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Trace metals in fluids lining the respiratory system of patients with idiopathic pulmonary fibrosis and diffuse lung diseases

Elena Bargagli[a,*], Federico Lavorini[a], Massimo Pistolesi[a], Elisabetta Rosi[a], Antje Prasse[b], Emilia Rota[c], Luca Voltolini[d]

[a] Section of Respiratory Medicine, AOUC, Florence, Italy
[b] Hannover Medical School, Clinic for Pneumology, Hannover, Germany
[c] Environmental Sciences Siena University, Siena, Italy
[d] Thoracic Surgery Unit, University Hospital Careggi, Largo Brambilla, 1, 50134, Florence, Italy

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ABSTRACT

Idiopathic pulmonary fibrosis (IPF) is an interstitial lung disease with a poor prognosis and an undefined etiopathogenesis. Oxidative stress contributes to alveolar injury and fibrosis development and, because transition metals are essential to the functioning of most proteins involved in redox reactions, a better knowledge of metal concentrations and metabolism in the respiratory system of IPF patients may provide a valuable complementary approach to prevent and manage a disease which is often misdiagnosed or diagnosed in later stages.

The present review summarizes and discusses literature data on the elemental composition of bronchoalveolar lavage (BAL), induced sputum and exhaled breath condensate (EBC) from patients affected by IPF and healthy subjects. Available data are scanty and the lack of consistent methods for the collection and analysis of lung and airways lining fluids makes it difficult to compare the results of different studies. However, the elemental composition of BAL samples from IPF patients seems to have a specific profile that can be distinguished from that of patients with other interstitial lung diseases (ILD) or control subjects. Suggestions are given towards standard sampling and analytical procedures of BAL samples, in the aim to assess typical element concentration patterns and their potential role as biomarkers of IPF.

1. Introduction

During biomolecular evolution, several elements such as Cr, Co, Cu, Fe, I, Mn, Mo, Ni, Se or Zn were selected to carry out a wide range of biological functions and traces of them (ng/g or μg/g) became essential for cell metabolism, including the activation or inhibition of enzymatic reactions, and the regulation of gene and membrane functions. All living organisms and tissues require the intake of essential elements in proper proportions: an excess, deficiency, or imbalance may disturb the cell functions and may seriously affect health [1,2]. Risks of developing adverse health effects are usually evaluated indirectly, by biomonitoring the dietary intake and/or the inhaled amounts of airborne trace elements. However, determining actual element concentrations in biological samples such as blood, urine, feces, bone, or cerebrospinal fluid has the advantage to better reflect their bioavailability and the amounts that can reach target tissues.

During the last decades, knowledge of metal transport proteins (including metallothioneins) and the transfer of their different chemical forms to different organs and tissues has significantly improved [3,4]. Unlike other organs, lungs are directly and continuously exposed to high oxygen concentrations, exogenous oxidants and pollutants; thus, they have the greatest susceptibility to oxidative stress and pollutant toxicity, from which they protect themselves through the action of own constitutive and inducible antioxidants and detoxification mechanisms [5]. The biological effects of inhaled metals occur at the sites of first contact and it is therefore necessary to study the metabolism and impact of essential and toxic metals in the respiratory system rather than by traditional exposure biomarkers such as blood or urine. Among

Abbreviations: IPF, idiopathic pulmonary fibrosis; ILD, interstitial lung diseases; COPD, chronic obstructive pulmonary diseases; CF, cystic fibrosis; PLCH, pulmonary Langerhans cell histiocytosis; BAL, bronchoalveolar lavage; EBC, exhaled breath condensate; TLC, total lung capacity; ROS, reactive oxygen species; SOD, superoxide dismutase; DMT1, divalent metal transporter 1; GPX, glutathione peroxidase; ETAS, Selectrothermal atomic absorption spectrophotometry; ICP, inductively coupled plasma spectroscopy; OES, optical emission spectroscopy; MS, mass spectrometry; NAA, neutron activation analysis; MS, mass spectrometry

* Corresponding author. AOUC Careggi University Hospital, Respiratory Medicine Unit, 50121 Florence, Italy.
E-mail address: bargagli2@gmail.com (E. Bargagli).

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essential trace elements, the understanding of Fe metabolism is the most advanced, and studies on lung physiology, dysfunction and injury usually consider only this metal [6,7]. Iron plays a fundamental role in the respiratory chain, as reactive forms of the metal are accumulated in the lung for cellular growth and proliferation, and decreased intracellular Fe concentrations suppress the generation of epithelial cell surface plasmin, which is essential for repairing damaged lung tissue [8]. However, if not appropriately chelated, Fe can promote the formation of harmful free radicals. Many other trace elements are involved in the regulation of Fe metabolism and contribute to the functioning and protection of the lung. Thus, a better knowledge of the occurrence and distribution of trace elements in the respiratory system and changes occurring during lung diseases could give new insights for diagnostic, therapeutic and preventive actions, especially for severe and complex diseases such as idiopathic pulmonary fibrosis (IPF).

