Biomarkers of World Trade Center Particulate Matter Exposure: Physiology of Distal Airway and Blood Biomarkers that Predict FEV_1 Decline

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Abstract

Biomarkers can be important predictors of disease severity and progression. The intense exposure to particulates and other toxins from the destruction of the World Trade Center (WTC) overwhelmed the lung's normal protective barriers. The Fire Department of New York (FDNY) cohort not only had baseline pre-exposure lung function measures but also had serum samples banked soon after their WTC exposure. This well-phenotyped group of highly exposed first responders is an ideal cohort for biomarker discovery and eventual validation. Disease progression was heterogeneous in this group in that some individuals subsequently developed abnormal lung function while others recovered. Airflow obstruction predominated in WTC-exposed patients who were symptomatic. Multiple independent disease pathways may cause this abnormal FEV_1 after irritant exposure. WTC exposure activates one or more of these pathways causing abnormal FEV_1 in an individual. Our hypothesis was that serum biomarkers expressed within 6 months after WTC exposure reflect active disease pathways and predict subsequent development or protection from abnormal FEV_1 below the lower limit of normal known as WTC-Lung Injury (WTC-LI). We utilized a nested case–cohort control design of previously healthy never smokers who sought subspecialty pulmonary evaluation to explore predictive biomarkers of WTC-LI. We have identified biomarkers of inflammation, metabolic derangement, protease/antiprotease balance, and vascular injury expressed in serum within 6 months of WTC exposure that were predictive of their FEV_1 up to 7 years after their WTC exposure. Predicting future risk of airway injury after particulate exposures can focus monitoring and early treatment on a subset of patients in greatest need of these services.

Keywords
- World Trade Center
- lung injury
- predictive biomarkers
- obstructive airway disease

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Occupational Exposure and the Development of Obstructive Airways Disease

There is mounting evidence that occupational exposures are a cause of obstructive airways disease (OAD).[1] Occupational exposures are varied but often consist of particulate matter (PM) and other toxins. Epidemiologic evidence links PM exposure to the development of vascular and pulmonary diseases.[2–4] The development of OAD from PM-induced inflammation and smoke is poorly understood,[5] but studies have shown that exposure to high ambient PM significantly decreases forced expiratory volume over 1 second (FEV_1) after 5 to 7 days.[6,7] Long-term exposure to air pollutants from motor vehicles and other sources impairs lung function.[8–12] Upper respiratory symptoms increase by 3% per 10 $\mu g/m^3$ of PM exposure.[6,13]

World Trade Center Particulate Matter Exposure

The destruction of the WTC led to the release of an estimated 10 million tons of material, exposing over 300,000 rescue workers and New York City (NYC) residents and local workers to World Trade Center particulate matter (WTC-PM).[14–16] The concentrations of airborne and respirable WTC-PM ranged from 1 to 100 mg/m^3 immediately after the WTC collapse.[17–19] One month after the event, $PM_{2.5}$ ($\leq$ 2.5 µm) concentration was 196 $\mu g/m^3$, three times the National Ambient Air Quality Standards 24-hour standard.[20] The toxicology and physical properties of WTC-PM have been well described.[18,21] WTC-PM is primarily composed of pulverized concrete, plastics, and other hydrocarbons. WTC-PM was found to be highly alkaline, pH 9–11.[18,22] Exposure to both fine ($PM_{2.5}$) and coarse (PM_{53}, $\leq$53 µm) PM has been implicated in the development of lung injury.[23,24]

Many rescue and recovery workers as well as residents and local workers continued to be exposed to dust for at least 3 months.[25] Induced sputum of NYC firefighters who were exposed to WTC-PM post-9/11 showed increased amounts of PM (1–50 µm), neutrophils, and eosinophils even 10 months after the original exposure.[26] In a case series of symptomatic local residents and community workers who underwent lung biopsy several years after 2001, emphysematous change, small airway abnormalities, and rare cases of interstitial fibrosis were seen. Furthermore, opaque and birefringent particles were found within the macrophages of all cases, and particulate analysis showed these particles to be similar in composition to WTC particulates.[27]

