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# Serum Insulin-like Growth Factor Binding Protein 2 (IGFBP2) as a marker of Idiopathic Pulmonary Fibrosis

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## 1. BACKGROUND

Idiopathic pulmonary fibrosis (IPF) is a rare parenchymal lung disease characterized by a chronic progressive interstitial fibrosis which has a worse prognosis than other forms of chronic interstitial pneumonia. The median survival time is about 2-3 years from diagnosis and varies from a few months to several years. Natural history of IPF is unpredictable and the course of disease can be highly variable. An early and accurate diagnosis of IPF is important to enable the initiation of specific therapies to reduce disease progression. Establishing the diagnosis of IPF remains challenging; therefore international guidelines advocate the importance of a multidisciplinary team in the initial assessment of patients with suspected IPF. Many biomarkers have been studied to solve this without real success.

## 2. AIMS OF THE STUDY

The aim of this study was to evaluate surrogate new biomarkers by comparing their levels in serum and induced from patients with IPF, other fibrosis of known origin, COPD (chronic obstructive pulmonary disease) and healthy subjects.

## 3. METHODS

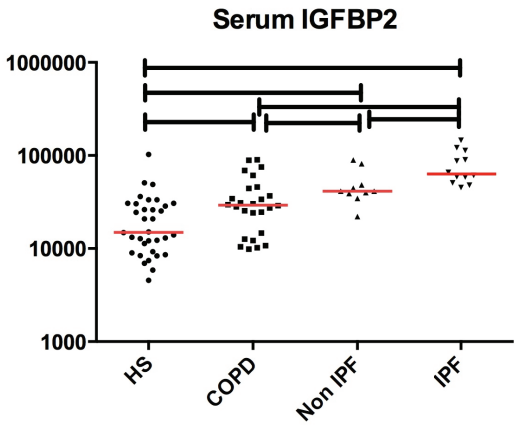
We analysed the serum and the induced sputum of 100 patients divided in 4 groups. The first group was the control group with healthy subjects (n=39). The second was a group of COPD (n=25) diagnosed according to the 2014 GOLD recommendation. The third group was the IPF group (n=17). The diagnosis of this group was made following the international recommendation of the ATS (1) using the pulmonary function tests, the chest-CT, the bronchoalveolar lavage (when available), the biopsy (when available) and the disease history. All cases were discussed in our multidisciplinary team composed of pulmonologists, rehabilitation specialised pulmonologists, rheumatologists, radiologists, pathologists, a work related disease doctor and an immunologist. Only one patient was already treated with a specific IPF therapy (pirfenidone). The last group was the non-IPF group (n=19) composed of multiples interstitial lung diseases at different time of their evolution without taking in consideration the received treatment (also discussed in our multidisciplinary team). This included NSIP (non specific interstitial pneumonia) (n=4), sarcoidosis (n=6), hypersensitivity pneumonitis (n=1), connective tissue disease (n=5), anthracosilicosis (n=1), and others of unknown origin (n=2).

Venous blood was collected in Vacutainer tubes from an antecubital site. Blood cell values included hemoglobin, platelet count, WBC count, and the differential leukocyte count, fibrinogen and C-reactive protein (CRP) levels were determined by the routine hospital laboratory.
Sputum induction and processing were performed according to a technique used in routine in our asthma clinic (2), and a differential leukocyte count was obtained using a cytospin stained with Rapi Diff II (Atom Scientific, Manchester UK) on 500 non squamous cells.
We analysed several biomarkers assumed to be critical growth factors by commercially available immunoassays (ELISA) in blood and sputum: TGFβ, IGF1 (Insulin-like growth factor), IGF2, IGFBP1 (Insulin-like growth factor binding protein), IGFBP2, IGFBP3 and IL-8.

