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Preliminary study of the anabolic/catabolic balance in patients with interstitial pulmonary fibrosis ☆

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ABSTRACT

Rationale: Idiopathic pulmonary fibrosis (IPF) is a specific form of chronic, progressively fibrosing idiopathic interstitial pneumonias (IIP), as the disease progress, patients become severely limited in their activity. Hypoxemia is a common finding in IPF and may influence skeletal muscles homeostasis in several ways by decreasing anabolic hormone level [insulin like growth factor-1 (ILGF-1)] with as opposite effect on pro inflammatory cytokines as interleukin-6 (IL-6). It has been speculated that peripheral muscle force is inversely related to IL-6 and disturbed systemic levels of ILGF-1 may be important in the development of muscle weakness.

Objectives: To assess the metabolic disturbance and its reflection on the muscular state in IPF patients.

Methods: The muscular state was assisted in 22 newly diagnosed IPF patients (not on steroids) (group 1) and 22 previously diagnosed IPF patients (on steroids) (group 2) by anthropometric measurements [Mid-thigh cross sectional area (MTCSA) and Mid- arm cross sectional area (MAC)], Body Mass Index (BMI) and measurements of serum levels of ILGF-1 and IL-6 by ELISA. Twenty two healthy subjects were selected as control (group 3).

Results: There were no significant difference between the three groups as regards BMI, MTCSA and MAC. However, there was a highly significant decrease in the mean of serum IGF-1 level of group 1 in comparison to the control group ($P < 0.001$). As regards, the mean of the serum IL-6 level there was no significant difference between the three groups.

Conclusions: The metabolic disturbance as regards the anabolic hormone level IGF-1 was the most affected in comparison to the other parameters.

Introduction

Idiopathic pulmonary fibrosis IPF is defined as a specific form of chronic, progressive fibrosing idiopathic interstitial pneumonias IIPs of unknown cause, occurring primarily in older adults, limited to the lungs, and associated with the histopathologic and/or radiologic pattern of usual interstitial pneumonia (UIP). The definition of IPF requires the exclusion of other forms of interstitial pneumonias including other idiopathic interstitial pneumonias and interstitial lung diseases ILD associated with environmental exposure, medication, or systemic disease [1].

In 2013, the American Thoracic Society/European Respiratory Society produced a statement to update the International Multidisciplinary Classification of the Idiopathic Interstitial Pneumonias. The major IIPs are grouped into chronic fibrosing (idiopathic pulmonary fibrosis [IPF] and idiopathic nonspecific interstitial pneumonia [NSIP]), smoking-related (respiratory bronchiolitis–interstitial lung disease) [RB-ILD] and desquamative interstitial pneumonia [DIP], and acute/subacute IIPs (cryptogenic organizing pneumonia [COP] and acute interstitial pneumonia [AIP]) [2].

As the disease progresses, the IPF patients become severely limited in their activity. The limitation is perceived to be due to exertional dyspnea, secondary to the lung dysfunction [3]. Moreover, hypoxemia is a common finding in IPF and may influence skeletal muscles homeostasis in several ways as it does in healthy individuals exposed to hypoxic environments references [4]. Hypoxemia may contribute to muscle wasting in IPF patients by decreasing

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anabolic hormone levels and opposite effect on pro-inflammatory cytokines. Overall hypoxemia may contribute to muscle wasting by displacing balance between anabolic /catabolic factors in favor of the latter [4,5].

Pro-inflammatory cytokines as interleukin-6 (IL-6) can exert a suppressive action on insulin like growth factor-1 (ILGF-1) hormone by upregulating the expression of its circulatory inhibitor insulin like growth factor binding protein-1 [6]. It has been speculated that peripheral muscle force is inversely related to IL-6 [7,8]. Also, disturbed systemic levels of ILGF-1 may be important in the development of muscle weakness [9].

Chronic obstructive pulmonary disease COPD is the most commonly studied lung disease in terms of impaired skeletal muscle function (muscle weakness, muscle wasting and/or exercise limitation) [10–13]. Although the mechanism of limitation of the muscular state in COPD patients is multifactorial, however; the anabolic/catabolic imbalance is considered to be an important factor that can contribute to skeletal muscle dysfunction [14,15]. Impaired skeletal muscle function is also observed in patients with chronic heart failure [16,17].

Limited data are available to date about the anabolic/ catabolic balance in IPF patients. Therefore, the objective of our study was to assess the metabolic disturbance and its reflection on the muscle state in IPF patients.