WTC-Associated Pulmonary Function and Radiographic Phenotype

Respiratory compromise has been documented in Fire Department of New York (FDNY) rescue workers,[19,28–32] other exposed workers,[33] and lower Manhattan residents.[34–36] These affected WTC-exposed individuals continue to have increased symptoms, medication usage, pulmonary disability, and lower quality of life 13 years after exposure.[15,19,20,22,24,28–32,37–75] Thus far, the physiologic and radiographic phenotype associated with WTC exposure has been heterogeneous in nature (►**Table 1**). Many exposed individuals have bronchial wall thickening and air trapping on computed tomography (CT). Emphysema, chronic obstructive pulmonary disease (COPD), and OAD occur, but some studies have shown that there is a significant restrictive phenotype seen.[79]

Table 1 Overview of the spirometric and radiographic findings in the WTC exposed cohorts

Source	Phenotype	Study cohort	Findings	References
PFT	OAD	FDNY, iron workers, NYPD, rescue-recovery workers, and volunteers	Decreased FEV_1, decreased FEV_1/FVC	39,41–44,46,47,50 51,61,66,155–159
	BD response	FDNY	Reversible abnormality on post-BD spirometry[a]	66
	MCT	FDNY	Bronchial hyperreactivity[b]	31,66
	Pseudorestrictive	FDNY, iron workers	FEV_1/FVC < LLN, FVC < LLN, TLC $\geq$ LLN	33,160
	Restrictive	FDNY, NYPD, community workers		24,27,79,161
	Small airways	FDNY, community workers	FVC < LLN, FEV_1/FVC and TLC $\geq$ LLN	66,79,162
Radiographic	Emphysema/COPD	FDNY, community workers		38,66
	BWT	FDNY		66,79
	Air trapping	FDNY, NYPD, technical and construction workers		66,79,163

Abbreviations: BD, bronchodilator; BWT, bronchial wall thickening; FDNY, Fire Department of New York; FEV_1, forced expiratory volume over 1 second; FVC, forced vital capacity; LLN, lower limit of normal; OAD, obstructive airways disease; PFT, pulmonary function test; TLC, total lung capacity.
[a]Post-BD $FEV_1 \geq 12\%$ change from pre-BD and improvement of $FEV_1 \geq 200$ mL.
[b]Methacholine $PC_{20} \leq 8$ mg/mL, < 16 mg/mL.

The Utility of Biomarkers of Occupational Lung Function Loss

Identification of biomarkers of disease progression is crucial to guide early intervention as well as treatment. In addition, identification of biomarkers of disease has potential to direct future research into mechanisms producing airflow obstruction. These biomarkers can also identify those at risk who would most benefit from avoidance of further exposure or aggressive management. Measuring biomarkers in serum is a powerful and cost-effective approach for risk factor discovery. Immediately after 9/11, the FDNY-Bureau of Health Services (BHS) began implementing protocols for obtaining, processing, storing, and retrieving serum from the WTC-exposed firefighters. This cohort of nearly 16,000 FDNY rescue workers (firefighters, paramedics, and emergency medical technicians) form a well-characterized cohort that has been a powerful resource for documenting the impact of WTC exposure on the lung (►**Fig. 1**). Serum samples were obtained on a majority of the cohort from September 2001 to February 2002, at initial development of airflow obstruction. Taking advantage of this unique cohort, our group has investigated predictive biomarkers of WTC-associated lung injury.[76–78] We have identified biomarker subtypes that may be indicators of associated pathways active in the development of WTC-associated end-organ dysfunction. This article is dedicated to reviewing our findings and their physiologic importance.

For biomarker discovery, we chose to focus on FEV_1 as outcome and indicator of disease state. Spirometry had been measured annually in the FDNY cohort 3 years prior to 9/11/2001, and this cohort continued to receive annual pulmonary function tests (PFTs) as part of the FDNY-WTC-Medical Monitoring and Treatment Program (MMTP). This longitudinal surveillance allowed us to document that in the first year after 9/11, there was a decline in FEV_1 in exposed FDNY rescue workers at a rate 12 times greater than that found pre-9/11.[29,49] Further evaluation showed that firefighters who had never smoked lost an average of 439 mL of FEV_1 in the first year post-9/11, followed by a mean annualized reduction in FEV_1 of 26 mL per year in the subsequent 6.5 years.[15,19] In addition, acute airway inflammation, reactive airway dysfunction, and overall decline in FEV_1 have been reported in rescue workers exposed to WTC-PM.[31,66]

