IPF patients. In patients with IPF the mean concentrations of HGF (1286.2 ± 238.3 pg/ml) were significantly higher vs controls (819.8 ± 60.9 pg/ml, $p<0.05$), but not significantly higher than in sarcoidosis patients (990.0 ± 52.2 pg/ml). In all patients with sarcoidosis, the mean levels of HGF did not differ significantly from levels obtained in the control group. However, the mean levels of HGF in patients with progressive sarcoidosis (1260.7 ± 83.7 pg/ml) were significantly higher ($p<0.001$) than in patients with non-active, stable sarcoidosis (802.7 ± 34.8 pg /ml) and controls ($p<0.05$) (Table 2). The concentrations of HGF were not significantly different among patients with stage I, II, and III of sarcoidosis. Similar values of FEV_1, FVC, and FEV_1% were observed in patients with progressive and non-active, stable disease and in stage I, II, and III disease. Negative relationships were observed between HGF values and FVC ($r = -0.51$, $p<0.05$) in patients with IPF. In patients with sarcoidosis no significant correlations between HGF and FVC ($r = -0.11$, $p=0.51$) or FEV_1 ($r = -0.14$, $p=0.37$) were found. In

	Controls N=20 (10 F,10 M)	IPF N=17 (7 F, 10 M)	Sarcoidosis total N=43 (20 F, 23 M)
Age (years) (mean ± SEM) Median (Interquartile range)	34.3 ± 1.2 33.5 (29.5 – 37.5)	58.3 ± 1.6 *** 58.0 (53.7 – 64.0)	35.7 ± 1.3 33.5 (29.5 – 40.0)
FEV1 (% of predicted) (mean SEM) Median (Interquartile range)		67.9 ± 2.3 +++ 69.0 (61.0 – 77.3)	86.1 ± 1.6 85.5 (81.0 – 93.0)
FVC (% of predicted) (mean ± SEM Median (Interquartile range)		70.3 ± 1.8 +++ 69.0 (63.5 – 79.0)	96.2 ± 2.1 98.0 (88.5 – 104.0)
FEV1%VC (%) (mean ± SEM) Median (Interquartile range)		77.0 ±1.8 76 (73.5 – 82.3)	75.7 1.0 75.0 (71.0 – 80.0)
HGF pg/ml Mean ± SEM Median (Interquartile range)	819.8 ± 60.9 819.5 (585.0 – 1093.0)	1286.2 ± 238.3 * 1000.0 (782.3 – 1252.0)	990.0 ± 52.2 941.5 (706.5 – 1172.5)

F-females M- males
*p<0.05 IPF vs controls (Mann-Whitheny test) +++ p<0.001 IPF vs sarcoidosis
***p<0.001 IPF vs controls and sarcoidosis

Table 1: Age, spirometric parameters and corresponding serum concentration of Hepatocyte Growth Factor (HGF) in patients with sarcoidosis or Idiopathic Pulmonary Fibrosis (IPF).

	Progressive sarcoidosis n=18	Non active sarcoidosis n=25	Sarcoidosis Stage I n=11	Sarcoidosis Stage II n=20	Sarcoidosis Stage II n=20
Age (years) (mean ± SEM) Median (Interquartile range)	35.1 ±1.9 32.5 (30.0 – 40.0)	36.2 ± 1.7 34.0 (29.0 – 40.0)	30.3 ± 1.5 29.0 (29.0 – 30.8)	35.7 ± 1.9 33.5 (30.5 – 39.0)	40.3 ± 2.3 40.0 (33.5 – 44.3)
FEV1 (% of predicted) (mean SEM) Median (Interquartile range)	87.1 ± 2.0 84.0 (81.0 – 92.0)	85.4 ± 2.4 87.0 (80.0 – 94.0)	87.7 ± 2.7 90.0 (82.8 – 101.0)	87.2 ± 1.8 85.0 (80.5 – 97.3)	83.1 ± 4.3 85.0 (81.0 – 91.5)
FVC (% of predicted) (mean ± SEM Median (Interquartile range)	96.8 ± 3.4 95.0 (88.0 – 108.0)	95.9 ±2.7 98.0(91.0 – 103.0)	100.2 ± 3.7100.0 (96.0 – 105.5)	97.6 ± 2.8 100.0 (89.5 – 104.0)	90.7 ± 4.6 90.0 (82.8 – 101.0)
FEV1%VC (%) (mean ±SEM) Median (Interquartile range)	75.6 ± 1.8 74.5 (70.0 - 82.0)	75.7 ± 1.2 75.5 (71.0 – 79.0)	77.0 ± 1.8 77.0 (74.0 – 80.0)	74.8 ± 1.5 74.0 (70.5 – 77.5)	75.8 ± 2.2 75.0 (68.8 – 83.5)
HGF pg/ml Mean± SEM Median (Interquartile range)	1260.7 ± 83.7 1204.0 (1054.0 – 1436.0) ***	802.7 ± 34.8 744.5 (677.0 – 935.0)	1105.4 ± 101.8 974.0 (914.0 – 1215.5)	947.5 ± 67.0 909.0 (694.5 – 1132.0)	958.0 ± 116.6 754.0 (690.5 – 1227.5)

*** p<0.001 progressive vs stable, non-active sarcoidosis

Table 2: Spirometric parameters and Hepatocyte Growth Factor (HGF) concentrations in progressive or non-active sarcoidosis assigned to clinical stages.

all examined patients no relationship between HGF levels and age was observed.

