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Review

Biomarkers of Patient Intrinsic Risk for Upper and Lower Airway Injury After Exposure to the World Trade Center Atrocity

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Background *High rates of upper and lower airways disease have occurred in Fire Department of the City of New York (FDNY) workers exposed to the World Trade Center (WTC) disaster site. Most experienced acute declines in pulmonary function, and some continued to experience decline over 14 years of follow-up. Similarly, some with rhinosinusitis had symptoms requiring sinus surgery.*
Aim *To increase generalizability of biomarker investigation, we describe biomarkers of risk for upper and lower airway injury that do not require stored serum.*
Methods *We review WTC biomarker literature.*
Results *Cytokines expressed in stored serum from the first 6 months post-9/11 can identify individuals at higher risk for future abnormal pulmonary function.*
Conclusion *This research will help identify individuals at high risk of lung and sinus disease that develop after these, or future, irritant exposures for intensive monitoring and treatment. It may also identify targets for effective therapeutic interventions. Am. J. Ind. Med.* 59:788–794, 2016.

KEY WORDS: World Trade Center; predictive biomarkers; lung injury; airways disease

The collapse of the WTC produced a massive dust cloud containing alkaline particles that overwhelmed the upper and lower respiratory systems defenses. Those who were present at the time of the collapse were caught in a dense dust cloud and sustained the highest exposures leading to more loss of lung function and a greater need for subspecialty pulmonary evaluation [Aldrich et al., 2010; Weiden et al., 2010]. Fires burned for months and rescue/recovery work re-suspended the dust producing lower level airway injury. In the 14.5 years since the exposure, a subgroup of those exposed have experienced recurrent inflammation at the mucosal surfaces in the nose, sinuses, and lungs, producing chronic rhinosinusitis, declining forced expiratory volume at one second (FEV_1) and reactive airway disease. While the first cases of disabling lower airway injury presented within weeks of 9/11/2001, it took many years for the extent of upper airway injury to emerge, such as chronic sinusitis requiring treatment with sinus surgery [Niles et al., 2013, 2014; Kwon et al., 2016; Weakley et al., 2016]. The combined effects of upper and

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lower airways disease has resulted in chronic, persistent symptoms and negative impacts on quality of life, in spite of optimal medical management [Weakley et al., 2011; Webber et al., 2011; Wisnivesky et al., 2011; Yip et al., 2015].

Initially, World Trade Center Cough was recognized as an acute syndrome of severe cough and shortness of breath leading to medical leave for 4 or more weeks [Prezant et al., 2002]. This was followed by an acute decline in lung function without recovery in a majority of the population [Aldrich et al., 2010]. Of those exposed most stabilized, however, 19.5% of the cohort experienced greater than 64 ml per year FEV_1 decline which was twice the average age-related FEV_1 decline of 32 ml/year [Aldrich et al., 2016]. Approximately 13% of the population had FEV_1 below the lower limit of normal post exposure [Aldrich et al., 2010]. Incident respiratory disability has persisted for many years following exposures lasting only days to months [Niles et al., 2011], suggesting that a relatively brief but intense irritant exposure has produced non-resolving inflammation with consequent respiratory symptoms and loss of lung function.

Extensive investigations of leukocyte derived inflammatory proteins as biomarkers of lung injury after WTC-exposure have been reviewed elsewhere [Nolan et al., 2012; Weiden et al., 2013]. Our group has 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 susceptibility and resistance to lung function decline post-WTC exposure (Table I). The initial series of investigations used serum collected during the evolution of disease before disability existed and lung disease was diagnosed. Thus, the results were not confounded by reverse causation where the disease produced alteration of the biomarker.

