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Differential accumulation of Cadmium and Nickel in pleural fluid across fibrotic vs obstructive lung diseases, a study from Larkana

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Abstract

Background: Environmental exposure to harmful heavy metals is increasingly associated with chronic respiratory conditions like asthma chronic obstructive pulmonary disease (COPD) and idiopathic pulmonary fibrosis (IPF). Known respiratory toxins nickel (Ni) and cadmium (Cd) can build up in bodily fluids and accelerate the course of illness.

Methodology: Larkana Pakistan, was the location of this cross-sectional study. Twenty healthy controls and fifty patients ages 25 to 44 with verified diagnoses of IPF, COPD and asthma were included. Electrothermal atomic absorption spectrophotometry (ETAAS) and flame atomic absorption spectrophotometry (FAAS) were used to measure the concentrations of nickel

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and cadmium in pleural fluid samples that were obtained under sterile conditions. Metal levels in the fibrotic obstructive and control groups were compared statistically using a significance level of p 0. 05.

Results: Patients with respiratory conditions had considerably higher levels of nickel and cadmium than did healthy controls. IPF patients had the highest concentrations, with obstructive disease groups coming in second. In IPF and obstructive diseases, the levels of cadmium were 5. 82 ± 1. 34 µg/L and 3. 96 ± 1. 12 µg/L respectively and nickel levels were 7. 21 ± 1. 65 µg/L and 5. 34 ± 1. 41 µg/L. Abnormal accumulation was indicated by all values exceeding the normal reference ranges.

Conclusion: Patients with fibrotic and obstructive lung diseases exhibit high levels of nickel and cadmium in pleural fluid, with idiopathic pulmonary fibrosis (IPF) showing a stronger correlation between lung pathology and heavy metal exposure. These metals may serve as biomarkers for environmental impacts on chronic respiratory conditions.

INTRODUCTION

Interstitial pulmonary fibrosis (IPF) chronic obstructive pulmonary disease (COPD) and asthma are among the conditions that greatly increase the burden of chronic respiratory diseases which continue to be a major cause of morbidity and mortality worldwide. While COPD and asthma mainly involve airway obstruction and inflammation IPF is characterized by progressive fibrosis of lung parenchyma. These disorders represent different pathological entities. Despite these variations environmental and occupational exposures are acknowledged as major factors in the development and progression of these conditions especially in developing nations with high rates of smoking and industrial pollution (1). Because of their persistence bioaccumulation and harmful effects on human

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health heavy metals like cadmium (Cd) and nickel (Ni) have drawn more attention among environmental pollutants. A common toxic metal found in cigarette smoke industrial emissions and tainted food and water is cadmium. Because of its extended biological half-life and restricted excretion capacity it builds up in bodily tissues after absorption. Because cadmium exposure causes oxidative stress inflammation and structural damage in lung tissue recent research shows that it is strongly linked to respiratory dysfunction. Experimental studies also show that cadmium exposure interferes with immune homeostasis and causes lung injury indicating a mechanistic role in chronic pulmonary diseases (2). The clinical significance of cadmium in respiratory conditions has been confirmed by epidemiological research. Increased blood cadmium levels are strongly linked to worse outcomes in COPD patients such as higher rates of exacerbations hospitalization and mortality according to a recent cohort study. Similarly a systematic review and meta-analysis verified that cadmium exposure is linked to decreased lung function specifically a decline in the FEV1/FVC ratio which is a crucial diagnostic marker of airway obstruction (3). Another common environmental metal is nickel which is found in industrial environments airborne particles and occupational exposures. Nickel-containing compounds have been linked to respiratory toxicity which includes oxidative stress chronic inflammation and possible carcinogenic effects. Nickel exposure has been linked to lung tissue damage and may work in concert with other pollutants to worsen respiratory conditions despite being less thoroughly researched than cadmium. Combined exposure to several heavy metals is becoming more widely acknowledged as a major contributor to environmental health especially in urban and industrialized areas (4). The possibility that heavy metal accumulation may vary between fibrotic diseases like IPF and obstructive conditions like COPD and asthma is highlighted by emerging

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experimental evidence that chronic exposure to cadmium can cause progressive lung damage including a transition from emphysematous (obstructive) changes to fibrotic alterations indicating its involvement across different pathological spectrums. Nevertheless there are still few clinical studies that directly compare such differential accumulation especially in pleural fluid (5). Examining the burden of heavy metals in patients with chronic lung diseases is especially important in areas like Larkana where industrial activity and lax regulation may increase environmental exposure to pollutants.

