Queens Beat One-Eyed Jacks, but Nobody's Played the Ace Yet

Adipokines as Chronic Obstructive Pulmonary Disease Biomarkers

Jeffrey L. Curtis[1,2,3]

[1]Pulmonary & Critical Care Medicine Section, VA Ann Arbor Healthsystem, Ann Arbor, Michigan; and [2]Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, and [3]Graduate Program in Immunology, University of Michigan Health System, Ann Arbor, Michigan

Discovering and validating biomarkers is a single, but crucial, step toward new therapies. All successful biomarkers necessarily correlate with a clinical outcome, although the relationship may be complex or indirect. By replacing biopsies with blood tests or motivating confidence in predictions of an 85% treatment response rate, biomarkers serve us constantly in daily practice. These are good reasons to be on the lookout for new ones, and why the "omics revolution" holds such promise (1).

Conceptually, biomarkers fall into two categories. Some correlate with an outcome without being involved in pathogenesis, but only biomarkers showing causality in relationship to the outcome are potential therapeutic targets. As a familiar example, elevated serum creatinine identifies renal dysfunction, but blocking creatinine synthesis will not fix it, placing creatinine in the first category. These considerations inform biomarker validation in chronic obstructive pulmonary disease (COPD), the subject of recent reviews (2, 3). They also relate directly to conflicting results of two recent articles in *AnnalsATS* (4, 5).

Among the most topical of potential COPD biomarkers are adipokines, adipose tissue-derived cytokines that centrally regulate metabolism and inflammation (6). Two key adipokines, leptin and adiponectin, are produced mainly by adipocytes and have broadly opposing functions (7). In health, leptin acts centrally to induce satiety; however, because of leptin resistance, most obese subjects have high leptin levels. Leptin structurally resembles the helical cytokine family. Its pro-inflammatory properties include stimulating macrophages to produce tumor necrosis factor α, IL-6, and several CC chemokines. Conversely, leptin itself is secreted in response to tumor necrosis factor α or LPS. Dysregulated leptin secretion and responsiveness fuels systemic inflammation in the metabolic syndrome. The presumed proinflammatory nature of emphysema makes leptin an obvious candidate biomarker.

Adiponectin is a collectin family member that antagonizes obesity-related metabolic dysfunction by reducing insulin resistance and stimulating skeletal muscles to oxidize fatty acids. In obesity, atherosclerosis, or diabetes, adiponectin levels correlate inversely to inflammatory markers such as C-reactive protein (7). Adiponectin acts on macrophages to inhibit foam cell formation, reduce LPS-stimulated tumor necrosis factor α production, and increase the antiinflammatory cytokine IL-10. Similar to other collectins, including C1q and surfactant proteins A and D, adiponectin facilitates apoptotic cell uptake ("efferocytosis"), which is dysregulated in smoking and COPD (8). These properties lead most authorities to consider adiponectin to be antiinflammatory and cardioprotective, despite some conflicting data (9).

Paradoxically, higher adiponectin levels in patients with COPD than in control patients (10), plus the protection of adiponectin knockout mice from cigarette smoke-induced emphysema (11), implied that elevated adiponectin nevertheless might be a COPD biomarker. That possibility was supported by a recent study analyzing data from an Asian discovery cohort (Hokkaido COPD) and a European validation cohort (the Danish Lung Cancer Screening trial) that differed in COPD severity (4). In those patients with airflow limitation, a higher plasma adiponectin and a lower leptin/adiponectin ratio at enrollment (Hokkaido COPD) or at 3 years (Danish cohort) significantly and independently correlated with annual FEV_1 decline. Thus, single adipokine measurements showed promise as novel COPD biomarkers, an important advance supported by an independent study of FEV1 decline in a general Japanese population (12).

In this month's issue of *AnnalsATS*, Oh and colleagues (pp. 1005–1012) re-examine the use of adipokine measurements, using longitudinal data on 196 subjects from the Korean Obstructive Lung Disease (KOLD) cohort (5). They correlated baseline plasma adiponectin and leptin concentrations to progression of COPD severity, which they assessed by serial spirometry and high-resolution computed tomography. They found that adiponectin independently and positively correlated with initial emphysema percentage, a radiographic result consistent with the previous cross-sectional

(Received in original form May 2, 2015; accepted in final form May 4, 2015)

The author is supported by Merit Review Award I01 CX000911 from the Clinical Research and Development Services, Department of Veterans Affairs; U01 HL098961 and Contract No. HHSN26820090016C Subpopulations and Intermediate Outcome Measure in COPD Study (SPIROMICS) from the U.S. Public Health Service.

