Correspondence

Metabolic Syndrome Biomarkers in Prediction of Lung Function Impairment

To the Editor:

We read with interest the study by Naveed and colleagues (1) that demonstrated an independent association between abnormal triglycerides and high-density lipoprotein cholesterol and greater susceptibility to lung function impairment after September 11, 2001 in Fire Department of New York personnel with normal FEV₁. The authors concluded that metabolic biomarkers may be useful for the assessment of risk of lung function impairment related to particulate matter inhalation (1). Previously, components of metabolic syndrome including lipids were linked to lung function impairment in a large cross-sectional population-based study (2). In contrast, among patients with chronic obstructive pulmonary disease (COPD), the all-cause mortality risk was reduced in overweight patients with severely impaired pulmonary function—a phenomenon known as the “obesity paradox” (3). Also, improvements in lung function following lung volume reduction surgery in COPD patients with severe emphysema were associated not only with weight gain but also with increases in total and high-density lipoprotein cholesterol, and triglycerides (4).

These data coupled with current findings (1) prompted us to test the hypothesis that higher triglyceride and cholesterol levels might relate to attenuated reductions in FEV₁ in patients with COPD, in contrast to healthy persons (1). We analyzed the data retrieved as a part of an ongoing study on the metabolic consequences of COPD (5) in which we performed repeated evaluation of pulmonary function tests, body composition, and serum lipids within 12–18 (12.2 ± 3.9) (mean $\pm$ SD) months after baseline measurements. Twenty-nine of 39 recruited patients completed the follow-up assessment (24 men; age 63.3 ± 7.5 yr; FEV₁ $52.9 \pm 24.5\%$; body mass index [BMI] 25.4 ± 5.5 kg·m⁻² [14 had BMI > 25 kg·m⁻²], 7 with dyslipidemia [1]). Baseline triglyceride and total cholesterol levels were inversely related to the FEV₁ decline ($R = -0.429$, $P = 0.023$; $R = -0.440$, $P = 0.019$; respectively); that is, patients with higher triglyceride and total cholesterol levels at baseline had lower FEV₁ decline during the follow-up. In multivariate analyses, baseline triglycerides and total cholesterol remained predictors of FEV₁ decline independently of age, gender, baseline FEV₁, and BMI ($R^2 = 0.238$, $P = 0.046$; $R^2 = 0.253$, $P = 0.035$, respectively).

Our data complement studies related to “obesity paradox” in COPD and demonstrate that increased triglycerides and cholesterol may relate to reduced deterioration of lung function in such patients, in contrast to healthy individuals (1). Nevertheless, due to small sample size we consider the present results as very preliminary and hypothesis-generating. Further studies are needed to shed more light on the mechanisms related to the effects of metabolic syndrome and its components on lung function in COPD.

Author disclosures are available with the text of this letter at www.atsjournals.org.

PAVOL JOPPA, M.D., PH.D.
PAVOL POBEHA, M.D., PH.D.
RUZENA TKACOVA, M.D., PH.D.
P. J. Safarik University
Kosice, Slovakia
and
L. Pasteur University Hospital
Kosice, Slovakia

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Reply

From the Authors:

We thank Drs. Joppa, Pobeha, and Tkacova for their interest in our article (1). The patients who are described in the letter of Joppa and colleagues are different in many ways from the cases of abnormal FEV₁ that our group has studied in the Fire Department of New York cohort (1). The 71 Fire Department of New York cases were never smokers with median body mass index of 30 and FEV₁ of 73% predicted at subspecialty pulmonary evaluation. They had normal FEV₁ prior to World Trade Center exposure. We provided evidence that dyslipidemia, with high-density lipoprotein less than 40 mg/dl and triglycerides greater than 150 mg/dl, increased the odds of progressing to abnormal FEV₁ within 6.5 years of an irritant exposure (1, 2).