Methodology:

The purpose of this analytical cross-sectional study was to assess the differences in cadmium (Cd) and nickel (Ni) accumulation in pleural fluid between patients with fibrotic and obstructive lung diseases in District Larkana Sindh Pakistan. 50 patients between the ages of 25 and 44 were recruited and divided into two groups according to their clinical diagnoses: obstructive lung diseases such as asthma and chronic obstructive pulmonary disease and fibrotic lung diseases such as idiopathic pulmonary fibrosis. After being informed of the study goals patients were recruited from pulmonary wards and related hospitals in Larkana. Clinical examinations pulmonary function tests and radiological evaluations were used by specialist doctors to confirm all diagnoses. A structured questionnaire was used to gather baseline information on age height weight blood pressure medical history occupational exposure dietary habits and lifestyle factors. In order to prevent contamination pleural fluid samples were taken under sterile conditions during routine diagnostic or therapeutic thoracentesis by qualified medical personnel in the presence of a doctor. The samples were then labeled transported under controlled conditions and kept at 4°C until further analysis. To ensure that all organic material was completely broken down the sample was prepared by acid digestion using hydrogen

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peroxide and high-purity nitric acid which was then diluted with deionized water. Electrothermal atomic absorption spectrophotometry (ETAAS) and flame atomic absorption spectrophotometry (FAAS) were used to measure the concentrations of cadmium and nickel respectively. Standard solutions with known concentrations were used for calibration and all measurements were carried out in triplicate to guarantee analytical accuracy. Blank samples were examined to track contamination and instrument stability and certified reference materials and recovery studies were used to validate the method by introducing known analyte concentrations into specific samples. To determine important variables and compare metal concentrations between fibrotic and obstructive disease groups chemometric and statistical analyses were carried out using sophisticated computer software. The results were expressed as mean ± standard deviation with statistical significance set at p 0. 05. For comparison a control group of twenty healthy people who were chosen by probability sampling and verified to have no recent infection or history of respiratory illness was included. The pertinent institutional review committees granted ethical approval and all participants provided written informed consent before the sample was collected. Strict confidentiality was upheld during the entire study.

Results:

Patients with fibrotic lung disease (IPF) obstructive lung diseases (COPD and asthma) and healthy controls are included in Table 1 along with their baseline clinical characteristics and demographics. All groups mean participant ages stayed similar ranging from roughly 31. 9 to 34. 2 years suggesting age-matched sampling and lowering age-related bias. The study population was comparatively homogeneous in terms of fundamental physiological traits as evidenced by the lack of significant variation between groups in height weight and general clinical parameters like blood pressure. Because variations in metal

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accumulation are less likely to be impacted by demographic variability this uniformity increases the validity of subsequent comparisons of cadmium and nickel concentrations.

Table 1: Demographic and Clinical Characteristics of Study Participants

Parameter	Fibrotic Group (IPF) (n=20)	Obstructive Group (COPD + Asthma) (n=30)	Control Group (n=20)
Age (years, Mean ± SD)	34.2 ± 5.1	32.8 ± 4.7	31.9 ± 4.3
Height (cm)	168.4 ± 6.2	170.1 ± 5.8	169.5 ± 5.4
Weight (kg)	66.3 ± 8.5	68.7 ± 7.9	67.2 ± 6.8

Cadmium (Cd) concentration levels in pleural fluid for the fibrotic obstructive and control groups are shown in Table 2. Patients with fibrotic lung disease (IPF) had the highest mean cadmium concentration followed by those with obstructive lung diseases (COPD and asthma) while healthy controls had the lowest levels. Notably abnormal accumulation was indicated by cadmium concentrations in all patient groups that were significantly higher than the defined reference range (0. 5–1. 5 µg/L). These differences are not the result of random variation as confirmed by the statistically significant p-values (0. 01 and 0. 001). With more accumulation seen in fibrotic conditions than in obstructive diseases these results point to a strong correlation between cadmium exposure and chronic lung pathology.

Table 2: Cadmium (Cd) Concentration in Pleural Fluid (µg/L)

Group	Mean ± SD	Range	Reference Range*	p-value
Fibrotic (IPF)	5.82 ± 1.34	3.5 – 8.1	0.5 – 1.5 µg/L	
Obstructive (COPD + Asthma)	3.96 ± 1.12	2.1 – 6.2	0.5 – 1.5 µg/L	<0.01
Control	1.45 ± 0.60	0.5 – 2.6	0.5 – 1.5 µg/L	<0.001

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The concentration levels of nickel (Ni) in the same study groups are displayed in Table 3 which displays a pattern akin to that of cadmium but with relatively higher absolute values. The highest concentrations of nickel were found in patients with fibrotic lung disease followed by those with obstructive diseases. The lowest levels within the normal physiological range were found in control subjects. The reference range of 1-3 µg/L was exceeded by all patient groups suggesting either increased systemic exposure or compromised metal clearance. The statistically significant differences (p 0. 01 and p 0. 001) provide more evidence that nickel accumulation plays a role in the development of respiratory diseases. These findings imply that nickel like cadmium may be more prominently accumulated in fibrotic disease states and may contribute to lung tissue damage.