Correspondence and requests for reprints should be addressed to Jeffrey L. Curtis, M.D., Pulmonary & Critical Care Medicine Section, VA Ann Arbor Healthsystem (506/111G), 2215 Fuller Road; Ann Arbor, MI 48105-2303. E-mail: jlcurtis@umich.edu

Ann Am Thorac Soc Vol 12, No 7, pp 971–973, Jul 2015

DOI: 10.1513/AnnalsATS.201505-256ED
Internet address: www.atsjournals.org

spirometry data (4), and that leptin independently and inversely correlated with initial FEV_1 (both absolute and percentage predicted), which was again consistent, but that unexpectedly, leptin, but not adiponectin, correlated with high-resolution computed tomography-assessed emphysema progression.

Strengths of this study from the KOLD investigators include its longitudinal clinical outcomes; sophisticated statistics, including linear mixed effects modeling; and use of Korean population-specific spirometric predicted values. Limitations are the single measurement of plasma adipokines; its acknowledged overwhelming male population, which precluded replication of the interaction between female sex and body mass index on the leptin/fat mass ratio in COPD (13); and potentially that the ELISA employed measures immunoreactive to adiponectin, whereas bioactivity *in vivo* varies with multimeric state (9).

The title's hierarchy of playing cards evokes how biomedical research ranks evidence from different source categories. Associations from cross-sectional studies are important but cannot distinguish cause from effect. For the moment, the KOLD longitudinal data appear to have trumped the purely cross-sectional data, with two implications: First, adiponectin seems not to be a biomarker of COPD progression but, instead, a possible compensatory response (ultimately insufficient) to ongoing lung inflammation, in line with conventional thinking about its effects. This result raises the intriguing question of whether down-regulated adiponectin responsiveness contributes to emphysema progression and, if so, via which target cell types. Second, leptin returns as a potential biomarker, although whether causal or coincidental remains to be determined. Leptin (and adiponectin) modulate behavior of conventional T cells and natural killer cells, which are implicated in emphysema pathogenesis (14, 15).

However, these adipokines (and possibly others, such as secreted frizzled-related protein 5 and the macrophage product wingless-type MMTV integration site family, member 5A [WNT5a] [7]) might contribute to COPD progression via complex, indirect interactions. Animal models imply that emphysema can result from distinct pathogenic mechanisms, notably accelerated lung cell death versus defective replacement. Circulating adipokines link the immune system to adipose tissue throughout the body. Perhaps in some individuals, obesity-associated changes in bone marrow adipose tissue impair endothelial progenitor delivery (16), leading to panlobular emphysema, whereas in nonobese subjects lacking leptin resistance, activated lung macrophages and cytotoxic lymphocytes instead induce focal epithelial injury, causing small airway disappearance or centrilobular emphysema. An intriguing possibility is that distinct anatomic patterns of emphysema result from such differing mechanisms, and hence require individualized therapies dictated by specific high-resolution computed tomography findings.

Not yet available is the "Ace" in this playing card analogy: actual clinical outcomes from human trials in which an adipokine is modified therapeutically. No matter how compelling the support from preclinical models, administrative databases, or other sources, no therapeutic innovation is proven without clinical testing, be it in classic randomized controlled trials or via newer pragmatic trials that aim for validation at more restrained costs. The results from the KOLD investigators argue that much greater understanding is needed before human trials to modulate adipokines could be contemplated, let alone designed. Interdicting leptin to slow emphysema progression might seem attractive, but the potential significant adverse effects on antimicrobial defenses require careful forethought. First, we need additional studies using human pathological tissues, animal models, and especially results from other cohorts, ideally assessing both biomarkers and outcomes longitudinally.

Finally, the article by the KOLD investigators raises a point as the National Heart, Lung, and Blood Institute solicits input on research directions for the next decade. Careful epidemiologic analysis of large observational cohorts contributed invaluably to identifying the roles of hypertension and lipid abnormalities in cardiovascular diseases. In contrast, there have been fewer and smaller similar studies of respiratory diseases. Rather than obviating large longitudinal cohorts, omics technology could supercharge them as biomarker discovery platforms. The falling rates of stroke and myocardial infarction in most industrialized nations contrast strikingly with the global surge in COPD among causes of death. Perhaps instead of asking lung disease researchers to do more with less, it is time to give us a chance to do more with more. ■

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

Acknowledgment: The author thanks Dr. Graham Barr, Dr. Christine Freeman, Dr. MeiLan Han, Dr. John Hokanson, Dr. Robert Paine III, Dr. Elizabeth Regan, and Dr. Prescott Woodruff for thought-provoking discussions, and Dr. Freeman for reviewing the manuscript.

