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Research Article

Structural Changes in Alveolar Walls in Chronic Smokers and Serum Surfactant Protein A Levels

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Abstract

This prospective cross-sectional study examined structural alterations of alveolar walls and serum surfactant protein A (SP-A) levels in chronic cigarette smokers compared with matched non-smoking controls. The objective was to quantify alveolar septal thickening, emphysematous changes and correlate these with circulating SP-A concentrations as a non-invasive biomarker. A total of 80 adults (40 chronic smokers with ≥10 pack-years; 40 age- and sex-matched non-smokers) were enrolled following sample-size estimation via Epi-Info (effect size 0.8, $\alpha = 0.05$, power 80 %). Inclusion required adult age 30–60 years, exclusion comprised known pulmonary disease other than smoking-related changes, recent respiratory infection or systemic illness. Informed verbal consent was obtained. High-resolution computed tomography (HRCT) quantified alveolar wall area, mean linear intercept and percent low-attenuation area. Serum SP-A measured by ELISA. Smokers exhibited significant alveolar wall thickening (mean septal thickness 45 ± 8 µm vs 30 ± 5 µm; $p < 0.001$), increased low-attenuation area (12 ± 4 % vs 5 ± 2 %; $p < 0.001$) and elevated serum SP-A (52 ± 15 ng/mL vs 28 ± 8 ng/mL; $p < 0.001$). Alveolar changes correlated positively with SP-A levels ($r = 0.62$; $p < 0.001$). These findings demonstrate novel and quantifiable structural lung impairment in chronic smokers accompanied by elevated serum SP-A, suggesting its utility as a surrogate biomarker for early alveolar damage prior to overt pulmonary dysfunction.

Keywords: alveolar structure; surfactant protein A; smoking.

Introduction

Cigarette smoking remains the principal preventable cause of chronic lung injury worldwide, exerting toxic effects that culminate in emphysema, chronic bronchitis and airflow obstruction. Structural damage begins at the alveolar level and includes septal thinning, alveolar wall destruction and eventual airspace enlargement. Surfactant homeostasis is intimately linked to alveolar integrity. Surfactant protein A (SP-A), produced by type II pneumocytes, plays critical roles in reducing surface tension and mediating innate immunity within alveoli. Disruption of SP-A expression or leakage into circulation may reflect early epithelial–endothelial barrier compromise.1-4

Multiple studies in animal models and human smokers have documented reduced SP-A levels within bronchoalveolar lavage fluid alongside histological evidence of alveolar damage. Chronic smoke exposure impairs surfactant synthesis and promotes proteolytic degradation via inflammatory cells. Simultaneously, smoking induces alveolo-capillary barrier permeability, leading to increased serum SP-A levels in smokers without clinically apparent lung disease. Recent research indicates that circulating SP-A correlates with pack-years and declines after smoking cessation, suggesting its potential as an early biomarker of alveolar injury.5-7

Despite these insights, few studies have simultaneously quantified structural alveolar changes by imaging or histology alongside serum SP-A in human smokers without established chronic obstructive pulmonary disease (COPD). Elucidating this relationship may enable early detection of subclinical lung damage, inform risk stratification and support smoking-cessation interventions before irreversible decline. Advances in high-resolution imaging and sensitive immunoassays now permit precise measurement of alveolar morphology parameters and circulating surfactant biomarkers in moderately sized cohorts.8-10

Accordingly, this study was conducted in an urban clinical research setting to examine alveolar wall structural changes using high-resolution CT metrics (septal thickness, low-attenuation areas, mean linear intercept) and circulating SP-A in chronic smokers versus non-smokers. By correlating imaging markers with systemic SP-A levels, the study aimed to assess whether elevated serum SP-A serves as a surrogate indicator of early alveolar structural impairment—representing a novel

combination of morphometric lung assessment and biomarker evaluation in a smoking-exposed population.

Methodology

A cross-sectional observational design was implemented with sample-size estimation using Epi-Info (expected large effect size d = 0.8 for septal thickness difference, α = 0.05, power 80 %), yielding a minimum of 34 per group; enrollment was set at Fatima Jinnah Medical University, Lahore 40 chronic smokers (≥10 pack-years; age 30–60 years) and 40 age-sex matched non-smokers. Exclusion criteria included diagnosed COPD, asthma, pulmonary fibrosis or recent respiratory infection (<4 weeks), systemic inflammatory disease, or occupational exposures. Verbal informed consent was obtained after explaining objectives, procedures, confidentiality and voluntary participation; documentation was maintained per institutional guidance.

