Effect of Smoking and Inhaled Steroid on Circulating Surfactant Protein D Level in COPD

THESIS

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ABSTRACT

The aim of the present work was to evaluate the utility of serum SP-D, a lung derived protein, as a biomarker for COPD and to assess the effect of smoking and inhaled steroid on its levels. Seventy subjects were enrolled in this study divided into 2 main groups: healthy control group (30 subjects) and COPD patients' group (40 subjects).Serum SP-D was measured using a colorimetric sandwich immunoassay method .Results revealed that COPD and smoking, each independently, is associated with significant higher levels of serum SP-D, while inhaled steroid is associated with significant lower serum SP-D levels. In addition, serum SP-D levels correlate positively with the severity of COPD disease. These results suggest that SP-D is a promising lung specific biomarker to track health outcomes of COPD patients and be useful as a marker for their response to steroid therapy.

Key words: SP-D, COPD, lung specific biomarker, inhaled steroid, smoking**.**

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List of Abbreviations

A	Aspergillus
AAT	Alpha 1 Antitrypsin Deficiency
ABPA	Allergic Bronchopulmonary Aspergillosis
APCs	Antigen Presenting Cells
Arg	Arginine
ATS\ERS	American Thoracic Society/European Respiratory Society Task Force.
BALF	Bronchoalveolar Fluid
Bode index	A Multidimensional scale of Body-mass index, airway Obstruction, Dyspnoea, and Exercise capacity
CD	Cluster of Differentiation
CDR	Complementary Determining Region
CF	Cystic Fibrosis
CLq	Complement Component
COPD	Chronic Obstructive Pulmonary Disease
CRD	Carbohydrate Recognition Domain
CRT	Calreticulin
DPPC	Dipalmityl Phosphatidyl Choline
DC	Dendritic Cell
Derp	Dermatophagoidespteronyssinus
DMPT	Deleted in Malignant Brain Tumor
E	Esherechia
ELISA	Enzyme Linked Immunosorbent Assay
ER	Endoplasmic Reticulum
FEV1	Forced Expiratory Volume in the first second
FVC	Forced Vital Capacity
Gln	Glutamine

Glu	Glutamate
Gly	Glycine
GM-CSF	Granulocyte Macrophage Colony Stimulating Factor
GOLD	Global Initiative for Chronic Obstructive Lung Disease
gp	Glycoprotein
HA	Hemagglutinin
HDLC	High Density Lipoprotein Cholesterol
His	Histidine
IAV	Influenza A virus
INF	Interferon
IPA	Invasive Pulmonary Aspergillosis
Ig	Immunoglobulin
IL	Interleukin
K	Klebsiella
KDa	Kilodalton
LPS	Lipopolysaccharide
Lys	Lysine
M	Mycobacteruim
MMP	Matrix Metalloproteinase
MRC	Medical Research Council
N	Neuraminidase
P	Pseudomonas
PAP	Pulmonary Alveolar Proteinases
PI	Phosphoinositol
RhSP-D	Recombinant Human Surfactant Protein D
RT-PCR	Reverse Transcriptase Polymerase Chain Reaction

S	Staphyloccocus
SIRPa	Single Regulatory Protein alpha
SP-A	Surfactant protein A
SP-B	Surfactant protein B
SP-C	Surfactant protein C
SP-D	Surfactant protein D
T-h	T-helper cell
TORCH	The Towards a Revolution in COPD Health
TNF	Tumor Necrosis Factor
USPSTF	US Preventive Services Task Force
WCF	Weak Culture Filtrate
WHO	World Health Organization

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Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a multi-component condition that is characterized by airways obstruction emphysema, mucus hypersecretion and systemic disease that vary in proportion between affected individuals (**Agusti, 2005).**

The development of disease is intimately associated with the inhalation of noxious agents and in particular cigarette smoke **(Rabe et al., 2007).**

There is clearly an urgent need for a simple biomarker that can be used in the diagnosis of COPD and to assess prognosis and the effectiveness of therapeutic interventions.

Biomarkers have been assessed in urine, blood, sputum, broncho-alveolar lavage, skin and exhaled breath condensate **(Cazzola et al., 2008).** Compared with markers measured in other sample material, biomarkers determined in serum are reliably measured using equipment that is cost-effective and readily available in clinical settings.

