A BLOOD TEST FOR SLEEP APNEA?
By Regina Patrick, RPSGT, RST

Screening for obstructive sleep apnea (OSA) can be problematic. For example, polysomnographic data may be insufficient for determining whether a person has OSA if a sensor is dislodged for a substantial amount of time during a home sleep apnea study or if a patient has difficulty sleeping in a strange bed in a sleep laboratory. A simple screening test could be helpful in detecting people who may have undiagnosed OSA. To this end, scientists have investigated several biomarkers (e.g., inflammatory substances, proteins) in the blood of people with OSA with the hope of using them as a screening test. No biomarker has been developed for clinical use. However, a few biomarkers appear to be promising candidates.

During an OSA episode, upper airway structures collapse into the upper airway and obstruct airflow. A person makes increasingly strong respiratory efforts to restore airflow while the blood oxygen level decreases because of the restricted airflow. When the blood oxygen level falls to a certain point, the respiratory center in the brain triggers a brief arousal, during which the person takes deep, quick breaths that restore the blood oxygen level.

The physiological processes occurring during an OSA episode can result in oxidative stress, repeated sympathetic activation, and systemic and vascular inflammation, among other negative effects. For example, the dramatic changes in intrathoracic pressure that occur as a person struggles to breathe and the hypoxia and reoxygenation process that occurs with each OSA episode results in oxidative stress in the lungs (i.e., an imbalance between the production of free radicals [i.e., highly reactive ions] and the ability of lung tissue to counteract or detoxify their harmful effects).[1] Trauma to epithelial upper airway tissues can contribute to systemic inflammation.

Many investigators have focused on using inflammatory substances as biomarkers because people with OSA often have

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systemic inflammation. For example, an analysis of 30 studies by Rashid Nadeem and colleagues[2] revealed that, compared to people without OSA, people with OSA have higher levels of the inflammatory substances C-reactive protein (CRP), tumor necrosis factor-alpha, certain interleukins (interleukin-6 [IL-6], interleukin-8 [IL-8], interleukin-10 [IL-10]), intercellular adhesion molecule 1, and vascular adhesion molecule 1. Nadeem concluded these substances could be biomarkers to distinguish between people with and without OSA. In a review of studies that focused on OSA-associated biomarkers in adults and children, Graziela De Luca Canto and colleagues[3] found that most studies measured serum levels of candidate biomarkers. Many of the adult studies investigated IL-6, tumor necrosis factor-alpha, and CRP as biomarkers, and generally indicated that IL-6 and IL-10 were good biomarkers for distinguishing between people with and without OSA. By contrast, De Luca Canto found that no specific biomarker was tested in most pediatric studies.

Some scientists have the hope that testing for biomarkers, when developed for clinical use, could be used to distinguish between different phenotypes of OSA (i.e., different forms of the disease). For example, one person with OSA may develop an OSA-related disease (e.g., cardiovascular disease, hypertension, atherosclerosis, coronary artery disease), whereas another person with a similar level of OSA severity may not. Biomarkers that would enable clinicians to identify patients who are more vulnerable to developing OSA-related diseases could help improve treatment outcomes. In a different review, De Luca Canto and colleagues[4] found that most studies that examined the feasibility of using biomarkers to detect OSA-associated diseases revealed that plasma levels of IL-6 and IL-10 are potentially good biomarkers for distinguishing between OSA patients (both adults and children) with OSA-related diseases and without OSA-related diseases.

Many studies investigating OSA and biomarkers have involved a small number of participants. Therefore, Izolde Bouloukaki and colleagues[5] measured the serum levels of the inflammatory biomarkers CRP and fibrinogen in a large sample of OSA patients to investigate whether any correlation existed between these biomarkers and OSA-related diseases. They categorized the patients as having mild OSA, moderate OSA, or severe OSA. Patients with <5 apnea/hypopnea events per hour were the controls. They found that an elevation in the serum level of CRP or fibrinogen was independently correlated with OSA severity. Based on this finding, they proposed that measuring the

blood levels of these biomarkers when patients undergo an initial screening for OSA could be valuable in indicating the presence of subclinical OSA-induced disease (e.g., vascular inflammation) before symptoms appear.