TABLE I. Biomarkers Associated With Susceptibility and Resistance to Lung Function Decline Post-WTC Exposure

	Susceptibility	Resistance
Inflammation	GM-CSF, MDC	Chitotriosidase
Metabolic syndrome	Leptin, dyslipidemia, glucose intolerance	Amylin
Vascular injury	Apo AII, Apo AI, CRP, sRAGE, LPA, PA/A	sVCAM, MIP-4, MPO
Protease/antiprotease	AAT, MMP-1, MMP-7, MMP-9,	MMP-2, MMP-3, MMP-12, TIMP-1

AAT, Alpha-1 antitrypsin; APO, apolipoprotein; Dyslipidemia, high density lipoprotein (HDL) $<$40 mg/dl and triglycerides $\geq$150 mg/dl; GM-CSF, granulocyte macrophage-colony stimulating factor; glucose intolerance, fasting glucose $>$100 mg/dl; HDL, high density lipoprotein; LPA, lysophosphatidic acid; MDC, macrophage derived chemokine; MIP, macrophage inflammatory protein; MMP, matrix metalloproteinases; MPO, myeoloperoxidase; PA/A, pulmonary artery/aorta; sVCAM, soluble vascular cell adhesion molecule; sRAGE, soluble receptor for advanced glycation end-products; TIMP, tissue inhibitors of matrix metalloproteinases.

The biomarkers, therefore, are more likely to reflect inflammatory processes that participated in altered airway function. Confirmation of a causal role in disease development, however, requires experiments in model systems or effective treatments directed at specific pathways identified by biomarkers in specific individuals.

The assays on inflammatory cytokines, however, are not commercially available and quite expensive, thereby limiting generalizability for use after this or future disasters. Another challenge of using cytokines as biomarkers is that venipunctures need to be carefully drawn because leukocytes in the blood can produce inflammatory proteins post-venipuncture, leading to false-positive results. In consideration of these challenges, this review describes our data on biomarkers of risk for upper and lower airway injury, concentrating on those studies that do not require stored serum.

A majority of the biomarker investigation on WTC-exposed firefighters has used FEV_1 falling below the lower limit of normal as the outcome. This is a widely used measure of poor outcome but is confounded by pre-exposure FEV_1. Those who had abnormal FEV1 post 9/11 had below average but normal pre-9/11 FEV_1 [Weiden et al., 2013]. One interpretation of this observation is in the subgroup with pre-exposure FEV_1 close to LLN, an injury that resulted in a fix proportion loss FEV_1 would be more likely to produce an abnormal FEV_1. Similarly, early lung function is important for interpreting lung function trajectories in chronic obstructive pulmonary disease cohorts [Lange et al., 2015]. Since pre-exposure PFT are not available on non-FDNY cohorts, the interpretation of post-exposure lung function can be difficult in other WTC-exposed cohorts. Additional information on the intrinsic risk factors, which do not depend on pre-9/11 data, of the patients for irritant induced upper and lower airways disease would be helpful in risk stratifying these patients.

The FDNY WTC Health Program is a resource for understanding occupational irritant-induced airways diseases related to smoke and particulate exposures after other irritant exposures among additional cohorts, such as, soldiers deployed to Iraq and Afghanistan [Caplan-Shaw et al., 2011; King et al., 2011]. Since irritants induce an innate immune response that is not initially antigen specific, the biomarker pathways identified by these investigations may be generalizable and valuable for further study. Acute and chronic WTC exposure occurred and produced non-resolving upper and lower airway inflammation [Kwon et al., 2016]. In future disasters, improved respiratory protection during the rescue/recovery phase may be effective in reducing the chronic recurrent component of the irritant exposure, but exposures will undoubtedly occur. Our current model asserts that irritant exposures induced and/or sustained this pathway to non-resolving inflammation. The patients with poor outcome

likely will have patient intrinsic characteristics that predispose them to exaggerated inflammation and/or poor healing. Biomarker studies will hopefully allow us to specifically identify at-risk patients, as well as provide additional screening and earlier intervention at a stage of evolution when therapy will be more effective.