Our study cohort demonstrated a reduced FEV_1 below the lower limits of normal (LLN) was consistent with an obstructive pattern[66,79] with a low FEV_1/forced vital capacity (FVC) ratio (median, 72; interquartile range [IQR], 65–77). This suggested that $FEV_1 < LLN$ could be used as a surrogate for obstruction in this population. We therefore defined WTC-Lung Injury (WTC-LI) in this population of firefighters by their $FEV_1 < LLN$ measured during subspecialty visit after exposure and upon becoming symptomatic. Measurement of FEV_1 is robust and easily measurable. Furthermore, FEV_1 has been the primary endpoint in trials of therapeutic agents and has been used to track health outcomes in numerous lung diseases, including COPD.[80]

Design of the FDNY-WTC Biomarker Study

At their first FDNY medical monitoring exam post-9/11, all participants received PFT and serum aliquots were collected and deposited in a biorepository (►**Fig. 1**). Symptomatic firefighters were referred to subspecialty pulmonary evaluation between 9/12/2001 and 3/10/2008.[66]

Nested Case–Cohort Control Study Design

We used a nested case–cohort control strategy to define biomarker expression (►**Fig. 1**).[81–84] The baseline cohort

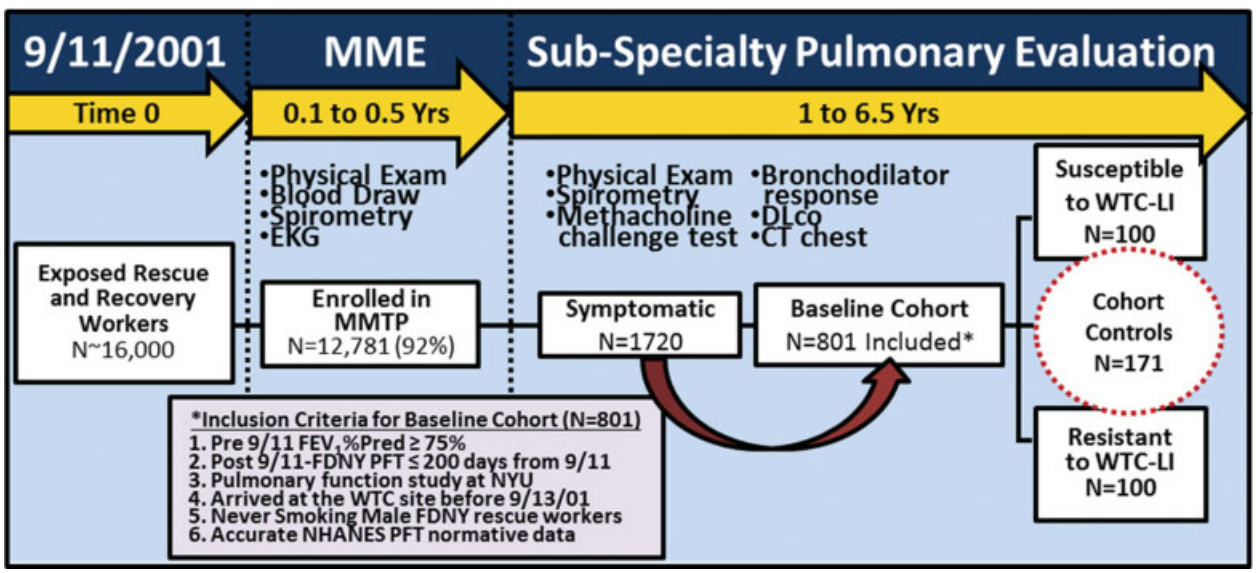

Fig. 1 WTC-FDNY biomarker timeline and development of nested case–cohort control study design. Summary of phenotyping that was done on the cohort and case susceptible and resistant to WTC-LI are shown in the inclusion criteria to develop the baseline cohort. Overlapping of cohort control with cases susceptible and resistant to WTC-LI is highlighted in the dashed red circle. FDNY, Fire Department of New York; WTC-LI, World Trade Center-Lung Injury; MME, first medical monitoring exam.