Subjects and methods

Study design

This study was conducted in the Chest Diseases Department in collaboration with the Chemical Pathology Department at Kasr El Ainy Hospital, Cairo University during the period between May 2015 and April 2016. It included 22 newly diagnosed IPF patients (they didn't receive steroids before) [group 1], 22 previously diagnosed IPF patients (they were on steroids) [group 2] and 22 healthy subjects as a control group [group 3]. All IPF patients were diagnosed using the diagnostic criteria in the official ATS/ERS consensus statement [2]. Surgical lung biopsies were performed in 10 patients, and pathologic diagnosis of IPF was also based on the consensus statement [2]. Chest high-resolution CT (HRCT) showed typical manifestations of IPF in all patients [1,2]. Patients were excluded if they had any of the following: concomitant pleuropulmonary disease, active coronary artery disease or other severe comorbid illness and patients with diabetes.

This work was approved by the Ethics Committee of the Faculty of Medicine, Cairo University and a written informed consent was obtained from all subjects enrolled in the study.

Clinical data

Age, gender and body mass index (BMI) were obtained for all groups. Smoking status, history of raising birds, presence of gastroesophgeal reflux (GERD) manifestations, modified British Medical Research Council scale (mMRC) for dyspnea, duration between onset of symptoms and diagnosis of IPF and requirement for oxygen therapy in IPF patients were collected. All the 3 studied groups underwent routine laboratory investigations including serum lactate dehydrogenase (LDH), serum creatine phosphokinase (CPK) and serum uric acid levels, anthropometric measurements [Mid-thigh cross sectional area (MTCSA) and Mid-arm cross sectional area (MAC)] and measurements of serum levels of ILGF-1 and IL-6 by ELISA. In IPF patients, chest HRCT, pulmonary function testing (spirometry), 6-minute walk test (6-MWT) and arterial blood gases ABGs) were performed.

Pulmonary function tests

All patients underwent spirometry (computer generated graphics using Sensor Medics V max 229.), according to the method described in the ATS 1994 update [18].

Six minute walk test

The 6-MWT was performed along a flat, straight indoor corridor of hard surface, with monitoring of oxygen arterial saturation with pulse oximetry, heart rate and breathing frequency according to the ATS recommendations [19].

Physical and anthropometric measurements

The height, weight, upper arm and thigh circumferences of all the study participants were measured. Height and weight were measured with subjects wearing a thin robe, and BMI was calculated by dividing mass (kg) by height squared (m_2). Mid-arm cross sectional area (MAC) was measured between the top of the shoulder (acromion) and the point of the elbow (olecranon process) using a tape measure when patients were standing with their arms comfortably spread. Mid-thigh cross sectional area (MTCSA) was measured at the level of the mid-point on the lateral surface of the thigh, midway between trochanterion (top of the femur) and tibiale laterale (top of the tibia bone) when the legs were spread 10 cm apart in the standing position. These measurements were taken on the right side of the body [20].

Measurements of serum ILGF-1 by ELISA

The DRG IGF-I 600 ELISA Kit is a solid phase enzyme-linked immunosorbent assay (ELISA), based on the principle of competitive binding. Patient samples, standards and controls are acidified and neutralized prior to the assay procedure. The microtiter wells are coated with a monoclonal antibody directed toward an antigenic site on the IGF-1 molecule. The pre-treated sample is incubated at room temperature with Conjugate (biotinylated IGF-1). The wells are washed and then incubated with Enzyme Complex (Streptavidin-HRP-Complex). After addition of the substrate solution, the intensity of color developed is reverse proportional to the concentration of IGF-1 in the patient sample [21].

Measurements of serum ILGF-1 by ELISA

This assay employs the quantitative sandwich enzyme immunoassay technique. A monoclonal antibody specific for human IL-6 has been pre-coated onto a microplate. Standards and samples are pipetted into the wells and any IL-6 present is bound by the immobilized antibody. After washing away any unbound substances, an enzyme-linked polyclonal antibody specific for human IL-6 is added to the wells. Following a wash to remove any unbound antibody-enzyme reagent, a substrate solution is added to the wells and color develops in proportion to the amount of IL-6 bound in the initial step. The color development is stopped and the intensity of the color is measured [22].

Statistical methods

Data were analyzed using SPSS (statistical package for social sciences; SPSS Inc., Chicago, IL, USA) version 22 for Microsoft windows. Numerical data were presented as mean ± standard deviation SD. Categorical data were presented as percentages. Number and percentages described qualitative data and Chi-square or/Fisher exact tested proportion independence. For comparing mean values of 2 independent groups, parametric and non-parametric t

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