Surfactant protein D (SP-D) is a large hydrophilic protein that is a member of the collagen containing C-type lectins called collectins **(Kishore et al., 2006).** Its structure is based on a triple helical collagen region and a C-terminal homotrimeric lectin or carbohydrate recognition domain. Four of the homotrimeric subunits of SP-D are assembled via their N-terminal region into a 520 kilo dalton (kDa) dodecamer structure that can further oligomerise to form multimers. SP-D is found in the endoplasmic reticulum of type II pneumocytes and in the secretory granules of Clara cells **(Mori et al., 2002).**

It makes an important contribution to surfactant homeostasis and pulmonary immunity **(Kishore et al., 2006).**

SP-D plays a role in protecting against viral infection, in the clearance of bacteria, fungi and apoptotic cells and in the resolution of inflammation **(Kierstein et al., 2006).** Mice that lack SP-D develop chronic inflammation and emphysema that can be prevented by administration of truncated recombinant human SP-D **(Knudsen et al., 2007).**

SP-D is predominantly synthesized within the respiratory tract, it has been evaluated as a potential biomarker in small numbers of individuals with community acquired pneumonia, drug induced lung disease, interstitial fibrosis, and allergic bronchopulmonary aspergillosis in cystic fibrosis **(Krane and Griese, 2003).**

Levels are reduced in bronchoalveolar lavage from individuals with COPD **(Sims et al., 2008).**

We hypothesized that chronic cigarette smoking and COPD would each be independently associated with lower SP-D levels in the lung and in turn elevated SP-D levels in serum. In order to determine the association between serum SP-D levels, cigarette smoke exposure, and inhaled steroid and to evaluate the utility of serum SP-D as a biomarker for components of the COPD phenotype we have conducted a cross-sectional study of healthy non, current and former smokers ,and current or former smokers with varying degrees of COPD.

Aim of the work

The aim of the present work was to review one lung-specific biomarker, surfactant protein D (SP-D) and to assess the effect of inhaled corticosteroids and smoking on levels of this biomarker in COPD.

1-Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a preventable and treatable disease with some significant extra pulmonary effects that may contribute to the severity in individual patients. Its pulmonary component is characterized by airflow limitation which is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases **(GOLD, 2006)**.

Chronic bronchitis is defined clinically as the presence of a chronic productive cough for 3 months during each of 2 consecutive years (other causes of cough being excluded). **Emphysema**, on the other hand, is defined pathologically as an abnormal, permanent enlargement of the air spaces distal to the terminal bronchioles, accompanied by destruction of their walls and without obvious fibrosis **(Nader et al., 2010).**

COPD is the fifth leading cause of death worldwide, accounting for more than 2 500 000 deaths every year **(WHO world health report, 2002).**

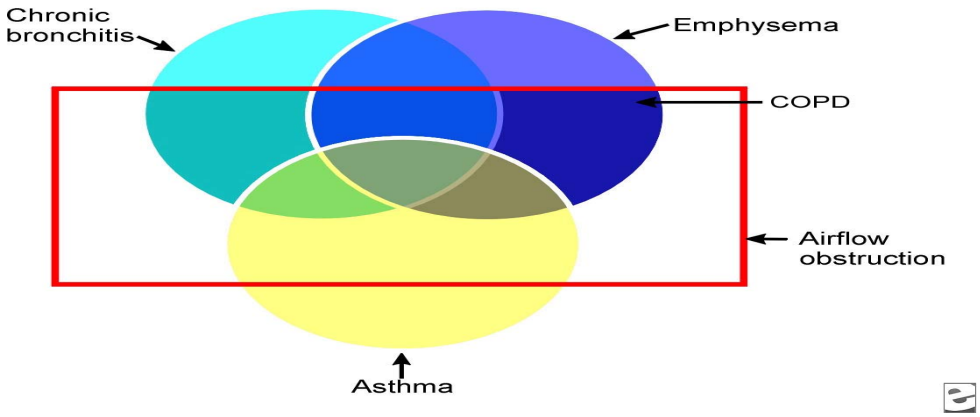

Figure (1): Venn diagram of chronic obstructive pulmonary disease (COPD). Chronic obstructive lung disease is a disorder in which subsets of patients may have dominant features of chronic bronchitis, emphysema, or asthma. The result is irreversible airflow obstruction. **(Joan et al., 2003).**