was derived from 1,720 exposed workers who needed subspecialty pulmonary evaluation and treatment within 6.5 years of 9/11. There was significant interindividual variation in lung function with some patients recovering and others suffering loss of lung function, thereby allowing us to study both outcomes in a similarly exposed cohort.[46,49] A homogeneous subcohort of subjects without prior lung disease or tobacco use was identified after applying inclusion criteria ($n = 801$). The two case subgroups ($n = 100$ for each) were intended to over-sample those *susceptible* and *resistant* to WTC-LI. Those susceptible to WTC-LI had $FEV_1 <$ LLN and included patients in the bottom octile of FEV_1% predicted at the time of subspecialty pulmonary exam. In contrast, the resistant population included those identified in the top octile of FEV_1% predicted at the same time point, and had $FEV_1 \geq$ LLN. The cohort ($n = 801$) was stratified on tertiles of FEV_1 and body mass index (BMI), and the cohort control ($n = 171$) was randomly selected. This cohort control has overlapping populations with the susceptible and resistant populations, and ensures sufficient representation of the general FDNY population. All subjects signed informed Institutional Review Board–approved consent at the time of enrollment allowing analysis of their information and samples for research (Montefiore Medical Center: #07-09-320 and New York University: #11-00439). Serum samples were analyzed utilizing Luminex as previously described.[40,50] Both case definitions and cohort controls were randomized to batches in a 1:1:2 ratio to avoid batch effect bias and analyzed contemporaneously to avoid variability in time-dependent sample decay.[82,85]

All demographics were obtained from the FDNY-WTC-monitoring database. Degree of exposure was self-reported at the first FDNY-WTC monitoring and was categorized using the FDNY-WTC Exposure Intensity Index based on arrival time: (1) Present on the morning of 9/11/2001 (2) Arrived between the afternoon of 9/11/2001 and 9/12/2001.[66] Those arriving after day 3 were excluded from analysis as a result of their low numbers in this sample.[49,86]

Serum Biomarkers of WTC-LI

Biomarkers of Inflammation

We hypothesized that individuals susceptible to airflow obstruction, induced by environmental irritants, would express different levels of proinflammatory cytokines compared with similarly exposed individuals in the cohort control. We identified inflammatory cytokines and chemokines in the serum of FDNY rescue workers obtained within 6 months of 9/11 using commercially available multiplex kits (►**Fig. 1**). We correlated inflammatory biomarkers at monitoring entry with FEV_1 at subspecialty pulmonary exam. Cases of those susceptible to WTC-LI with $FEV_1 <$ LLN were compared with controls with $FEV_1 \geq$ LLN. From monitoring entry to subspecialty pulmonary exam years later, FEV_1 declined 12% in cases and increased 3% in controls. Elevated granulocyte-macrophage colony-stimulating factor (GM-CSF) and macrophage-derived chemokine (MDC) increased the risk for subsequent $FEV_1 <$ LLN by 2.5- and 3.0-fold in a logistic regression model adjusted for exposure, BMI, age on 9/11, and neutrophil (►**Fig. 2A**). Roles for GM-CSF and MDC in airway injury are biologically plausible in that human bronchial epithelial cells produce GM-CSF in response to PM and MDC is elevated in bronchoalveolar lavage of asthmatics. The model had sensitivity of 38% and a specificity of 88%. The low sensitivity suggested that other biomarkers not yet identified were significant risk factors for accelerated decline of lung function after irritant exposure at the WTC site.

Metabolic Biomarkers as Predictors of WTC Lung Function Loss

Metabolic syndrome (MetSyn) is a principal contributor to systemic inflammation-associated end-organ damage.[87] This interaction is best understood in vascular diseases, but previous cross-sectional studies have suggested associations of impaired lung function with MetSyn.[88–92]

Utilizing our case–cohort control study design, we diagnosed MetSyn using World Health Organization (WHO)-modified National Heart Lung and Blood Institute/American Heart Association criteria. Subjects had to meet three of the following five criteria: (1) elevated triglycerides $\geq$ 150 mg/dL (1.7 mmol/L); (2) reduced high-density lipoprotein (HDL)

