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BIOMARKERS IN OCCUPATIONAL LUNG DISEASES: ADVANCES AND FUTURE DIRECTIONS

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ABSTRACT

Background: Occupational lung diseases (OLDs) remain a major global health concern, arising from chronic exposure to hazardous airborne agents such as mineral dusts, fumes, and chemical vapors. Early detection is essential to prevent irreversible damage, yet conventional diagnostic methods often identify disease only after substantial structural changes have occurred. Biomarkers offer an opportunity for earlier recognition of exposure, effect, and individual susceptibility. **Objective:** To review and summarize recent advances in biomarkers relevant to the early detection, monitoring, and risk stratification of occupational lung diseases. **Methods:** A narrative review of published literature was conducted, focusing on biomarkers associated with classical pneumoconioses, chronic granulomatous disorders, and occupational airway diseases. Emphasis was placed on inflammatory markers, cytokine signatures, susceptibility indicators, and disease-specific markers in asbestosis and silicosis. **Results:** Multiple classes of biomarkers—including oxidative stress markers, pneumoproteins, cytokines, acute-phase reactants, and transition metals in exhaled breath condensate—demonstrate strong potential for early detection of occupational respiratory injury. Disease-specific biomarkers such as soluble mesothelin-related peptide (SMRP), osteopontin, and 8-oxo-dGuo show promise in asbestos-related disorders, while elevated TNF-α, IL-1β, IL-6, IL-8, serum ACE dysregulation serve as key indicators in silicosis. Combined biomarker panels improve diagnostic accuracy and may allow earlier recognition of disease before radiologic changes appear. **Conclusion:** Biomarkers represent a critical advancement in the prevention and early detection of occupational lung diseases. Integrating exposure, effect, and susceptibility markers can enhance clinical decision-making, facilitate timely interventions, and support precision medicine approaches in occupational respiratory health. Future research should prioritize standardization, validation, and multi-marker profiling to enable routine clinical application.

KEYWORDS: Occupational lung diseases, biomarkers, inflammatory markers, mesothelin, osteopontin.

INTRODUCTION

Occupational lung diseases (OLDs) comprise a broad group of preventable respiratory disorders resulting from chronic or repeated exposure to hazardous agents in the workplace.[1] These conditions differ from non-occupational lung diseases primarily in their etiology, as they arise from or are exacerbated by inhalation of dusts, fumes, gases, or chemical vapors associated with specific work environments.[2,3]

Workplace exposures contribute not only to classical pneumoconioses such as asbestosis and silicosis but also to the development and progression of more common respiratory disorders, including asthma, COPD, and hypersensitivity pneumonitis.[4] The clinical manifestations of OLDs vary widely, ranging from acute to chronic presentations, and may involve any region of the respiratory tract depending on the nature, intensity, and duration of exposure.[2]

CLASSIFICATION

Occupational lung diseases can be categorized into

- Classical Pneumoconiosis
- Chronic Granulomatous Disease (CGD), and

- Airway Disorders[1]

(1) CLASSICAL PNEUMOCONIOSIS

It primarily comprises three major diseases: asbestosis, silicosis, and coal worker's pneumoconiosis.[1]

Asbestosis: Asbestosis is an interstitial lung disease characterized by diffuse pulmonary fibrosis resulting from chronic inhalation of asbestos fibers. High-risk occupations include asbestos mining and processing, insulation work, construction, and shipyard industries. The disease typically demonstrates a long latency period of 20–30 years after initial exposure.[1]

Asbestos comprises several fiber types, including chrysotile, amosite, crocidolite, and tremolite, all of which are highly resistant to heat and chemicals. Inhaled fibers deposit in the lower respiratory tract, initiating persistent inflammation and fibrosis. Chronic exposure significantly increases the risk of asbestos-related malignancies, particularly lung cancer and malignant pleural mesothelioma.[5]

Silicosis: Silicosis results from inhalation of respirable crystalline silica particles typically 1–2 µm in size, commonly encountered in mining, quarrying, sandblasting, and ceramic industries.[6] These fine particles are engulfed by alveolar macrophages, causing macrophage injury and the release of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6. This inflammatory cascade stimulates fibroblast proliferation and collagen deposition, leading to the development of well-formed hyalinized silicotic nodules. When nodules coalesce, progressive massive fibrosis (PMF) may occur. Accelerated silicosis follows the same pathological process but progresses more rapidly due to high-intensity exposure over a shorter duration.[3]