α1-ANTITRYPSIN

The identification of latent risk factors is important for disease prevention and early intervention strategies for WTC-related exposure. One example of a patient intrinsic latent risk factor for WTC-related respiratory injury is mild to moderate α1-Antitrypsin (AAT) deficiency. AAT is a protease inhibitor that targets neutrophil elastase, a serine protease that neutrophils deploy to before traveling through the collagen in basement membranes as they migrate from the blood stream into the alveolar space. AAT covalently binds and permanently inactivates neutrophil elastase. The protease inhibitor (Pi) M allele is the most frequent and those with PiM homozygosity have normal AAT levels and function. The PiZ allele carries an AAT mutation that in homozygous individuals produces severe deficiency leading to emphysema and airway reactivity [Kohnlein and Welte 2008]. Individuals carrying PiZ allele heterozygosity have moderate genetic deficiency, while those with PiS homozygosity or PiS heterozygosity without concomitant PiZ heterozygosity have mild deficiency. These mild and moderate AAT genetic deficiencies can produce reduced AAT levels $\leq$20 μmol/L [Banauch et al., 2010]. Individuals with AAT heterozygosity have increased risk for smoking related lung function decline [Molloy et al., 2014].

In a longitudinal study of WTC-exposed firefighters with mild and moderate AAT deficiency, pre-WTC exposure lung function and FEV_1 change over time was normal [Banauch et al., 2010]. After WTC exposure, however, lung function decline was related to AAT genotype or AAT serum level. Those with normal AAT genes (79/90, 88%) and serum AAT concentration (77/90, 86%) lost 37 ml/year of FEV_1. Alternately, mild AAT genetic abnormality (7/90, 8%) lost 69 ml/year and moderate AAT genetic abnormality (4/90, 3%) lost 147 ml/year. Similarly, those with reduced serum AAT levels (13/90, 14%) had 86 ml/year FEV1 decline. Mild to moderate AAT genetic abnormality is a latent risk factor that can be identified by genetic testing at any time before or after exposure. Functionally, the at-risk population can be identified by defining those with serum AAT levels $\leq$20 μmol/L.

Those with mild to moderate AAT deficiency have a latent risk. Importantly, it was only after exposure to irritants at the WTC collapse that the negative potential of this latent risk was revealed. WTC-exposed firefighters with reduced AAT levels or carrying PiZ or PiS alleles had FEV_1 decline greater than 64 ml/year. Since 8.8% of the American population are heterozygous carriers with mild to moderate AAT deficiency [de Serres et al., 2003], this genetic risk will account for a large proportion of the 19.5% of the cohort that experienced greater than 64 ml per year FEV_1 decline in the FDNY [Aldrich et al., 2016] and other WTC-exposed populations. Further investigation is needed to confirm the sensitivity and specificity of serum AAT concentration as a screening test for accelerated FEV_1 decline risk. If these initial observations are confirmed, screening of individuals post-exposure may identify at risk individuals who warrant close observation and early intervention.

The AAT neutrophil axis is a well-defined component of the innate immune response. Our observations that reduced AAT levels increased the risk for FEV_1 decline after an irritant exposure supports the current understanding of irritant induced lung injury.

IgE

There is increasing data that IgE and eosinophils are biomarkers of innate immune injury to the upper and lower airway in WTC exposed firefighters. IgE and eosinophils are well defined biomarkers of allergy produced by the Th2 response [Stone et al. 2010]. IgE is an antibody that binds to basophils and mast cells, thereby activating them and causing airway constriction when bonded to antigens. Anti-IgE therapy is an effectively and widely used therapy for atopic asthma demonstrating that IgE is on the causal pathway for allergic asthma. The role of IgE in the innate immune response is poorly defined.

In addition to accelerated FEV_1 decline, development of airflow obstruction defined by a low FEV_1/FVC ratio is a well-defined adverse pulmonary outcome in occupational cohorts [Mohner et al., 2013]. In the first few months post-WTC-exposure, both FEV1 and FVC dropped to similar extents thereby preserving the FEV1/VC ratio and producing a "pseudo restrictive" pattern on pulmonary function testing (Table IIA). When WTC-exposed firefighters became sufficiently symptomatic to present for subspecialty pulmonary evaluation, the FEV_1/FVC ratio had dropped in many individuals who also manifested symptoms of overt airflow obstruction [Weiden et al., 2010]. In a nested case control study of never-smokers, serum IgE within 6 months post-9/11 predicted abnormal FEV_1/FVC ratio in the following 7.5 years [Cho et al., 2013]. Each 100 IU/ml increase in IgE increased the odds of abnormal FEV_1/FVC ratio by 38%. Importantly, these patients' pre-exposure lung function was normal and their IgE was in the normal range in a vast majority of the cohort (Table IIB). Only 4% had IgE levels greater than 500 IU/ml. There was no association between IgE concentration in the 6 months post-9/11 and