References

1 Wheelock CE, Goss VM, Balgoma D, Nicholas B, Brandsma J, Skipp PJ, Snowden S, Burg D, D'Amico A, Horvath I, *et al.*; U-BIOPRED Study Group. Application of 'omics technologies to biomarker discovery in inflammatory lung diseases. *Eur Respir J* 2013;42: 802–825.

2 Agusti A, Sin DD. Biomarkers in COPD. *Clin Chest Med* 2014;35: 131–141.

3 Faner R, Tal-Singer R, Riley JH, Celli B, Vestbo J, MacNee W, Bakke P, Calverley PM, Coxson H, Crim C, *et al.*; ECLIPSE Study Investigators. Lessons from ECLIPSE: a review of COPD biomarkers. *Thorax* 2014;69:666–672.

4 Suzuki M, Makita H, Östling J, Thomsen LH, Konno S, Nagai K, Shimizu K, Pedersen JH, Ashraf H, Bruijnzeel PL, *et al.*; Hokkaido COPD Cohort Study; Danish Lung Cancer Screening Trial Investigators. Lower leptin/adiponectin ratio and risk of rapid lung function decline in chronic obstructive pulmonary disease. *Ann Am Thorac Soc* 2014; 11:1511–1519.

5 Oh Y-M, Jeong B-H, Woo S-Y, Kim S-Y, Kim H, Lee J-H, Lim SY, Rhee CK, Yoo KH, Lee JH, *et al.* Association of plasma adipokines with chronic obstructive pulmonary disease severity and progression. *Ann Am Thorac Soc* 2015;12:1005–1012.

6 Ali Assad N, Sood A. Leptin, adiponectin and pulmonary diseases. *Biochimie* 2012;94:2180–2189.

7 Ouchi N, Parker JL, Lugus JJ, Walsh K. Adipokines in inflammation and metabolic disease. *Nat Rev Immunol* 2011;11:85–97.

8 McCubbrey AL, Curtis JL. Efferocytosis and lung disease. *Chest* 2013; 143:1750–1757.

9 Esmaili S, Xu A, George J. The multifaceted and controversial immunometabolic actions of adiponectin. *Trends Endocrinol Metab* 2014;25:444–451.

10 Chan KH, Yeung SC, Yao TJ, Ip MS, Cheung AH, Chan-Yeung MM, Mak JC; COPD Study Group of the Hong Kong Thoracic Society. Elevated plasma adiponectin levels in patients with chronic obstructive pulmonary disease. *Int J Tuberc Lung Dis* 2010;14: 1193–1200.
11 Miller M, Pham A, Cho JY, Rosenthal P, Broide DH. Adiponectin-deficient mice are protected against tobacco-induced inflammation and increased emphysema. *Am J Physiol Lung Cell Mol Physiol* 2010;299:L834–L842.
12 Sato K, Shibata Y, Abe S, Inoue S, Igarashi A, Yamauchi K, Aida Y, Nunomiya K, Nakano H, Sato M, *et al*. Association between plasma adiponectin levels and decline in forced expiratory volume in 1 s in a general Japanese population: the Takahata study. *Int J Med Sci* 2014;11:758–764.
13 Breyer MK, Rutten EP, Vernooy JH, Spruit MA, Dentener MA, van der Kallen C, vanGreevenbroek MM, Wouters EF. Gender differences in the adipose secretome system in chronic obstructive pulmonary disease (COPD): a pivotal role of leptin. *Respir Med* 2011;105: 1046–1053.
14 Lee SH, Goswami S, Grudo A, Song LZ, Bandi V, Goodnight-White S, Green L, Hacken-Bitar J, Huh J, Bakaeen F, *et al*. Antielastin autoimmunity in tobacco smoking-induced emphysema. *Nat Med* 2007;13:567–569.
15 Freeman CM, Stolberg VR, Crudgington S, Martinez FJ, Han MK, Chensue SW, Arenberg DA, Meldrum CA, McCloskey L, Curtis JL. Human CD56+ cytotoxic lung lymphocytes kill autologous lung cells in chronic obstructive pulmonary disease. *PLoS ONE* 2014;9: e103840.
16 Agustí A, Barberà JA, Wouters EFM, Peinado VI, Jeffery PK. Lungs, bone marrow, and adipose tissue. A network approach to the pathobiology of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2013;188:1396–1406.