Coal Worker's Pneumoconiosis: CWP, often known as black lung disease, is a chronic respiratory condition that arises from prolonged exposure to coal dust in occupational settings. Chronic inhalation of coal dust during mining and processing leads to particle accumulation and subsequent inflammation.[7]

(2) CHRONIC GRANULOMATOUS DISEASES

Chronic Beryllium Disease: CBD is a hypersensitivity disorder triggered by exposure to beryllium used in aerospace, nuclear, ceramics, and electronics industries. It is characterized by non-caseating granulomas in the lungs and skin. Symptoms include cough, fatigue, weight loss, chest pain, and dyspnea. Inhalation and dermal exposure are primary routes of entry.[8]

Hypersensitivity Pneumonitis: HP is an immune-mediated lung disease resulting from inhalation of organic dusts or chemicals. It is associated with exposures in farming, bird breeding, metalworking, and paint spraying. HP presents in acute, subacute, or chronic forms and is managed primarily by avoidance of antigen exposure. Corticosteroids may benefit acute cases but have limited benefit in chronic HP.[1,3]

(3) AIRWAY DISEASES

Asthma: Work-related asthma encompasses both occupational asthma triggered by workplace factors and asthma that, while not initially caused by work, worsens due to work-related exposures.

Sensitizer – induced asthma: Triggered by specific high-molecular-weight agents such as proteins and glycopeptides, these substances induce IgE-mediated allergic responses in a subset of exposed workers.[9]

Work – exacerbated Asthma: Work-exacerbated asthma refers to asthma that, while not stemming from occupational factors, is worsened by workplace conditions. This refers to pre-existing asthma worsened by workplace exposures such as dusts, fumes, extreme temperatures, allergens, stress, or physical exertion.[10,11]

Chronic Obstructive Pulmonary Disease (COPD): Although smoking remains the primary cause, occupational exposures account for a significant proportion of COPD risk. Dusts (silica, organic), gases, welding fumes, diesel exhaust, and irritants contribute to disease onset and progression. COPD manifests as emphysema, chronic bronchitis, or a combination of both.[12]

BIOMARKERS

A biomarker is a measurable indicator of normal biological processes, disease processes, or responses to exposure or therapy.[13] Biomarkers may indicate exposure, susceptibility, or early pathological changes.[1]

Characteristics of an ideal biomarker[16]

General characteristics

- Sample collection should be minimally invasive or non-invasive.
- The analytical method should be simple, cost-effective, and feasible for routine use.
- The biomarker should be measurable with high accuracy, reliability, and reproducibility.
- The information provided should not be obtainable through simpler or conventional methods.
- Measurement and application should comply with ethical standards.

Biomarkers of exposure

- Should be specific to a particular agent or type of exposure.
- Must correlate with environmental or atmospheric concentrations.
- Should reflect relevant exposure routes and pathways.
- Should demonstrate an association with clinical outcomes or health risks.

Biomarkers of susceptibility

- Should indicate an individual's inherent or acquired sensitivity to harmful agents.
- May influence toxicity, disease progression, or response to therapeutic interventions.
- Can reflect genetic, metabolic, or immunological predisposition.
- Should not result in stigmatization or discrimination.

Biomarkers of effect
- Should be biologically and clinically relevant.
- Must reflect early or measurable biological changes related to exposure.
- Should respond predictably to disease progression or therapeutic interventions.
- Ideally, should be reversible or modifiable following intervention.

APPLICATIONS OF BIOMARKERS

Biomarkers are instrumental in:
- Identifying occupational exposures (e.g., asbestos, cigarette smoke)
- Detecting early disease
- Predicting disease progression
- Assessing individual susceptibility
- Understanding mechanisms of occupational and environmental illnesses

Toxicologists also use them in animal studies to validate biomarkers, discover new ones, and clarify toxic and pathogenic process.[15]

CLASSIFICATION OF BIOMARKERS

There are three main categories of biological markers that have been identified: exposure markers, effect or response markers, and markers indicating host susceptibility.
- Markers of Exposure – measure external, internal, or biologically effective doses.
- Markers of Effect – reflect early or ongoing biological changes.
- Markers of Susceptibility – indicate genetic or acquired factors that alter vulnerability.[15]

