Systemic inflammatory response in patients with clinically stable COPD

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ABSTRACT

Introduction:
Chronic inflammation of the lower airways is a primary aspect of the pathogenesis of COPD. This local inflammation produces cytokines that reach the circulation resulting in systemic inflammation. The characteristics of systemic inflammation during exacerbations of COPD are well described. Data on systemic inflammation in patients with COPD that are clinically stable are scarce.
The objective of this study was to define key inflammatory mediators that are elevated in the systemic circulation in patients with clinically stable COPD.

Methods:
This was a secondary data analysis of the ongoing study titled Impact of Oxidative Stress on HIV-Induced Lung Disease study database. The Luminex High Sensitivity multiplex assay was used to measure picogram levels of the following cytokines in plasma: TNF-α, MIP-3α, MIP-1β, MIP-1α, ITAC, IL-23, IL-21, IL-17A, IL-13, IL-12 (p70), IL-10, IL-8, IL-7, IL-6, IL-5, IL-4, IL-2, IL-1β, IFNγ, GM-CSF, and Fractalkine. Patients with stable COPD were compared to healthy controls.

Results:
A total of 37 patients were evaluated, 11 with COPD and 26 healthy controls. Significantly higher levels were identified in 13 of the 22 cytokines for COPD patients (TNF-α, MIP-3α, IL-6, IL-23, IL-21, IL-17A, IL-12 (p70), IL-10, IL-8, IL-7, IL-2, IFNγ, and Fractalkine).

Conclusions:
This study indicates that patients with clinically stable COPD have a high baseline systemic inflammatory response. A better understanding of the thirteen mediators of inflammation in stable COPD patients may help in the development of interventional studies with the goal to control the level of systemic inflammation.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) afflicts 26.8 million of the US population with almost half undiagnosed with a total estimated economic burden of 68 billion dollars [1]. Along with asthma, COPD is the third leading cause of death in the US [2]. With this economic and social burden in mind, it is warranted to have improved ways of managing and treating the disease. Therefore, the first step would be to better understand the underlying pathogenesis behind COPD.

The principal part of the pathogenesis of COPD is abnormal inflammation of the lower airways. There is a chronic release of local inflammatory mediators which can reach the circulation resulting in a systemic inflammatory response with extrapulmonary effects. Subsequently, among other systemic effects (Figure 1), there is endothelial dysfunction, an increase in activation of the complement system and prothrombotic process [3].

INTRODUCTION

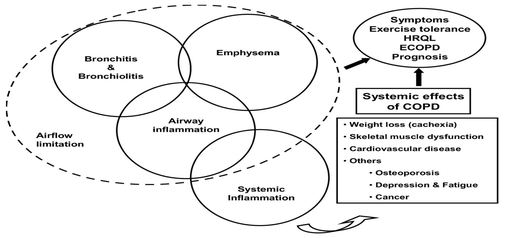

Figure 1. Chronic obstructive pulmonary disease (COPD) can be considered to have several domains, both inside and outside the lungs, that contribute to the physiologic (airflow obstruction) and clinical characteristics of patients. ECOPD = exacerbation of COPD; HRQL = health-related quality of life.

Patients with COPD are prone to developing exacerbations that may be severe enough to require hospitalization. There are multiple studies describing an upregulation of a number of cytokines in the circulation of COPD patients during such an exacerbation [4], including interleukin 6 (IL-6), tumor necrosis factor alpha (TNF-alpha), and IL-10. However, there is scarce data on the level of these inflammatory mediators in the systemic circulation in the stable clinical phase of COPD. Previous studies are also limited in the number of different cytokines measured.

In addition to smoking cessation which remains the single most important intervention to decrease progression of COPD, it is important to explore medical options that may target this underlying pathogenesis directly. For example, a currently studied antibiotic, doxycycline, has been known to possess anti-inflammatory and immunomodulatory properties. A study of the effect of doxycycline on stable COPD patients has shown possible contribution to the improvement of patients' pulmonary functions, symptoms and CRP level [5].
Therefore, the more information gained about systemic inflammation in stable COPD patients, the better our understanding will be of COPD pathogenesis and, in so doing, possibly facilitate future target therapy research.
Thus, the objective of this study was to define the key inflammatory mediators that are elevated in the systemic circulation in patients with clinically stable COPD.

METHODS

This was a secondary data analysis of the ongoing study titled Impact of Oxidative Stress on HIV-Induced Lung Disease study database. COPD was defined as a diagnosis documented by a physician in the medical records as well as through pulmonary function tests.