The work of Joppa and colleagues describes a cohort of 29 heavy smokers with mean 35.5 ± 25.7 pack-years of cigarette consumption and advanced chronic obstructive pulmonary disease with FEV₁ $52.9 \pm 24.5\%$. The body mass index of the cohort was 25.4 ± 5.5 , so few of the patients were obese (3). Joppa and coworkers state that baseline triglyceride and total cholesterol levels were inversely related to the decline in FEV₁ with a similar proportion of the cohort with dyslipidemia as in our cohort (1).

In advanced obstructive lung disease, malnutrition and associated weight loss is a poor prognostic indicator (4–7). The

“obesity paradox” mentioned by Joppa and colleagues is likely related to the differences in the study populations. Our report was intended to provide insight on how the obesity epidemic in developed nations may contribute to development of lung disease in patients with normal lung function. It is not surprising that biomarkers of a high-calorie Western diet identify a subgroup with better outcome in advanced smoking-related obstructive lung disease. The report of Joppa and colleagues is likely to reflect the interaction of nutrition with lung function in these “obesity paradox” patients.

There is still much work that needs to be done to clarify a relationship between metabolic syndrome and lung function loss. However, we stand by the conclusion of our paper that there is a correlation between biomarkers of metabolic syndrome and eventual decline in FEV₁ in the never-smoking World Trade Center–exposed firefighter cohort. A better understanding of the impact of dyslipidemia on lung function at different stages of disease needs further investigation.

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ANNA NOLAN, M.D.
MICHAEL WEIDEN, M.D.
New York University School of Medicine
New York, New York
and
Fire Department of New York
New York, New York

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Airway Smooth Muscle Hypertrophy and Hyperplasia in Asthma

To the Editor:

We were pleased to see our publication (1) on airway smooth muscle editorialized (2) in the *Journal* and were very happy with the prominence and context afforded to our work in this

thoughtful overview, which also provided useful insights into basic mechanisms. However, we wish to draw attention to a misinterpretation of our data that may lead to an incorrect emphasis being given to our findings.

The editorial stated that our study showed hyperplasia of airway smooth muscle in the large airways of nonfatal cases of asthma and that, because the changes in hypertrophy were relatively less pronounced than those of hyperplasia, and the *volume fraction* of extracellular matrix (ECM) was not increased (in fact was reduced in cases of fatal asthma), then hyperplasia was the major contributor to the increased thickness of the layer of airway smooth muscle in asthma. This conclusion was not supported by our data.

Although we observed a trend to airway smooth muscle cell hyperplasia in large airways in cases of nonfatal asthma, this was not significant ($P = 0.082$), whereas significant hypertrophy was present in the large airways of both cases of nonfatal asthma and cases of fatal asthma, compared with control subjects. Although the volume fraction of matrix was decreased in the large airways in cases of fatal asthma, the absolute amount of ECM was increased. Therefore, we conclude that in fatal asthma more ECM, hypertrophy, and hyperplasia all contribute to a thicker layer of ASM and that in nonfatal asthma hypertrophy and more ECM contribute to a thicker layer of ASM in large airways.

Because the processes that lead to hyperplasia or hypertrophy may be different (3), and because hyperplasia seems to influence asthma severity, it is important to consider how both hypertrophy and hyperplasia, and increased ECM deposition may arise. We agree with the editorial that it is likely that these changes occur early in the natural history of asthma.

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ALAN JAMES, M.B.B.S., M.D.
West Australian Sleep Disorders Research Institute
Perth, Western Australia, Australia
and
University of Western Australia
Perth, Western Australia, Australia
THAIS MAUAD, M.D., PH.D.
University Medical School
Sao Paulo, Brazil

MICHAEL ABRAMSON, M.B.B.S., PH.D.
Monash University
Melbourne, Victoria, Australia

FRANCIS GREEN, M.D.
University of Calgary
Calgary, Alberta, Canada

ON BEHALF OF ALL THE AUTHORS

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