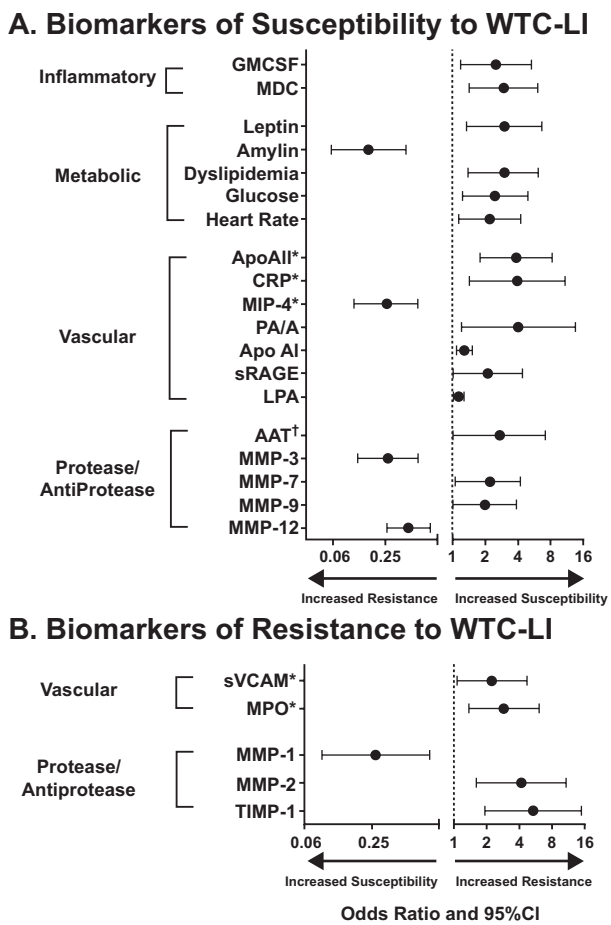

Fig. 2 Overview of biomarkers predicting WTC-LI as defined by $FEV_1 <$ LLN. (**A**) Utilizing a susceptible case–cohort control design. (**B**) Utilizing a resistant case–cohort control design. *Relative risk.

< 40 mg/dL in men; (3) elevated systolic blood pressure (BP) ≥ 130 mm Hg or diastolic BP ≥ 85 mm Hg; (4) elevated fasting glucose ≥ 100 mg/dL[93,94]; (5) BMI >30 was substituted for increased waist circumference as per WHO criteria.[95] Concurrent fasting blood levels of HDL, glucose, and triglycerides were assayed when the subjects' first post-9/11 serum samples were collected and banked at monitoring entry.

We found that cases of WTC-LI had significantly higher glucose and heart rate at monitoring entry than controls. However, cases did not have significantly different triglycerides, systolic BP, or HDL. There was a trend of a higher percentage of individuals with MetSyn in cases compared with controls (27 vs. 16%, $p = 0.07$). Cases had a larger proportion of individuals with higher glucose (28 vs. 16%, $p = 0.03$) and lower HDL (32 vs. 20%, $p = 0.05$). The differences in lipid profiles between cases and controls were accentuated when individuals had combined abnormalities in triglycerides and HDL (dyslipidemia, defined as triglycerides ≥ 150 mg/dL and HDL< 40 mg/dL) (28 vs. 14%, $p = 0.006$). In addition, we defined a heart rate above the median of 66 beats per minute (bpm) as elevated for the entire nonsmoking cohort. Cases compared with controls had a larger proportion with elevated heart rate (65 vs. 48%, $p = 0.02$). We then defined cut points for metabolic analytes using the top quartile for leptin and amylin.

We assessed if any of the biomarkers with significantly different prevalence altered the odds ratio (OR) of being a case using logistic models adjusted for BMI, age on 9/11, race, and WTC arrival time. When biomarkers and clinical parameters were included in the final model, dyslipidemia, elevated heart rate, and elevated leptin significantly increased the odds of being a case: dyslipidemia, OR = 3.03, heart rate ≥ 66 bpm, OR = 2.20 and leptin ≥ 10,300 pg/mL, OR = 3.00 (►**Fig. 2A**). Elevated amylin was strongly protective, decreasing the odds of being a case by 84% (►**Fig. 2A**). We assessed the ability of the final logistic regression model to predict case status using receiver operating characteristic analysis. The final model had an area under the curve (AUC) of 0.774 after adjusting for previously mentioned covariates.

Biologically active lipid metabolites are plausible pathways of disease and can be attenuated pharmacologically. As a logical extension of our earlier work, we turned our attention to lysophosphatidic acid (LPA), a low-density lipoprotein derivative, and apolipoprotein (Apo)A1, a component of HDL. LPA activates pathways involved in vascular injury.[96–99] Vascular injury occurs early in smoking-related COPD with pulmonary perfusion abnormalities and reduced blood return to the heart observed before development of abnormal FEV_1.[100,101] Similar pathophysiology likely occurs in irritant induced COPD. Pulmonary arteriopathy was present in 58% of lung biopsies from non-FDNY WTC-PM exposed individuals and in 74% with constrictive bronchiolitis after inhalational exposures suffered during military service in Iraq and Afghanistan.[27,102]

To assess the relationship between LPA and ApoA1 with the outcome of being a susceptible case, we used a multivariable logistic model (adjusted for BMI, exposure intensity, pre-9/11 FEV_1% predicted, age on 9/11, race, WTC exposure, dyslipidemia, and platelet and neutrophil count). In the adjusted model, a 10-μM increase of LPA was associated with a 14% increase in the odds of having WTC-LI, while an increase of 1 mg/mL of ApoA1 increased the odds of developing WTC-LI by 29%. These findings further demonstrate the biological relevance of lipids and their metabolites in the progression of OAD after WTC exposures.