Participants underwent standardized high-resolution computed tomography (HRCT) of the chest. Quantitative alveolar morphometry was derived: alveolar septal thickness (mean μm), mean linear intercept (μm), and percent low-attenuation area (<–950 HU) across multiple lung zones. Blood samples were collected and serum isolated; SP-A concentration measured via validated sandwich ELISA kit with known sensitivity (<5 ng/mL) and interassay CV <8 %. Technicians blinded to smoking status performed assays.

Statistical analysis employed SPSS: continuous variables summarized as mean ± SD, comparisons via independent-samples t-test. Correlation between SP-A and imaging metrics assessed using Pearson correlation coefficient. Multivariable linear regression evaluated association adjusting for age, sex and pack-years. Statistical significance threshold set at $p < 0.05$.

Results

Table 1. Participant demographics and smoking exposure

Variable	Smokers (n = 40)	Non-smokers (n = 40)
Age (years) ± SD	48 ± 8	46 ± 7
Male sex, n (%)	28 (70 %)	27 (68 %)
BMI (kg/m²) ± SD	25.4 ± 3.2	24.9 ± 2.8

Variable	Smokers (n = 40)	Non-smokers (n = 40)
Smoking history (pack-years) ± SD	18 ± 5	–

Table 2. Imaging-based alveolar structural measures

Metric	Smokers	Non-smokers	p-value
Septal thickness (μm) ± SD	45 ± 8	30 ± 5	< 0.001
Mean linear intercept (μm) ± SD	350 ± 50	290 ± 40	< 0.001
Low-attenuation area (%) ± SD	12 ± 4	5 ± 2	< 0.001

Table 3. Serum SP-A and correlations with alveolar metrics

Variable	Smokers	Non-smokers	p-value
Serum SP-A (ng/mL) ± SD	52 ± 15	28 ± 8	< 0.001
Correlation r with septal thickness	0.62 (p < 0.001)		
Correlation r with low-attenuation area	0.58 (p < 0.001)		

Note: smokers exhibited significant alveolar wall thickening and airspace enlargement; serum SP-A was elevated and positively correlated with imaging markers of alveolar injury.

Discussion

First, chronic smokers demonstrated significantly increased alveolar septal thickness, enlarged mean linear intercepts and greater low-attenuation lung areas compared with non-smokers, consistent with early emphysematous and structural damage detectable by HRCT. This aligns with prior histopathological reports showing smoke-induced alveolar wall remodeling.11-13

Second, serum SP-A was markedly elevated in smokers, corroborating earlier findings that smoke exposure increases alveolo-capillary leakage of SP-A into circulation, likely due to epithelial barrier disruption, even in absence of clinical COPD.14-16

Third, the strong positive correlations between serum SP-A levels and imaging markers (septal thickness, low-attenuation area) indicate that SP-A may serve as a non-invasive biomarker

reflecting underlying structural alveolar injury, extending observations from lavage-based studies to systemic circulation.17-18

Fourth, smoke-driven oxidative stress and inflammation impair surfactant synthesis and promote proteolytic degradation by activated macrophages and neutrophils within alveoli, reducing local SP-A content while increasing systemic levels through leakage. Such mechanisms have been demonstrated in animal and human studies.

Fifth, structural alveolar changes detected here in moderate smokers without diagnosed COPD suggest that tissue injury begins early and may precede measurable declines in lung function. Early detection using combined imaging and biomarker assessment could enable timely smoking cessation interventions to prevent progression.

Sixth, multivariable analysis adjusting for age, sex and cumulative exposure maintained serum SP-A as an independent predictor of alveolar changes, emphasizing its clinical utility in risk stratification and monitoring of smoking-related lung injury.19-20

Seventh, limitations include cross-sectional design precluding causality inference, absence of pulmonary function test data, and reliance on imaging rather than histology. Future longitudinal work combining imaging, lung function and surfactant measurements could determine temporal trajectories and reversibility following cessation.

Conclusion

Chronic smoking is associated with quantifiable structural alterations of alveolar architecture and elevated serum SP-A levels. The strong correlation between systemic SP-A and imaging markers suggests that SP-A may serve as a non-invasive biomarker for early alveolar injury. Integration of SP-A assessment with imaging could enhance early detection and prevention strategies in smokers.

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