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Leptin Resistance May Prevent Severe Lung Disease in Patients With Diabetes

Resistance to leptin, a protein that plays a key role in regulating metabolism and appetite, may help prevent the development of Acute Respiratory Distress Syndrome (ARDS) and Acute Lung Injury (ALI) in individuals with type II diabetes, according to a study conducted by researchers in Chicago. The study indicates leptin resistance, a common characteristic of diabetes, may help prevent the formation of inflexible, fibrous tissue that develops in ALI and ARDS.

The findings were published online ahead of the print edition of the American Thoracic Society's American Journal of Respiratory and Critical Care Medicine.

"Previously it was hypothesized that hyperglycemia, the hallmark of diabetes might be responsible for the lower level of ARDS seen in these patients," said study author Gökhan M. Mutlu, MD, Associate Professor, Division of Pulmonary and Critical Care Medicine, Northwestern University Feinberg School of Medicine. "However, subsequent studies have indicated hyperglycemia exacerbates inflammation and worsens lung injury. Our findings provide support for the hypothesis that leptin resistance plays a key role in offering protection against ARDS in diabetic subjects."

ALI and ARDS are common clinical conditions affecting almost 200,000 people per year in the United States, with mortality rates of about 40 percent. Severe infection, or sepsis, is the most common cause of ALI/ARDS. There are no therapies directly targeting ALI and ARDS and the treatment remains largely supportive, including the use of mechanical ventilation. Some patients with ARDS develop lung scarring, which is associated with worse prognosis.

Previous studies have shown patients with diabetes have about a 50 percent lower incidence of ALI than non-diabetic patients, and indicate diabetic patients who do develop ALI are less likely to die than non-diabetic patients.

"People with type II diabetes develop an acquired resistance to leptin signaling -- the level of hormone is high but it does not function," Dr. Mutlu said.

In this study, diabetic and non-diabetic, wild-type mice were given bleomycin, a chemotherapy agent, to induce acute lung injury and scarring (fibrosis). Fluid and tissue samples from the lungs were obtained from both strains of mice and evaluated for lung fibrosis and levels of leptin and transforming growth factor-beta (TGF-ß), a major regulator of lung fibrosis.

To determine the relationship between leptin levels and the development of ARDS in humans, lung fluid samples from ARDS patients and mechanically ventilated patients without lung disease were also taken and evaluated for levels of leptin and TGF-ß.

The researchers found that while non-diaetic mice exhibited severe lung fibrosis, diabetic mice showed no signs of lung fibrosis after bleomycin treatment. Non-diabetic mice also had a sixfold increase in lung scarring compared with diabetic mice. Similarly, when evaluating the human lung fluid samples they found levels of leptin were six times higher in patients with ARDS compared to the patients without lung disease.

"We found that obese, type II diabetic mice which exhibit resistance to leptin due to lack a functional leptin receptor had much less scarring in the lung after injury," Dr. Mutlu said. "We also found evidence that leptin augments the signaling through transforming growth factor, a major regulator of lung fibrosis".

"In non-obese patients with ARDS, the levels of leptin were high and correlated with poor clinical outcomes, as indicated by death and length of stay in the intensive care unit," he added.

Dr. Mutlu said based on the results of this study therapies might be developed to prevent or lessen the severity of ARDS and ALI by increasing leptin resistance.

"Leptin is an attractive potential therapeutic target as most of its normal effects are mediated in the brain and it is relatively easy to develop drugs that are not delivered to the brain," Dr. Mutlu said. "The results of our study and those of other groups studying the effects of leptin signaling on the development of injury and fibrosis in other organs highlight the need for further prospective studies examining the influence of leptin in the outcome of patients suffering from ARDS."

Source: Manu Jain, GR Scott Budinger, Amy Lo, Daniela Urich, Stephanie E Rivera, Asish K Ghosh, Angel Gonzalez, Sergio E Chiarella, Katie Marks, Helen K Donnelly, Saul Soberanes, John Varga, Kathryn A Radigan, Navdeep S Chandel, Gökhan M Mutlu. Leptin Promotes Fibroproliferative ARDS by Inhibiting Peroxisome Proliferator-activated Receptor-?. American Journal of Respiratory and Critical Care Medicine, 2011; DOI: 10.1164/rccm.201009-1409OC