Links between Lung Dysfunction and Glucose Metabolism Dysregulation: Does Lung Dysfunction Represent a Systemic Disorder?

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Chronic obstructive pulmonary disease (COPD) is regarded as a systemic inflammatory disorder with extra-pulmonary manifestations, such as malnutrition, osteoporosis, depression, and vascular events. Compromised lung function may be an indicator of systemic conditions in patients with COPD. However, it remains to be clarified whether or not lung function can be used to assess systemic disease in healthy individuals. This question has been addressed by several cross-sectional epidemiologic studies, which showed that lung dysfunction is associated with glucose metabolism dysregulation (1-6). These findings raised several questions regarding the association between lung function and diabetes: namely, is lung dysfunction exclusively an event in the lung, or is it systemically associated with disorders of other organs? Does deteriorated lung function result from diabetes or influence its development? What are the key molecules? What is the clinical and scientific significance of this link?

A retrospective and longitudinal observation by Oda, published in this issue of Internal Medicine, provides evidence for the link between lung dysfunction and diabetes. This study included 1,704 men and 1,016 women in Japan and determined factors that were significantly associated with diabetes development. The results of a multivariate analysis revealed that high-sensitivity C-reactive protein (hs-CRP) and percent vital capacity (%VC) were independently associated with the development of incident diabetes in women within four years (7). Although the lowest tertile of %VC in this cohort failed to predict the groups at higher risk of developing diabetes, this study was the first attempt at elucidating the association between lung dysfunction and impaired glucose metabolism in East Asian women. These results were supported by those of other longitudinal studies, further demonstrating that lung dysfunction precedes glucose metabolism dysregulation (8-10). However, these studies did not reach the conclusion that lung dysfunction led to glucose metabolism dysregulation, because participants who were already diabetic were excluded from the analyses (7-10). In fact, several studies have shown that diabetic individuals are more likely to develop lung dysfunction (2, 3, 5). In addition, based on other analyses of the same cohort, Oda et al. previously reported that lower VC was associated with diabetes in lean Japanese men (6), suggesting that the association is present in both sexes. Therefore, the relationship between lung dysfunction and glucose metabolism dysregulation might not be directly related in terms of cause and effect. Rather, these controversial results indicate that both lung dysfunction and glucose metabolism dysregulation share some common pathogenetic pathways or environmental factors. Environmental air pollution, for example, seems to be associated with both deteriorated lung function (11-13) and abnormal glucose metabolism (14, 15). Exposure to air pollutants, including diesel exhaust particle (DEP), exacerbates inflammatory reactions in cells and induces airway inflammation in mouse models and asthmatic patients, partly via the suppression of nuclear factor-like 2 (Nrf2)-linked signals (13). On the other hand, uncoupling protein 1 (UCP-1) expression is suppressed (14) and hepatic glucose metabolism is impaired (15) by exposure to air pollution, particulate matter (PM) 2.5, and either of these events results in glucose intolerance.

One of the candidate molecular events that occur in response to certain environmental changes and accounts for lung dysfunction and glucose metabolism dysregulation, is the up-regulation of SIRT-1, the mammalian ortholog of sir-tuin (16-18). Reduced SIRT-1 expression and/or activity is...
caused by cigarette smoke exposure and is associated with accelerated ageing of the lung (16, 17). Conversely, its enhancement, which occurs in response to calorie restriction, is associated with increased longevity (18). Animal model studies demonstrated that mice exposed to cigarette smoke exhibited reduced SIRT-1 levels, together with enhanced neutrophilic inflammation and increased matrix metalloproteinase (MMP)-9 levels (17). This neutrophilic inflammation was attenuated in mice treated with a SIRT-1 activator. Similarly, patients with COPD showed reduced SIRT-1 expression (18). Animal studies (19, 20) and human clinical trials (21, 22) have both demonstrated that treatment with SIRT-1 activator has a beneficial effect on glucose metabolism regulation.

Reflecting these molecular events, it is well known that several proinflammatory cytokines and mediators, including tumor necrosis factor (TNF)-alpha, interleukin (IL)-1, IL-6, leptin, adiponectin, and resistin, are in common between COPD and diabetes (23), which will provide some insight into their pre-disease stages. In addition to these proinflammatory molecules, MMPs were reported to be increased both in COPD and diabetic patients; these proteases digest extracellular matrix, which is also a characteristic of the ageing process (16-18).

Collectively, these epidemiologic observations and molecular data led to the hypothesis that lung dysfunction reflects systemic disorders. To test this, health check up data and biomarker results for molecular events in a body should have been collected and analyzed. However, Oda’s study still has a very important and universal message that lung dysfunction may reflect not only the direct environmental effects on the lung, but also that of systemic processes in the body. The close link between lung dysfunction and glucose metabolism dysregulation will increase the understanding of both conditions, and further studies on this link are likely to identify novel molecular mechanisms of the development of lung disease and glucose metabolism abnormalities. Ultimately, such research will clarify what lifestyles or behaviors will favorably affect our health and longevity and which biomarkers should be used to estimate them.

Author’s disclosure of potential Conflicts of Interest (COI). Shin-ichi Hagiwara: Employment, Honda Engineering.

References


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