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LETTER TO THE EDITOR

The Vicious Cycle of Leptin-Insulin Resistance Predicts Impaired Glucose Metabolism in Obese Adults with Obstructive Sleep Apnea

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Sleep is an overlooked area of metabolic processes and an important modulator of endocrine function. Despite a large body of evidence suggesting that obstructive sleep apnea (OSA) is an independent risk factor for type 2 diabetes, the underlying pathogenesis of impaired glucose metabolism (IGM) in OSA remains less well understood. The recent findings of Papaioannou and colleagues showed no clinically significant abnormalities of appetite regulating hormones in OSA that would suggest a cause for IGM.[1] While the study provides an important insight into the phenotypic spectrum of OSA, it also raises questions related to possible yet unexplored more complex pathomechanisms linking appetite hormones with IGM in OSA.

From a pathophysiological point of view, insulin resistance (IR) and beta-cell dysfunction both play a role in the development of IGM. While research has documented that OSA can contribute to IR independent of obesity, there is a paucity of information on leptin resistance-related IR in OSA that may potentially impair glucose homeostasis. Leptin is a well-known adipose tissue-derived hormone that binds to receptors in the brain and inhibits expression of neuropeptide Y (NPY). Most obese humans produce large quantities of leptin but are insensitive to its effects. The suggested mechanisms underlying leptin resistance include defective leptin receptors and/or post-receptor signal transduction, reduced numbers of leptin receptors, interactions between leptin and plasma circulating factors, and other factors that override the leptin satiety signal. It is plausible that OSA-stress-related release of NPY from sympathetic nerves and activation of its Y2 receptors in the adipose tissue might stimulate fat angiogenesis and the proliferation and differentiation of new adipocytes, resulting in abdominal obesity, while closing a vicious cycle of increasing leptin-insulin resistance. Considering different receptor-mediated effects of NPY, the plasma level of NPY might not necessarily be the best parameter to assess NPY effects in peripheral tissues.

In our study,[2] we demonstrated that OSA is associated with specific cytokines that reflect link between OSA and glucose metabolism. Specifically, nocturnal oxyhemoglobin desaturations in OSA were closely associated with interleukin-6 (IL-6) production in obese women with IGM, but not in controls with normal glucose metabolism matched individually for sex, age, adiposity, and apnea-hypopnea index. Moreover, cross-sectional data from our study showed additional close associations of IL-6 with leptin-to-leptin receptor ratio and markers of adiposity only in IGM. These findings support the role that IL-6 plays in obesity and extend it to possible pathophysiological processes linking obesity to IGM via leptin resistance and hypoxic stress in OSA.

Further prospective studies are needed to explore the dynamic interactions among appetite regulating hormones, their receptors, and glucose homeostasis in OSA to develop novel interventions to prevent metabolic sequelae of OSA.

CITATION

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DISCLOSURE STATEMENT

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