Venous blood of all subjects was collected using sodium citrate Vacutainer tubes. Following centrifugation at 300 x g for 10 min, the plasma was separated by aspiration, aliquoted and stored frozen at -80oC until assayed.

The concentrations of the following 21 different cytokines and chemokines in plasma were determined using Milliplex MAP Multiplex kits (EMD Millipore, Billerica, MA) according to the manufacturer's instructions: TNF-α, MIP-3α, MIP-1β, MIP-1α, ITAC, IL-23, IL-21, IL-17A, IL-13, IL-12 (p70), IL-10, IL-8, IL-7, IL-6, IL-5, IL-4, IL-2, IL-1β, IFN-γ, GM-CSF, and Fractalkine.

The plasma concentrations of the cytokines in patients with stable COPD were compared to healthy controls.

RESULTS

- A total of 37 patients were evaluated, 11 with COPD and 26 healthy controls.
- Significantly higher levels were identified in 13 of the 22 cytokines for COPD patients (TNF-α, MIP-3α, IL-6, IL-23, IL-21, IL-17A, IL-12 (p70), IL-10, IL-8, IL-7, IL-2, IFNγ, and Fractalkine). These 13 aforementioned cytokines are bolded in red color in Table 1.

Table 1 13 ELEVATED CYTOKINES IN THE COPD PATIENTS GROUP

Cytokine	Source	Primary Activity
TNF- α	Leukocytes	Apoptosis
MIP-3α	Epithelial cells	Leukocyte Chemotactic
MIP-1α	Macrophages	Leukocyte Chemotactic
MIP-1β	Macrophages	Leukocyte Chemotactic
ITAC	Multiple tissues including lungs and leukocytes	Chemotactic for activated T-cells
IFN-γ	NK cells, T-cells	Antiviral, antitumor, leukocyte migration
GM-CSF	Leukocytes, endothelial cells	Granulocyte production, macrophage activation
Fractaline	Endothelial cells	Leukocyte adhesion molecule and chemotactic
IL-1β	Macrophages	cell proliferation, differentiation and apoptosis
IL-2	Activated T-cells	T-cell regulation
IL-4	T-cells, possibly basophils	T-cell differentiation, Activated B and T-cell proliferation
IL-5	T-cells, Mast cells	Eosinophil activation, antibody secretion
IL-6	T-cells, macrophages, smooth muscle cells, osteoblasts	Inhibits TNF-alpha and IL-1, increasing body temperature, fever, neutrophil production
IL-7	Bone marrow, thymus	Stimulates T and B-cell proliferation, synthesis of IL-1,6 and MIP
IL-8	Various leukocytes, fibroblasts, endothelial cells, hepatocytes	Leukocyte chemotactic, neutrophil granulocyte, mediating pain, angiogenesis
IL-9	T-cells	Proliferation of T-helper and mast cells
IL-10	Monocytes, T-cells	Anti-inflammatory, inhibit NK cells,
IL-12 (p70)	Lymphocytes, dendritic cells	Activates NK cells, stimulates production TNF-alpha and IFN-gamma
IL-13	Activated T-helper 2 cells	Reduces production of multiple cytokines and nitric oxide, induction of metalloproteinases in airways
IL-17A	Activated T-cells	Maturation of hematopoietic precursors into neutrophils
IL-21	T-cells	NK cell, CD8+ T-cell activity
IL-23	Lymphocytes	Pro-inflammatory, proliferation of Th-cells

Various cytokine sources and functions
(TNF: Tumor necrosis factor, MIP: Macrophage Inflammatory protein, ITAC: Interferon-inducible T-cell alpha chemoattractant, GMCSF: Granulocyte-macrophage colony-stimulating factor, IL: Interleukin, NK cell: Natural killer cell)

CONCLUSIONS

- This study indicates that patients with clinically stable COPD have a high baseline systemic inflammatory response.
- COPD produce a local pulmonary inflammation, but our study documents the "spill-over" of mediators into the systemic circulation.
- This documented systemic inflammatory response is likely the reason why COPD present with multiple comorbidities, such as: cardiac disease, osteoporosis, metabolic syndrome, anemia, myopathy, depression, and cachexia.
- Our data merits additional studies to define the role of these thirteen inflammatory mediators in the systemic inflammatory response in patients with stable COPD. This may ultimately aid in the development of interventional studies with the goal to control the level of systemic inflammation.

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