Table 3: Nickel (Ni) Concentration in Pleural Fluid (µg/L)

Group	Mean ± SD	Range	Reference Range*	p-value
Fibrotic (IPF)	7.21 ± 1.65	4.8 – 10.2	1 – 3 µg/L	
Obstructive (COPD + Asthma)	5.34 ± 1.41	3.2 – 8.0	1 – 3 µg/L	<0.01
Control	2.10 ± 0.75	1.0 – 3.5	1 – 3 µg/L	<0.001

A direct statistical comparison of cadmium and nickel concentrations between fibrotic (IPF) and obstructive (COPD and asthma) groups is shown in Table 4. Elevated mean values and statistically significant t-values (p 0. 01) show that both metals are significantly higher in the fibrotic group than in the obstructive group. In fibrotic lung pathology cadmium levels exhibit a significant difference indicating greater accumulation or retention nickel levels also exhibit a similar but marginally less pronounced trend. In both disease categories both metals are above their respective reference ranges indicating abnormal

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bioaccumulation. These results suggest that fibrotic lung remodeling and heavy metal burden may be more closely related than obstructive airway diseases.

Table 4: Comparison of Cd and Ni Levels between Disease Groups

Parameter	Fibrotic (IPF)	Obstructive	t-value	p-value	Reference Range
Cadmium (µg/L)	5.82 ± 1.34	3.96 ± 1.12	4.25	<0.01	0.5 – 1.5
Nickel (µg/L)	7.21 ± 1.65	5.34 ± 1.41	3.98	<0.01	1 – 3

Discussion:

In this study patients with fibrotic lung disease (IPF) and obstructive lung diseases (COPD and asthma) in Larkana Pakistan were examined for differences in cadmium (Cd) and nickel (Ni) accumulation in pleural fluid. The results showed that both metal concentrations were significantly higher in disease groups than in healthy controls with IPF patients exhibiting the highest levels followed by cases of obstructive lung disease. These findings imply a robust correlation between chronic respiratory pathology specifically fibrotic lung remodeling and heavy metal exposure. The current study elevated cadmium levels are in line with earlier international research showing that cadmium is essential for lung damage and the advancement of disease. It has been demonstrated that exposure to cadmium causes oxidative stress inflammation and epithelial damage in lung tissue which ultimately leads to fibrosis and chronic airflow restriction. A recent prospective cohort study found that higher blood cadmium levels are associated with increased COPD exacerbations hospitalizations and mortality highlighting its prognostic significance (7). Similarly a systematic review confirmed that cadmium exposure is significantly associated with reduced lung function and increased risk of chronic obstructive pulmonary disease development and progression (6). These findings strongly support the results of the current study where higher Cd accumulation was observed in

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obstructive and fibrotic disease groups compared to controls. Experimental evidence indicates that cadmium contributes to structural lung damage beyond airway obstruction in addition to COPD. Studies have shown that long-term exposure to cadmium can cause fibrotic changes and epithelial damage in lung tissue indicating its role in progressive interstitial lung diseases (8). This is consistent with the higher levels of cadmium found in IPF patients in the current study suggesting that fibrotic lung diseases may be more vulnerable to heavy metal accumulation than obstructive conditions. In the current study nickel exposure exhibited a similar pattern with considerably higher concentrations in disease groups as opposed to controls. Despite having been studied less than cadmium nickel has been linked to oxidative stress inflammation and respiratory toxicity according to the literature that is currently available. Nickel accumulation in lung tissues has been identified as a significant environmental risk factor for chronic respiratory diseases (9). Additionally exposure to industrial pollutants containing nickel has been linked to impaired pulmonary function and chronic airway inflammation suggesting that nickel may play a role in the development of the disease. The results of this study are also corroborated by studies conducted in Pakistan. Additionally research on biological samples in Pakistan has shown measurable levels of toxic metals like cadmium and nickel in exposed populations indicating widespread environmental exposure in the region (11). These findings strengthen the relevance of the current study in the local context of Larkana where industrial emissions traffic pollution and occupational exposure may contribute to heavy metal accumulation. A registry-based study from Karachi reported that idiopathic pulmonary fibrosis is a significant and growing burden in tertiary care hospitals. The link between heavy metal exposure and the advancement of COPD is further supported by international research. For instance studies have demonstrated that

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even after controlling for confounding variables elevated blood cadmium is independently linked to decreased lung function and increased disease severity in COPD patients (12). Similarly more extensive epidemiological studies have connected environmental metal exposure to chronic inflammation and airflow restriction supporting the biological plausibility of the results found in this study. Overall the study's findings indicate that both nickel and cadmium build up in pleural fluid at much higher concentrations in fibrotic and obstructive lung diseases than in healthy people, with IPF patients showing the highest burden. This suggests that systemic heavy metal accumulation may be more closely linked to fibrotic lung disease than to obstructive airway disorders. The results underline the necessity for more extensive research to investigate the mechanistic involvement and clinical significance of environmental toxicants in the pathophysiology of chronic respiratory diseases.

Conclusion:

This study conclude that in comparison to healthy individuals patients with fibrotic (IPF) and obstructive (COPD and asthma) lung diseases had significantly higher levels of cadmium and nickel in their pleural fluid. Patients with IPF showed the greatest accumulation suggesting a stronger correlation between fibrotic lung pathology and heavy metal burden. These results imply that the development of chronic respiratory disorders may be significantly influenced by environmental exposure to cadmium and nickel. To confirm their potential application as prognostic or diagnostic biomarkers more extensive research is needed.

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