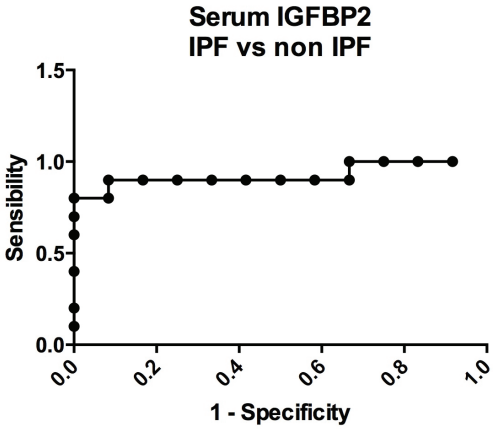
## 4. RESULTS

Serum, but not sputum, IGFBP2 levels are significantly higher in the IPF group and the non IPF group than in healthy subjects ($p<0.01$) (Table 1, Graph 1). This is not linked with a high level of IGF1 or IGF2 meaning that this is not an IGF mediated phenomenon. Serum IGFBP2 in IPF was not correlated with levels of IGFBP2 in induced sputum. The ratio IGF2/IGFBP2 in the serum of IPF patients strongly correlated with the severity of the disease assessed by FVC($r=0,8144$; $p<0,05$). The ROC curve analysis (Graph 2) showed that IGFBP2 in serum could be discriminant between the IPF group an non IPF group with a sensitivity of 92% and a specificity of 90% (Area under ROC curve: 0.91) with the best cutpoint at 49 ng/ml.

### GRAPH 1




### GRAPH 2




### Table 1

| Level in serum | | | | |
|---|---|---|---|---|
| | Healthy subjects | COPD | IPF | Non IPF |
| | nb = 31 | nb = 25 | nb = 7 | nb = 9 |
| tgf-beta (pg/ml) | 27195,5(6069,6) | 26591,3(8686,5) | 25024,1(7438,6) | 28041,4(8856) |
| IL-8 (pg/ml) | 4,4(1-37,7) | 2,9(0-18,1) | 6,8(4,3-27,4) | 8,8(4,5-57,6) |
| igfbp-1 (pg/ml) | 8(0,1-179,6) | 9,4(1,7-195,6) | 31,6(3,5-110,2) | 13,7(4,2-30,6) |
| igfbp-2 (ng/ml) | 15(4,6-102,8) | 29,3(9,9-89,8) | 73,7(48-145,6) | 41,3(22,1-89,2) |
| igfbp-3 (ng/ml) | 32(18,6-63) | 28,7(16-48,4) | 39(20,3-60,6) | 34(27,5-73,4) |
| igf-1 ((ng/ml) | 68,7(33,2-196,5) | 52,1(18,6-199,8) | 44,4(0-108,8) | 78,6(25-117,4) |
| igf-2 (ng/ml) | 1084(668-4258,6) | 1568(516-7895,7) | 1405,5(400-3131,8) | 1128,8(740-3175,9) |
| ratio igf2/igfbp1 | 187,5(12,2-21652,3) | 158,9(8,2-5470,4) | 55,7(5-432,5) | 162,7(48,6-994) |


| | | | | |
|---|---|---|---|---|
| ratio igf2/igfbp2 | 110,6(18,9-522,4) | 105,6(18-865,1) | 21,9(6,8-58,2) | 44,3(22,6-106,4) |
| ratio igf2/igfbp3 | 51,4(18,7-220,9) | 133(37,9-317,5) | 46,6(14,6-136,9) | 48,3(31,1-137) |
| ratio igf1/igfbp1 | 9,9(0,7-1611,8) | 3,8(0,2-112,6) | 1,5(0-24) | 5,8(1,8-36,1) |
| ratio igf1/igfbp2 | 5,067(1,368-34,008) | 1,844(0,517-17,808) | 0,666(0-1,756) | 2,432(0,704-3,756) |
| ratio igf1/igfbp3 | 2,8(1,076-4,695) | 2,69(1,44-6,536) | 1,513(0-3,549) | 2,401(0,971-4,981) |
| résults are expressed en médian (min-max) | | | | |

## 5. CONCLUSION

Serum IGFBP2 could be a new interesting discriminant biomarker to identify and grade the severity of idiopathic pulmonary fibrosis. This observation is highly interesting and could lead to a new diagnostic algorithm.