TABLE II. Blood IgE Concentration Obtained Within 6 Months of 9/11/2001 in Never Smoking Firefighters Who Worked at the World Trade Center Site During the First 2 Weeks after 9/11 Predicts Subsequent Airflow Obstruction Defined by Abnormal FEV1/FVC Ratio

Panel A: Longitudinal FEV1/FVC ratio, N = 282

Percentile	Pre-9/11	10/2001–3/2002	Subspecialty pulmonary evaluation
25	80.8	79.9	72.4
50	84.6	84	77.3
75	88.2	87.3	81.8

Panel B: Serum IgE 10/2001–3/2002, N = 279

Percentile	IgE IU/ml
10	6.18
20	12.92
30	20.81
40	31.98
50	42.06
60	62.45
70	88.43
80	150.21
90	284.77

Panel C: Association between IgE 10/2001–3/2002 and FEV_1/FVC 10/2001–3/2002

	B	Std. error	*P*-value
Doubling IgE	−0.206	0.183	0.263

Panel D: Association between IgE 10/2001–3/2002 and FEV_1/FVC at subspecialty pulmonary evaluation

	B	Std. error	*P*-value
Doubling IgE	−0.722	0.236	0.002

Presented is a reanalysis of IgE and pulmonary function data presented in Cho et al., 2013. Panel A: Longitudinal FEV1/VC ratio demonstrates normal pre-9/11 values. There was little change in the 6 months post-9/11 but a large decline at the time of subspecialty pulmonary evaluation prior to 3/2008. Panel B: Distribution of IgE levels in the 6 months post-9/11 demonstrates a vast majority of the study cohort have IgE in the normal range. Panel C: There is no association between FEV1/FVC ratio within 6 months of 9/11/2001 and IgE drawn at the time of pulmonary function test. Panel D: There is a significant association between FEV1/FVC ratio at the time of subspecialty pulmonary evaluation and IgE within 6 months of 9/11/2001.

FEV_1/FVC ratio measured at the time the serum was drawn (Table IIC). By the time this group of symptomatic never-smokers presented for subspecialty pulmonary evaluation, there was a significant association between IgE concentration and FEV_1/FVC ratio measured at that time (Table IID). Each doubling of IgE was associated with a reduction of $0.7 \pm 0.24\%$ FEV_1/FVC ratio. This demonstrates IgE predicts both abnormal FEV_1/FVC ratio as a dichotomous variable and FEV_1/FVC ratio as a continuous variable. FEV_1/FVC ratio was not associated with Th2 cytokines IL-4, IL-5 or IL-13 (Spearman's rho $= -0.076$, $P = 0.206$; rho $= -0.069$, $P = 0.246$; and rho $= -0.031$, $P = 0.606$, respectively). This suggests that this group with irritant-induced airways disease had no evidence of atopic disease in spite of the association between IgE and FEV1/FVC ratio.

Since IgE is a risk factor for development of irritant-induced airflow obstruction, it is possible that IgE is related to the pathogenesis of lung injury. IgE is a widely used serum biomarker for atopy. It is on the causal pathway to asthma and atopic dermatitis since antibodies to IgE are effective treatment for these diseases [Milgrom et al., 1999]. Further work is required to better define if IgE is a causal biomarker of irritant-induced lung injury.