Discussion

We believe that this is the first study to show that serum levels of HGF in patients with progressive sarcoidosis, i.e. with radiological deterioration, were significantly higher than in patients with non-active, stable sarcoidosis. Results from our study also showed that mean concentrations of HGF were significantly higher in IPF compared with healthy controls, and there was a significant negative relationship between HGF and FVC in IPF patients.

None of our examined patients with sarcoidosis had Loffgren syndrome, which is associated with good prognosis [8,9]. We selected patients with evident radiological and functional deterioration. So we can speculate that HGF serum levels reflects the extent of epithelial damage; higher concentrations should have been expected in patients with extensive parenchymal involvement and worse LFT results, because HGF is a molecule necessary for effective epithelial healing.

The role of HGF in repair of lung tissue is well known. The regeneration of lung epithelium and endothelium is necessary for repair of injured tissue. HGF mRNA levels are elevated following injury in damaged lung tissue [18]. Post acute lung injury in rodents, HGF mRNA and protein levels apparently increase within 24 hours [18], and exogenous HGF administration enhanced mitogenesis occurs in the lung airways and alveoli [19]. In addition, alveolar repair in rats after transient lung ischemia was associated with increased HGF production [20].

Increased plasma HGF level results in a systemic exposure of numerous organs to circulating HGF; however, HGF accumulated primarily in injured organs. Thus, intact organs can escape c-Met activation by blood HGF, and this may be due to the fact that no tissue repair is needed, although the molecular basis for this phenomenon remains unclear [2].

Yamanouchi et al. [21] reported elevated serum and BAL fluid levels of HGF in IPF patients [21]. HGF levels in sera correlated significantly with elastase levels and C-reactive protein and correlated negatively with PaO_2. Levels of HGF in sera were significantly higher in smokers with pulmonary fibrosis compared with non-smokers. Our study group and controls contained only non-smoking subjects.

Sakai et al. [12] found elevated HGF levels in BAL fluid both in IPF and sarcoidosis. Immunohistochemical evaluation demonstrated that hyperplastic alveolar-type epithelial cells and pulmonary macrophages were strongly stained with anti-HGF antibody in tissues of IPF patients. These findings suggest that increased HGF concentrations in patients' peripheral air spaces are due to augmented HGF production by alveolar macrophages and alveolar epithelial cells. These researchers [12] suggested that HGF, through a paracrine mechanism, may possess a key role in healing inflammatory lung damage in pulmonary fibrosis. Higashio et al. [22] found that human lung fibroblasts secrete Tumor Cytotoxic Factor (TCF) that is molecularly identical to HGF. However, production and activation of HGF may be reduced in fibroblasts in IPF secondary to a defect in prostaglandin E2 secretion [23,24]. Crestani et al. [25] found that alveolar neutrophils may be an additional source of HGF in patients with IPF.

Recently, Piotrowski et al. [13] detected HGF in BAL fluid and exhaled breath condensate in 100% and 56% of patients with pulmonary sarcoidosis, respectively. However, HGF concentrations did not differentiate sarcoidosis patients from healthy subjects and did not correlate with disease activity, radiologic stage, LFTs, disease duration, and prognostic markers.

More recently, Faehling et al. [14] found elevated HGF levels in BAL fluid only in patients with active sarcoidosis. Through a pulmonary fibroblast model, these researchers demonstrated that HGF prevented TGF-beta-induced matrix deposition and TGF-beta-induced transdifferentiation of fibroblasts into myofibroblasts [14].

We applied the same method as Riccieri et al. [7] and detected a significant increase in plasma levels of HGF in patients with active systemic sclerosis compared with healthy controls. These findings suggest a potential role of HGF as an additional serum marker in systemic sclerosis.

Serum concentrations of HGF significantly increase during lung-transplant rejection, indicating the potential role of HGF as a biomarker for graft rejection in lung transplantation [26]. After treatment with steroids, HGF concentrations decreased to near preoperative values within 3 days [26]. None of our examined patients received steroid or immunosuppressive therapy at time of blood collection for HGF estimation.

In our opinion, the role of serum HGF as a potential biomarker in sarcoidosis requires further evaluation, and serial measurements are recommended to answer the question whether increased serum level of HGF can accurately predict a deterioration of the disease or only

accompanies disease progression, reflecting lung epithelial injury by granulomatous inflammation.

Since exacerbation in both illnesses is associated with considerable lung tissue remodeling, one may conclude that the serum level of HGF may serve as a marker of sarcoidosis progression in clinical stages I – III and IPF severity.

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