IPF is a complex interstitial lung disease of unknown etiology, characterized by severe and progressive fibrosis of the alveolar interstitium with histopathological or radiological patterns typical of usual interstitial pneumonia. Probably, it is the result of complex interactions between genetic and environmental factors [9,10]. Several infectious, occupational and toxic etiologies have been suggested and epidemiological studies have shown associations between IPF development and cigarette smoke, wood and metal dust, silica and other inhaled environmental agents as well as co-morbidities with gastroesophageal reflux and type 2 diabetes [11,12]. In general, it is believed that IPF results from the aberrant activation of injured alveolar epithelial cells producing mediators that promote the proliferation of fibroblasts and fibrocyte recruitment with the formation of myofibroblastic foci, the accumulation of excessive extracellular matrix and lung remodeling [13–15]. Although barely investigated, the assessment of trace element distribution in the lung tissue and lining fluids could probably be an useful prognostic/predictive tool providing additional and complementary information with respect to genetic, proteomic, or molecular biology approaches. The chemical analysis of lung tissue samples is the most realistic way to assess the elemental composition of lung, but this invasive approach is rarely used for the diagnosis of IPF. Through an up-to-date literature survey of data on the elemental composition of airway secretions and breath condensates, this paper aims at providing an overview of available knowledge on trace element concentrations in IPF patients and an evaluation of their potential role as biomarkers of the disease.

2. Trace elements in BAL samples

Bronchoalveolar lavage (BAL) is a rather simple method to obtain a biological matrix for histopathological and chemical analysis. Although the chemical composition of this non-homogenous matrix can be contaminated by element contribution from the saline solution and the bronchoscope, working with BAL samples, instead of small lung biopsies, increases the sample representativeness and as a rule, reduces contamination by blood elements. Surveys on the elemental composition of BAL began 30 years ago [16,17] and although already in 1987 Sabbioni et al. [18] investigated on what should be the most suitable technique to analyze samples from differently exposed workers and the composition of the saline solution used for bronchoalveolar lavage, standardized methods for the collection and analysis of BAL are still lacking. Due to the inhomogeneous nature of samples, some authors [19] suggested that the amount of a trace element per 1000 macrophages should be the best way to establish baseline concentrations in BAL; on the contrary, other authors [20] found that concentrations (μg/l) of several elements in BAL were unrelated to age, sex, recovered volume of fluid, as well as to the total number of cells and alveolar macrophages. Thus, element concentrations in BAL have been expressed in different ways (mass/volume, mole/volume or on the basis of total cell number or number of macrophages), and for a given element available data are variable and difficult to compare. Harlik et al. [21] analyzed Zn, Cu and Fe concentrations (expressed in μg/kg) in 157 whole samples of BAL obtained for other diagnostic purposes. The supernatant was separated from cells and solid particles by centrifugation. The results showed that metal concentrations in the whole sample and the supernatant were linearly correlated and almost all elements (about 90%) were in the supernatant. With few exceptions, the increase of Cu concentrations was associated to a decrease of Zn content, and low Fe concentrations were found in a few BAL samples with high Zn levels. Analytical determinations were performed by atomic absorption spectrophotometry without any pre-treatment and in most samples the concentrations of Cu, Fe and Zn were < 15, 120 and 200 μg/kg, respectively. However, as shown in Table 1 for BAL samples from healthy controls, the results of analytical determinations are affected by pre-treatment methods, and their complete chemical digestion in a Teflon bomb or irradiation followed by NAA analysis [17,18] give the highest values. Since the study by Sabbioni et al. [18] it was known that the elemental composition of BAL changes among subjects working in different industries as well as between control groups and patients affected by sarcoidosis. Thus, reliable comparisons of the elemental composition of BAL can only be made among samples collected within homogeneous groups of persons (e.g. patients with the same disease, workers with the same occupational exposure), pretreated and analyzed with the same procedures. To evaluate if data on BAL elemental composition, integrated with those from clinical examinations, can be used as a diagnostic tool for lung diseases Bargagli et al. [22] compared Cd, Cr, Cu, Fe, Mn, Ni, Pb, V, and Zn concentrations in BAL samples from control subjects and from patients with pulmonary Langerhans cell histiocytosis (PLCH), sarcoidosis, and IPF. Among the analyzed elements, the concentrations of Cd and V were below detection limits; those of the other elements varied widely and some outlier values were also found, especially for Cu and Mn. BAL from IPF patients showed significantly lower median concentrations of Cr, Mn, Ni and Zn and a slightly higher Fe content than control subjects. Results expressed in ng/macrophages showed the highest Fe content and the lowest Mn and Zn contents in samples from IPF patients (Table 3) [22].

Table 1
Mean concentrations of Cu, Fe, and Zn (μg/l; ± SD) in whole BAL samples from control subjects, following different pre-treatments and analytical methods.

Metal	(μg/l)	Sample pre-treatment	Analytical technique[a]	References
Cu	215 ± 122	dissolved in Teflon bomb	ETASS/ICP	[18]
	2.81 ± 3.02	slight acidification with HCl	ETASS	[22]
Fe	758	Irradiation	NAA	[17]
	508 ± 204	Irradiation	NAA	[18]
	32.3 ± 26.1	slight acidification with HCl	ETASS	[22]
Zn	695	Irradiation	NAA	[17]
	510 ± 120	Irradiation	NAA	[18]
	8.21 ± 4.31	slight acidification with HCl	ETASS	[22]

[a] ETASS: Electrothermal Atomic Absorption Spectrophometry; ICP: Inductively Coupled Plasma Spectroscopy; NAA: Neutron Activation Analysis.

3. The elemental composition of induced sputum

Induced sputum is a heterogeneous matrix obtained by inducing expectoration through the inhalation of nebulized hypertonic saline. This approach is less invasive than bronchoscopy and BAL and allows the collection of a fluid phase with a mixture of cells and solutes which are considered representative of the larger airways. If in the clinical practice the differential cell count in BAL is widely accepted and recommended as a diagnostic/prognostic tool for sarcoidosis, PLCH, IPF and other ILD [23,24], the cell count and FeNO values in induced

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