EOSINOPHILS

The concentrations of blood leukocytes, such as eosinophils, are stable post-venipuncture and easily obtained via commercially available, inexpensive cell blood counts. A study of 1,517 non-FDNY WTC-exposed patients from the World Trade Center Environmental Health Center/Survivors Health Program assessed the association between blood eosinophils and symptoms of asthma or obstructive airways physiology. The study cohort had no pre-9/11 asthma or other respiratory symptoms, had less than 5 pack years of smoking history, and no current smoking. Blood eosinophil differential greater than 4% of total leukocytes or greater than 500 cells per microliter was associated with increased wheezing. Elevated blood eosinophil on cell differential increased the odds of abnormal FEV1/FVC ratio by 2.4-fold ($P < 0.002$) [Kazeros et al., 2013]. In a cross-sectional study of 148 patients who presented to the WTC Environmental Health Center/Survivors Health Program, and were $\leq$18 years old on September 11, 2001, residence in home at least 1 day in the period September 11–18, 2001 was associated with a 65 cell/ml increase in eosinophil concentration ($P = 0.027$) and a 1.4% increase in the proportion of eosinophil on blood leukocyte differential ($P = 0.007$) [Trasande et al., 2013]. In these studies, other biomarkers of atopy were not available so it was not possible to exclude the possibility of enhanced Th2 responses producing the eosinophilia.

Chronic rhinosinusitis can be caused by infections, allergy, irritant exposure, and sinus polyps, and interactions with bacteria and irritants worsen chronic rhinosinusitis [Akdis et al., 2013]. As the prevalence of chronic rhinosinusitis has increased among WTC-exposed rescue/recovery workers [Weakley et al., 2011], the cost of caring for those with this disease has vastly increased [Niles et al., 2014]. In a small cross-sectional study of FDNY firefighters, increasing eosinophil concentration increased the odds for

sinus polyps, a strong predictor of sinus surgery [Cho et al., 2014]. We then conducted a study of 8,227 firefighters with WTC-exposure between 9/11/2001 (9/11) and 9/25/2001. One of the aims of this study investigated the association between eosinophil concentration measured between 9/11 and 3/10/2003 and sinus surgery [Kwon et al., 2016]. This study used sinus surgery as its outcome since this was a manifestation of disease with non-resolving inflammation where symptoms remained uncontrolled despite medical management. This longitudinal investigation enabled a more complete assessment of the association between elevated eosinophils and non-resolving upper airway inflammation.

High rates of incident sinus surgery have persisted for over a decade following WTC-exposure, maintaining the relationship between exposure intensity and upper airways disease rates [Kwon et al., 2016]. Arrival at the WTC site on 9/11 or 9/12/2001 increased the risk of sinus surgery by 43% when compared with arriving on or after 9/13/2001. Working 6 or more months at the WTC-site increased the risk of sinus surgery by 48% when compared with working up to 1 month. Increased surgery risk was associated with increasing blood eosinophil counts controlling for WTC exposure. Each 100 cells/ul was associated with a 12% increase in the risk of sinus surgery. Further those with eosinophils in the top 25% of the distribution, greater than or equal to 240 cells/μl had a 45% greater risk of sinus surgery compared with those with eosinophils below 240 cells/μl [Kwon et al., 2016].

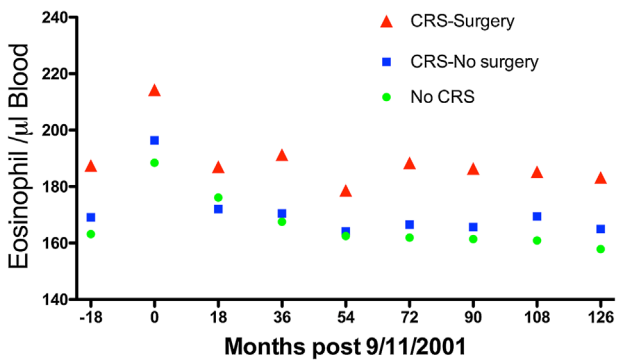

FIGURE 1. Blood eosinophil concentration in firefighters who worked at the World Trade Center site during the First 2 Weeks after 9/11 is associated with sinus surgery. The graph is from Kwon et al. [2016] and represents the median eosinophil concentrations from March 10, 2000 to March 10, 2015, in 18-month intervals. The blue dots show data for Fire Department of New York City Firefighters who worked at the World Trade Center site during the first 2 weeks after the attack of September 11, 2001 (9/11) and who had eosinophil measurement between September 11, 2001 and March 10, 2003. The red triangles show data from the group who had surgical treatment for CRS by the end of the study. The number of measurements contributing to the values in each interval are shown below each data point. The top row of values show in red represents the number of eosinophil measurements in the surgical-CRS group. The bottom row of values show in blue represents the number of eosinophil measurements in the study cohort.