Some recent research has compared the use of a single biomarker versus a combination of biomarkers to identify people with OSA. De Luca Canto and colleagues[3,6] found that a concurrent elevation in the levels of the proteins kallikrein-1, uromodulin, urocotin-3, and orosomucoid-1 was sufficiently accurate to be a diagnostic test for OSA in children, and that plasma levels of IL-6 and IL-10 plasma are potentially good biomarkers for OSA in adults. In an all-male population, Wesley Fleming and colleagues[7] measured the levels of the following biomarkers to test the feasibility of using them to screen for OSA: the proteins hemoglobin A1c, CRP, erythropoietin and insulin-like growth factor 1; the metabolite uric acid; the inflammatory substance IL-6; and the hormones cortisol, human growth hormone, prolactin, testosterone, and dehydroepiandrosterone. They found that the concurrent elevation of hemoglobin A1c and CRP levels were predictive of OSA. They further found that a concurrent elevation in the serum levels of hemoglobin A1c, CRP, and erythropoietin, compared to these markers individually, had a high sensitivity (i.e., rate of true-positives) of 85% and specificity (i.e., rate of true-negatives) of 79% for detecting people with moderate to severe OSA. Such findings suggest that using a combination of biomarkers rather than one biomarker may more accurately detect people with OSA.

Some investigators have examined whether substances associated with oxidative stress could be used as biomarkers. One substance is the glycoprotein KL-6, which normally exerts a protective role in the lung by binding to pathogens. It is also elevated when lung tissues experience oxidative stress or injury. Lederer and colleagues[8] hypothesized that patients with OSA would have increased levels of biomarkers associated with oxidative stress. On comparing the plasma levels of KL-6 in people with and without OSA, they found that the plasma KL-6 levels were higher in people with OSA. Lederer further found that, among people with OSA, plasma KL-6 levels were higher in individuals who had spent a greater amount of time asleep with a blood oxygen saturation level of <90%, or who had a low saturation nadir (i.e., the lowest level the blood oxygen saturation reached during the night), or who had frequent desaturations of >4% during sleep. The increase in the blood levels of KL-6 in OSA patients was modest; however, it was in a range similar to that of patients with acute lung injury. Therefore, Lederer and colleagues propose that increased levels of KL-6 is potentially a biomarker of OSA, and encourage more research for corroboration of their findings.

Biomarkers among children with OSA have not been as extensively studied as in adults. However, in a pediatric study, Rakesh Bhattacharjee and colleagues[9] examined level of CRP as a biomarker among children who had undergone adenotonsillectomy for OSA. They hypothesized that serum levels of the CRP would be predictive of residual OSA after adenotonsillectomy. The children underwent a polysomnography study before and after the surgery, and the serum CRP levels were measured before and after surgery. Residual OSA was defined as a post-adenotonsillectomy apnea/hypopnea index of >5 events per hour. Before surgery and after surgery, the CRP level was positively correlated with OSA severity. The post-surgery polysomnography studies revealed that 25% of children had residual OSA, and that the post-surgery CRP levels were elevated for children with moderate to severe residual OSA, compared to children with resolved OSA. Bhattacharjee proposed that the CRP level could be useful in predicting residual OSA in children who have undergone adenotonsillectomy.

A screening blood test that detects OSA-related biomarkers could allow more people with undiagnosed OSA to be referred to a sleep center for assessment and treatment of the disorder. In addition, if future studies confirm that certain biomarkers or combinations of biomarkers could distinguish between OSA phenotypes, then treatment could be more individualized for people with OSA. For example, if the CRP level indicates residual OSA in child post-adenotonsillectomy, then a child may undergo another polysomnographic study for further assessment or other strategies for treating their residual OSA such as anti-inflammatory medications.[10] For now, the prospect of using a blood test to screen people with OSA continues to stimulate research.

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