Vascular Biomarkers of WTC-LI

Recent studies associate systemic vascular involvement with lung disease.[103,104] Prospective studies have demonstrated an association between systemic inflammation, impaired lung function, and central arterial stiffness that occurs prior to the development of cardiovascular disease (CVD).[105–107] Similarly, perfusion abnormalities and reduced pulmonary blood flow occur prior to development of abnormal FEV_1 in smokers at risk for COPD. Lung biopsies from WTC-PM-exposed individuals showed pulmonary arteriopathy and constrictive bronchiolitis secondary to inhalational exposures, and hinted at the potential use of vascular biomarkers associated with WTC-LI.[27,102]

Vascular biomarkers were investigated in subjects who went on to develop WTC-LI and in those who did not. Individuals with elevated apolipoprotein (Apo)AII and C-reactive protein (CRP) levels within 6 months of 9/11 had significantly increased risk of developing decreased lung function over the subsequent 6 years while elevated macrophage inflammatory protein-4 (MIP-4) reduced the risk of susceptibility to decreased lung function (►**Fig. 2A**). Alternately, firefighters with elevated soluble vascular cell adhesion molecule and low myeloperoxidase (MPO) levels within 6 months of 9/11/2001 predicted recovery of lung function, and showed return of FEV_1 to pre-9/11 values after an acute decline post-9/11 (►**Fig. 2B**).

The biologic plausibility of our findings is significantly supported by the literature. CRP is a known marker of acute systemic inflammation and CVD that has been shown to have an inverse relationship with FEV_1.[108–110] CRP levels were elevated in individuals with COPD independent of any CVD risks.[111] Pulmonary hypertension, a disease of the pulmonary vasculature, is associated with CVD biomarkers such as apolipoprotein.[112] This parallels our prior observation that dyslipidemia predicts poor outcome after WTC dust exposure.

MIP-4 was inversely associated with odds of developing WTC-LI. This finding contrasts with that of the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) cohort, in which elevated MIP-4 was associated with concurrent COPD, increased risk of cardiovascular hospitalization and mortality.[113] The difference in the association of MIP-4 may be due to the timing of the biomarker studies; our cohort had blood biomarkers before disease presentation, whereas the ECLIPSE study focused on end-stage disease. MIP-4 (CCL18, PARC) is an early promoter of regulatory T-cell differentiation and may generate an anti-inflammatory counter-regulatory response that leads to protection of lung injury in our group.[114,115] Finally, low levels of MPO demonstrate less neutrophil activation, an important mediator of PM-induced pulmonary and cardiovascular

injury. In our group, it was associated with resistance to the damaging effects of WTC-PM exposure.[116,117] Our data and other recent reports emphasize the need to better understand the mechanisms by which inhaled irritants damage pulmonary vessels.

In addition to serum biomarkers of vascular involvement, our group and others have investigated quantifiable vasculometric changes associated with OAD. An increased ratio of the pulmonary artery to aorta (PA/A) diameter measured by CT has been associated with pulmonary hypertension and poor outcomes in various disease states. The elevated PA/A ratio implies relative pulmonary vascular enlargement and has been associated with past and future exacerbations in patients with moderate-to-severe COPD.[118] PA/A has been associated with a decreased FEV_1 in the same population. Furthermore, in patients with CVD, a PA/A ratio >1 has been associated with increased mortality.[119] PA/A from chest CT scans obtained for clinical indications in our case–cohort control population were calculated. Using the Youden index, a PA/A value of 0.92 was selected as the cutoff for best predicting the development of WTC-LI in a logistic regression analysis. After adjusting for age at CT, pre-9/11 FEV_1, BMI at subspecialty pulmonary evaluation, and exposure, the odds of having WTC-LI in patients with a value of PA/A $\geq$ 0.92 was 4.02 (►**Fig. 2**).