Firefighters who had sinus surgery had higher blood eosinophil levels than the study cohort throughout the study period, including pre-9/11 levels (Fig. 1). This suggests that an elevated eosinophil set-point is intrinsic to this vulnerable group. Importantly, increasing eosinophils served as a biomarker for a population that had increased vulnerability to upper airway injury after WTC-exposure. There are immunological differences between those who proceed to sinus surgery and the rest of the cohort manifest by elevated eosinophil concentration, albeit within the normal range, that were evident years before disease presentation.

Since both acute and chronic exposures to the WTC-site were significant risk factors for surgical treatment of chronic rhinosinusitis, there is a need for usable and effective respiratory protection during long-term rescue or recovery work at future disasters. As this is often difficult to achieve, blood eosinophils obtained before or immediately post-exposure could identify those who might benefit the most from early monitoring and targeted treatment. Blood eosinophil concentration is a widely available, well-studied biomarker of upper and lower respiratory disease that is inexpensive, externally valid and currently collected in many longitudinal cohorts.

WTC-exposure intensity, defined by arrival time, was associated with physician-diagnosed obstructive airways disease until September 2008 [Hall et al., 2015]. After the first 7 years, WTC-exposure intensity was no longer associated with incident disease even though elevated incidence of physician diagnosed lower airways disease has persisted throughout the post-exposure follow-up period. Since intensity of exposure is no longer a significant risk, patient intrinsic risk factors that interacted with WTC-exposure independent of exposure intensity, are needed for current risk stratification. Future investigation should test if other blood leukocytes behave like eosinophils and can be used as additional biomarkers of risk for airway injury.

CONCLUSION

This review has described our biomarker results concentrating on three well-defined, readily available inflammatory factors: AAT, IgE, and Eosinophils. The protease/anti-protease imbalance defined by mild to moderate genetic deficiency of ATT and the elevated set-point of eosinophils observed in those with non-resolving sinus inflammation are intrinsic characteristics of patients that can be assessed post-exposure, even currently, and, therefore, do not require stored serum drawn prior to or shortly after the exposure. Further longitudinal assessment of IgE levels is required to test if IgE concentration is also an identifier of intrinsic populations without characteristics of patients that has predictive validity in the current era. As the association between exposure and disease weakens, these and other

biomarkers of risk for innate immune injury will become important for risk stratification of WTC-exposed FDNY rescue/recovery workers. The findings that elevated eosinophils are associated with respiratory disease in WTC Environmental Health Center/Survivors Health Program suggest that future research may also demonstrate that AAT and IgE will also be useful in other WTC-exposed populations. 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.

AUTHORS' CONTRIBUTIONS

MDW, RZO, DJP conceived the study and designed it with the assistance of AN and BP. MDW and AN acquired the data. RZO, AS, and BP analyzed and interpreted the data. MDW and RZO drafted the first manuscript with critical revisions from AN, BP, AS, and DJP. MDW and DJP agree to be accountable for all aspects of the work so that questions related to the accuracy and integrity of the research are appropriately investigated and resolved.

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ETHICS APPROVAL AND INFORMED CONSENT

The Institutional Review Boards for Albert Einstein College of Medicine/Montefiore Medical Center and New York University approved this study. Consent was waived by both review boards.

DISCLOSURE (AUTHORS)

The authors report no conflicts of interest.

DISCLOSURE BY AJIM EDITOR OF RECORD

Steven Markowitz declares that he has no competing or conflicts of interest in the review and publication decision regarding this article.

DISCLAIMER

None.

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