EFFECTS OF BIOMARKERS IN OLD

Inflammatory Markers: Exposure to airborne particulate matter is linked with increased systemic inflammation. Key inflammatory biomarkers include:
- C-reactive protein (CRP)
- Fibrinogen
- Leukocyte counts
- Myeloperoxidase
- Eosinophil cationic protein (ECP)[17,18]

Cytokine Markers: Cytokines involved in Th1 and Th2 pathways contribute to airway inflammation and fibrosis. Important cytokines include IL-1, IL-6, IL-12, IL-10, TGF-β, TNF-α, and IFN-γ.[19]

BIOMARKERS OF SUSCEPTIBILITY

Biomarkers of susceptibility evaluate how individual responses to environmental stress vary, largely based on the person's inherent traits. These biomarkers encompass genetic elements that could affect the body's interaction with a chemical, as well as various biological factors linked to nutritional health, overall wellness, lifestyle choices, and life stages that may influence an individual's sensitivity to chemical exposure.[16]

Markers in exhaled breath condensate (EBC)—including transition metals such as iron, manganese, copper, zinc, and selenium—provide insight into oxidative stress, antioxidant activity, and susceptibility to lung injury.[20]

BIOMARKERS IN SPECIFIC OCCUPATIONAL LUNG DISEASES

Biomarkers of Asbestos Exposure: The key indicators of exposure to asbestos fibers include identifying and quantifying fibers or asbestos bodies (Abs) found in pulmonary fluids. Specifically, Abs are clusters of fibers (typically longer than 8 μm) coated with protein and iron (commonly referred to as ferruginous bodies) that, when observed alongside fibrosis in lung tissue sections, have been suggested as a diagnostic criterion for asbestosis.[16]
- Oxidative Stress Biomarkers: Oxidative DNA damage can be assessed using urinary or leukocyte levels of 8-oxo-7,8-dihydro-2′-deoxyguanosine (8-oxo-dGuo), a widely used marker reflecting asbestos-induced reactive oxygen species.[21]
- Mesothelin (SMRP): Soluble mesothelin-related peptide (SMRP) is a validated early biomarker for asbestos-related malignant mesothelioma. Serum levels can be measured using ELISA assays such as the FDA-approved Mesomark test.[21]
- Osteopontin: Osteopontin, an extracellular matrix glycoprotein involved in inflammation and tumor progression, is elevated in asbestos-exposed individuals and patients with mesothelioma. Its levels in plasma or serum may help differentiate exposed but healthy workers from those with malignancy.[22]

Biomarkers of Silicosis: Histologically, silicosis is defined by the presence of fibrotic and hyalinized nodules, thickening of the alveolar interstitium, and a buildup of inflammatory cells, including alveolar macrophages (AM) and lymphocytes. The pro-inflammatory cytokine TNF-α is crucial in silicosis as it orchestrates a broad inflammatory response and contributes to the subsequent fibrogenic reaction.[23]
- **Cytokine Profile:** Silicosis is characterized by heightened production of pro-inflammatory and fibrogenic cytokines. Elevated levels of TNF-α, IL-1β, IL-6, and IL-8 released by activated alveolar macrophages contribute to persistent inflammation, fibroblast proliferation, and collagen deposition, ultimately driving nodule formation and fibrosis.[23]
- **Evidence:** Multiple studies have demonstrated increased concentrations of these cytokines in bronchoalveolar lavage fluid (BALF) of patients

with silicosis compared with healthy controls. Research also indicates dysregulation of apoptosis pathways, particularly involving Fas/FasL expression, and raised serum copper levels linked to enhanced ceruloplasmin activity. Serum ACE activity has consistently been reported as elevated in granulomatous diseases, including silicosis, supporting its role as an auxiliary biomarker.[24]

- **Angiotensin-Converting Enzyme (ACE):** ACE is a membrane-bound glycoprotein responsible for converting angiotensin I to angiotensin II and degrading bradykinin. Its high expression in pulmonary endothelial cells makes serum ACE activity a useful indicator in diseases involving granulomatous inflammation, including silicosis.[25]

CONCLUSION

Workplace exposures continue to play a major role in the development of airway and lung diseases. Early identification of hazardous exposures, combined with biomarker-based screening, offers opportunities for timely diagnosis, risk stratification, and prevention. The future of occupational respiratory care lies in integrated biomarker panels that combine exposure, effect, and susceptibility indicators to support precision medicine.

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