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Xilei Xu Chen
George Washington University

Deepa Rastogi
George Washington University

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CHEST

Triglyceride-Glucose Index

A Potential New Biomarker for Lung Disease Associated with Metabolic Dysregulation

Xilei Xu Chen, MD
Deepa Rastogi, MBBS, MS
Washington, DC

Sustained increase in obesity prevalence around the world over the past 50 years has made it a global endemic.[1] Obesity adversely influences several systems such as cardiovascular, metabolic, and musculoskeletal,[2] and its effects on the respiratory system increasingly are being recognized.

Obesity negatively impacts the respiratory system in several ways. It causes sleep disordered breathing by altering upper airway dynamics,[3] while its influence on chest wall mechanics leads to impaired lower airway function associated with incident asthma and poor disease control among those with COPD.[4] Nevertheless, the mechanisms by which obesity causes or exacerbates respiratory morbidity are poorly understood.

Of the several mechanisms that link obesity with the respiratory system, the mechanical effect of adipose tissue load was proposed early on. However, the absence of a direct link between weight gain and respiratory illnesses suggests that other effects, such as metabolic dysregulation and low-grade inflammation, are more likely to explain obesity-mediated pulmonary morbidity. This speculation is supported by epidemiologic and mechanistic studies that link metabolic abnormalities, which include insulin resistance and dyslipidemia and systemic inflammatory responses, with pediatric and adult obesity-related pulmonary morbidity.[5,6] However, methods used to quantify metabolic dysregulation, which includes homeostatic measurement of insulin resistance, have been limited to research settings, which prevents their extension into clinical care.

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AFFILIATIONS: From Division of Pulmonary and Sleep Medicine, Children's National Hospital, George Washington University School of Medicine and Health Sciences.

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CORRESPONDENCE TO: Deepa Rastogi, MBBS, MS; email: drastogi@childrensnational.org

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In this issue of *CHEST*, Wu et al[7] address this limitation of clinically accessible diagnostic testing for obesity-related pulmonary morbidity by studying, for the first time, the use of triglyceride-glucose index (TyG) in assessing lung health. Using the National Health and Nutrition Examination Survey from 1999 to 2012, the authors analyzed data on respiratory symptom questionnaires, physical examinations, laboratory assessment, and spirometry from 6,893 participants who were ≥40 years old. They reported a direct association between TyG and respiratory symptoms (cough, phlegm production, dyspnea) and self-reported chronic bronchitis but found no association with emphysema or asthma. They also found an inverse association between TyG and percent-predicted FEV_1 and FVC, which suggests that elevated TyG is associated with restrictive pulmonary function. These relationships were not influenced by demographic factors such as sex or race. Moreover, TyG demonstrated good-to-excellent discrimination for metabolic syndrome but correlated moderately with homeostatic measurement of insulin resistance. Homeostatic measurement of insulin resistance and metabolic syndrome did not correlate with respiratory symptoms; but despite that, TyG continued to predict cough and restrictive spirometry patterns after adjustment for these parameters. Although the association of TyG with pulmonary outcomes is novel, it is intriguing that the magnitudes of association (OR, 1.2 to 1.5) are very similar to those reported between obesity and incident asthma in both children and adults,[8,9] which suggests that metabolic abnormalities may be the primary drivers of obesity-mediated respiratory disease.

The relevance of this study resides in TyG being a more inclusive measure of metabolic dysregulation, because it has components of both insulin resistance and dyslipidemia that are quantified routinely in the

clinical setting. It also correlated with several aspects of pulmonary disease, such as symptoms, diseases (ie, chronic bronchitis reported by participants), and pulmonary function. This suggests that TyG may serve as a better biomarker for respiratory disease due to metabolic dysregulation, particularly given its correlation with lung impairment (independent of obesity), insulin resistance, and metabolic syndrome. As stated by the authors, because TyG has been associated with cardiovascular diseases and diabetes mellitus, its links with pulmonary disease fit in well with its use as a composite measure of metabolic dysregulation that affects several body systems.

Although the findings by Wu et al[7] initiate a consideration of TyG as a measure of metabolic dysregulation with relevance to pulmonary outcomes, there are some limitations of this study. The cross-sectional nature of the study precludes it from identifying a causal association of TyG with lung disease. Limiting the study population to adults >40 years old limits the generalizability of the biomarker and excludes an understanding of its relationship with disease in children or younger adults, who are impacted by obesity as early as in utero and who present with disease morbidity that overlaps with adult patterns. Identification of TyG as a measure of lung disease due to metabolic dysregulation early in life would increase its uptake as a biomarker; lack of an association in younger populations would suggest that TyG is a marker of more established lung disease, particularly in light of its association with chronic bronchitis and restrictive patterns on spirometry. Furthermore, it is important to ascertain its effect on reversible airway obstruction in younger individuals as compared with irreversible restrictive lung disease reported in this study. Because the pulmonary function analysis only included spirometry, there is limited understanding of the restrictive pattern. Although few studies have examined the chronology of the effect of obesity on lung function, both obstructive and restrictive defects have been reported,[10] with a role identified for both chronicity of disease and differences in ethnicity-specific fat distribution and body habitus. Large databases such as the National Health and Nutrition Examination Survey allow for such subgroup analyses to discriminate the utility of TyG across age span and between ethnicities.

Despite these limitations, the association of TyG with pulmonary morbidity provides mechanistic evidence for beneficial effects of metformin and statins in pulmonary disease,[11,12] which supports a role for therapeutics for metabolic abnormalities in the pulmonary field. However, before TyG enters prime time for use as a measure of pulmonary impairment, continued endotyping of obese individuals is needed to identify the independent effects of metabolic abnormalities, mechanical effect of body fat distribution, and systemic inflammatory response to facilitate appropriate management of the underlying cause (ie, weight loss/bariatric surgery) for those who may be affected due to mechanical effect of fat load, management of metabolic abnormalities in individuals in whom the abnormalities are associated of lung disease, and consideration of immune modulation for those with evidence of links between immune dysregulation and pulmonary disease. Longitudinal studies that incorporate TyG as a predictor of pulmonary disease are necessary to address whether it is a singular biomarker of disease due to metabolic dysregulation or, given the links between metabolic dysregulation and immune responses,[6] may serve as a more generalizable biomarker for pulmonary disease that is mediated by metabolic dysregulation.

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