In the ECLIPSE/COPD Gene cohort, PA/A >1 was associated with disease severity and subjects had more advanced disease than in the FDNY-WTC cohort.[118] Although our cohort's mean PA and A were similar to those measured in ECLIPSE/COPD Gene cohort, 81% of our cohort did not meet GOLD COPD criteria. Therefore, it was expected that the PA/A would be less than previously reported ratios of 1.[118] When comparing our cohort to the Framingham Heart Study, our case mean PA/A and PA values are similar to their 90th% upper limit of normal.[120] Our study suggests that the PA/A ratio $\geq$ 0.92 may represent a marker of early vascular injury in PM-related lung disease and is in line with these recent publications.

Protease/Antiprotease Balance as Biomarkers of WTC-LI

The balance of protease/antiprotease activity is the crux of many diseases including cigarette-induced chronic lung disease and other causes of accelerated lung function decline.[121–124] The serine antiprotease α-1 Antitrypsin (AAT) predicts accelerated FEV_1 decline in WTC-exposed firefighters and is a well-studied biomarker of smoking-associated lung disease.[63] To determine the impact of AAT levels on FEV_1 decline after WTC exposure, AAT levels and genotype were assayed in 90 randomly selected subjects. The rate of FEV_1 loss increased with increasing AAT deficiency defined either by genotype or serum concentration. Moderately (MS or SZ genotype) deficient rescue workers' FEV_1 declined 110 cm^3/year more than normal, while mildly (MS or SS genotype) deficient rescue workers lost 32 cm^3/year more than normal. Rescue workers with AAT serum levels below 20 μmol/L lost 49 cm^3/year of FEV_1 compared with workers with AAT levels $\geq$ 20 μmol/L. There was no impact of AAT levels or genotype on spirometric decline rates prior to 09/11/2001 suggesting an interaction between low AAT and WTC exposure.[63] In data previously unreported, utilizing our case–cohort control study we found that AAT < 85 mg/dL increased the risk of developing WTC-LI (►**Fig. 2A**).

Matrix metalloproteinases (MMPs) can catabolize and degrade the extracellular matrix.[125] Many are known intermediates of each other, and their levels are affected by environmental factors such as hypoxia, inflammation, and oxidative stress. Several MMPs can be either directly inhibited by or form complexes with tissue inhibitors of matrix metalloproteinases (TIMPs). MMP/TIMP balance is another well-defined mediator of COPD.[125]

Genetic association studies with MMPs demonstrate a strong association with the development of lung disease.[121] MMP-1 is induced in smokers with COPD and its overexpression in mice causes emphysema.[126,127] The destructive effects of MMPs are inhibited by TIMPs. There are little data on the role of MMPs and TIMPs in the resistance to the damaging effect of dust exposure.[128–131] One carefully done pathologic study demonstrated increased MMP-2 and TIMP-1 mRNA expression in surgically removed lung and predicted improved FEV_1 in COPD patients.[132] As serum MMP and TIMP expression is related to the development of COPD, the link between serum MMP/TIMP balance and lung function in the WTC-exposed cohort became the focus of our next set of investigations.[133]

In investigating susceptible cases, elevated serum levels of MMP-3 and MMP-12 reduce the risk of developing WTC-LI. Increased time between 9/11 and blood draw is associated with a diminished protective effect. Specifically, early elevated expression of MMP-3 and MMP-12 in serum within 200 days after WTC exposure predicts protected lung function over the subsequent seven years (2001–2008). We found that MMP-3 and MMP-12 ranges of the cohort were comparable to other published patient populations, including healthy controls and patient cohorts with emphysema or rheumatoid arthritis.[134,135] MMP-3 was found to be more protective than MMP-12 (►**Fig. 2A**). Both biomarker models displayed robust predictive ability by logistic regression with AUC > 0.8.

