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Commentry

Gut microbiome: Role in insulin resistance in obstructive sleep apnea

Allan I. Pack

John Miclot Professor of Medicine, Division of Sleep Medicine/Department of Medicine, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, United States

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In this issue, there is an interesting article "Circulating Exosomes and Gut Microbiome Induced Insulin Resistance in Mice Exposed to Intermittent Hypoxia: Effects of Physical Activity" (EBIOM-D-20-02763) by Khalyfa A, et al. [1]. It addresses the important question as to the mechanism of insulin resistance in the subjects with the common disorder—obstructive sleep apnea. Specifically, it asks whether cyclical intermittent hypoxia in mice, modeling the pattern of deoxygenation/reoxygenation that occurs in the common condition of obstructive sleep apnea (OSA), results in changes in the gut microbiome and whether such changes contribute to insulin resistance. They further address whether physical activity ameliorates this effort.

The study is based on 4 groups of lean C57BL/6 male mice. The 4 groups are as follows:(a) sham control, no exercise; (b) sham control, exercise; (c) cyclical intermittent hypoxia, no exercise; and (d) cyclical intermittent hypoxia, exercise.

The overall investigation is a tour de force. It involves a number of experimental approaches that include the following: (a) sequencing of the gut microbiome; (b) fecal transplants; (c) unbiased metabolomic analyses of fecal samples with liquid chromatography-mass spectrometry (LC-MS); d) Western blots to assess expression of specific proteins in white adipose tissue; (e) cell cultures; (f) assessment of insulin sensitivity in vitro; (g) assessment of electrical resistance across monolayers of murine primary small interstitial epithelial cells; (h) characterization of circulating exosomes; (i) assessment of impact in vitro of exosomes on macrophages; and (j) measurement of interstitial permeability in vivo in mice.

Thus, there are multiple results presented. The most interesting is the demonstration that cyclical intermittent hypoxia alters the gut microbiome. There was alteration in the relative abundance of 29 operational taxonomic units. Exercise also altered the gut microbiome with increases in “richness” and alpha-diversity. This altered pattern of the gut microbiome was successfully transferred to donor mice with a fecal transplant from mice exposed to cyclical intermittent hypoxia.

Mice exposed to cyclical intermittent hypoxia had evidence of insulin resistance that was attenuated by exercise. This alteration in insulin resistance could be transferred to donor mice with fecal transplant. Thus, the proposal is that changes in gut microbiome are causal and contribute at least in part to increased insulin resistance with cyclical intermittent hypoxia.

While the results are interesting, there are issues with the studies. As the authors indicate, obesity is a major risk factor for OSA [2] such that the majority of OSA in human subjects are obese [3]. The studies were done in nonobese mice of one genotype. It is an important start. It needs to be questioned whether obesity such as diet-induced obesity in mice [4] will alter the response. It is known that obesity in both humans [5] and mice [6] alters the gut microbiome.

The study does not address the “why”. Why does cyclical intermittent hypoxia alter the gut microbiome? There are reductions in body weight with intermittent hypoxia even in the absence of increased exercise. The basis of this is unclear, e.g., is it the result of feeding patterns? Alterations in feeding pattern are known to affect the gut microbiome [7]. The study thus raises important questions to address not only in mice but also humans. One great advantage of studying OSA in humans is that the disorder can be “turned off” by use of nasal CPAP [8]. Thus, future studies in patients with OSA both before and after successful treatment with nasal CPAP and in controls are needed.

The authors argue that the result of this alteration in the gut microbiome in insulin resistance is mediated by increases in the interstitial epithelial permeability and changes in circulating exosomes and they have data to support this assertion.

Thus, this is an important study. It draws attention to the potential role of alteration of the gut microbiome in OSA. It provides evidence that there are likely to be alterations in the gut microbiome in OSA and that such alterations could play a causative role in the insulin resistance that occurs in such patients. The study calls for more studies in mice, in particular in obese mice, and in humans with OSA.

Declaration of Competing Interest

Dr. Pack has nothing to disclose.

Contributors

Dr. Pack wrote the commentary on his own and did the relevant manuscript review.

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E-mail address: pack@pennmedicine.upenn.edu

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