Compared with susceptible cases, the resistant cases had greater than average reduction in FEV_1 immediately after exposure, but returned to pre-exposure FEV_1 over the next 6.5 years. Because serum was drawn well before the pulmonary function test that demonstrated recovery, the biomarker information reflected evolving injury. All subjects in this nested case–control investigation had heavy WTC dust exposure and arrived at the collapse site within 2 days of 9/11/2001. MMP-2 and TIMP-1 expression above the 75th percentile are protective biomarkers, significantly increasing the odds of resistance between 4.2- and 5.4-fold. Alternately, elevated MMP-1 is a risk factor, reducing the odds of resistance by 73% (►**Fig. 2B**). The biomarker model using serum MMP-1, MMP-2, and TIMP-1 concentration predicted resistance with a sensitivity of 74%, a specificity of 86%, and a receiver operator characteristic of 0.90.[40]

Innate and Humoral Mediators

The ratio of FEV_1/FVC is another well-validated spirometric measure of airflow obstruction. Genome wide association studies (GWAS) observed that a set of genetic variants of chitinases is associated with only FEV_1. Polymorphisms at other loci can predict FEV_1/FVC and both FEV_1 and FEV_1/FVC.[136,137] Biomarkers predicting abnormal FEV_1/FVC may therefore be distinct from those predicting abnormal FEV_1. Hence, we investigated if biomarkers expressed within 6 months of 9/11/2001 predicted future abnormal FEV_1/FVC in this WTC-exposed cohort. In this investigation, we evaluated innate and humoral mediators. We found that increased serum chitotriosidase (CHIT) reduces the odds of developing obstruction after WTC-PM exposure and is associated with recovery of lung function. Alternately, elevated immunoglobulin E (IgE) was a risk factor for airflow obstruction and progressive lung function decline.

CHIT belongs to the glycosyl hydrolase 18 gene family that binds and cleaves chitin. CHIT is part of the innate host defense against bacterial and fungal infections, as chitin is a major structural component in bacteria, fungi, insects, and crustaceans.[138–142] CHIT is produced in mature monocyte-derived macrophages, lung macrophages, and other specific subsets of tissue macrophages.[143–146] Elevated CHIT expression is associated with smoking-induced and fibrotic lung disease.[147,148] However, its biological function has not been clearly defined.

IgE-mediated humoral immunity is another important immune response mechanism in the respiratory tract.[149] Elevated IgE is a key immune mediator in asthma. Children and adults with asthma have higher IgE than normal controls and anti-IgE antibody is an effective asthma modulator.[150–153] Elevated serum IgE is strongly associated with low FEV_1/FVC in patients with chronic obstructive lung disease.[154]

Summary

Identification of serum biomarkers that predict lung disease can direct future research into mechanisms producing airflow obstruction, fuel future work about their downstream effects, and aid in the development of diagnostic markers and potential therapeutic targets in clinical trials. Our study cohort, with clinical information before and after a significant environmental exposure, serves as a unique opportunity to identify biomarkers associated and predictive of lung and vascular disease. Although many studies have focused on occupational biomarker identification, our study cohort has lung function assessment prior to exposure and development of disease. This is ideal for the study of predictive biomarkers, and has allowed us to establish leadership in pathophysiologic investigation of WTC-LI.[76–78]

We have developed a high-dimensional dataset that includes at least 130 serum and radiographic biomarkers in a cohort of firefighters with intense exposure to WTC dust. We have identified multiple biomarkers of biologically plausible pathways that are active in the development of WTC-associated end-organ dysfunction. It was necessary to develop a parsimonious biomarker model that would generate reproducible and generalizable findings. To optimize identification of candidate biomarkers from a relatively small sample size, we utilized a case–cohort control for much of our work. Furthermore, the small sample size in a high-dimensional biomarker dataset could obscure potential pathways of interest. We studied biomarkers in separate but often related pathways to further optimize signal to noise. Future work will include repeated serum sampling to add a longitudinal component to the FDNY-NYU biorepository. This will expand our understanding of biomarker evolution and will be a resource for investigating other long latency WTC-related diseases.

Development of OAD following PM exposure is a major health concern worldwide. First responders and the military may be specifically more affected by the high amounts of particulate exposure during disasters and conflict. Identifying predictive biomarkers of FEV_1 loss allows for early identification of at-risk individuals allowing for early screening, necessary treatment, and risk avoidance. While unique in many ways, the exposures on 9/11/2001 have allowed us to make observations related to lung disease progression that may translate to other occupationally and environmentally exposed populations. The processes initiated by WTC exposure impacted multiple distinct injury and repair pathways. Our prior studies and this review emphasize the utility of serum stored in the aftermath of a disaster. The insight into protein expression in OAD gained from the analysis of this serum has the potential to guide future mechanistic and therapeutic studies designed to blunt the impact of the worldwide COPD epidemic.

Conflict of Interest

There are no conflicts of interest.

Note

Michael D. Weiden and Sophia Kwon contributed equally to this article.

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