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## Incretins and Insulin Resistance in Obstructive Sleep Apnea Chicken or the Egg?

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One common frustration when reading the scientific medical literature is the adage that observational studies do not allow us to establish cause-and-effect relationships, but merely associations. Although this may be mostly true, observational studies do offer helpful links and can be hypothesis-generating. For example, observational studies have shown that central adiposity (commonly seen in obstructive sleep apnea [OSA]) is independently associated with insulin resistance (1, 2). However, a meta-analysis of several randomized controlled trials (RCTs) shows improvement in insulin resistance with continuous positive airway pressure (CPAP) in nondiabetic patients with OSA without any changes in the amount of visceral adipose fat or, for that matter, in adiponectin (3).

In this instance, the lack of a causal direction from RCTs does not necessarily mean visceral adiposity has no role to play in insulin resistance. This could mean there must be other intermediary pathways to explain this process in prediabetics that are linked with already known factors such as intermittent hypoxic stress and sympathetic activation (4).

As is so often true, exploration begins with association studies. In this month's issue of *AnnalsATS*, Matsumoto and colleagues (pp. 1378–1387) report their observations on associations between OSA and incretin hormone levels, a topic relatively unexplored in understanding the mechanistic links between OSA and insulin resistance (5).

Incretins, specifically glucose-dependent insulinotropic peptide (GIP) and glucagon-like peptide-1 (GLP-1) are gut hormones that are secreted from enteroendocrine cells into the blood briskly

after eating. GLP-1, in particular, is known to affect gut motility, inhibit gastric acid secretion, and inhibit glucagon secretion. In the central nervous system, GLP-1 induces satiety. In the pancreas, GLP-1 induces expansion of insulin-secreting  $\beta$ -cell mass in addition to augmentation of glucose-stimulated insulin secretion, the latter function in common with GIP. Both GLP-1 and GIP are rapidly deactivated by dipeptidyl peptidase 4 (6).

Matsumoto and colleagues (5) analyzed data from 96 consecutively recruited nondiabetic study participants who underwent a baseline sleep study followed by a meal tolerance test the morning after. Only those with apnea-hypopnea index (AHI)  $\geq 20$  were started on CPAP treatment. A follow-up sleep study and a meal tolerance test at 3 months were advised. However, of the 68 patients started on CPAP, only 43 followed up. Postprandial glycemic response was assessed by measuring the incremental area under the curve (IAUC) for both GLP-1 and GIP. The authors studied the association of these with AHI and 3% oxygen desaturation index (3%ODI; both markers of intermittent hypoxia), as well as with cumulative percentage of time with  $SpO_2 < 90\%$  (CT90; a marker of sustained hypoxia). Although both fasting and IAUC GLP-1 were significantly correlated (albeit in opposite directions) with AHI, 3%ODI, and CT90, fasting and IAUC GIP were not. After controlling for other confounding factors, AHI, 3%ODI, and CT90, analyzed separately, were independently associated with fasting GLP-1. However, only AHI and 3%ODI were associated with IAUC GIP.

In all the models, including one that used arousal index, waist circumference

(sometimes used as a surrogate for central adiposity) was also associated with IAUC GLP-1. This suggests that central adiposity does attenuate postprandial glycemic responses, despite the inconsistent results on causality from earlier studies (7, 8). Using an AHI cut-off of 50, the authors found significant differences in fasting GLP-1, fasting GIP, IAUC GLP-1, IAUC GIP, insulin resistance as assessed by the homeostatic model assessment of insulin resistance (HOMA-IR), and HbA1c. These differences were not seen in IAUC GLP-1 and IAUC GIP, using an AHI cut-off of 30. One obvious reason as to why this difference manifested using a higher AHI cut-off is the AHI threshold itself. Another explanation could be the subtle difference in visceral adiposity between those with AHI  $\geq 50$  and those with AHI  $\geq 30$  (mean waist circumference,  $99.1 \pm 8.8$  cm vs.  $96.4 \pm 8.8$  cm), with not much difference in their mean body mass indexes ( $29.8 \pm 4.7$  kg  $\cdot$  m<sup>-2</sup> vs.  $28.4 \pm 4.4$  kg  $\cdot$  m<sup>-2</sup>).

Despite the noticeable differences in fasting and IAUC GIP using a higher AHI cut-off, lack of an association, as well as correlation, between fasting GIP and dipeptidyl peptidase 4 with markers of intermittent and sustained hypoxia is intriguing. This perhaps could be because of the relatively small size of patients with AHI greater than 50, at which this association could have otherwise been detected. In addition, when many variables in complex systems are studied, spurious associations and nonassociations can arise, and one needs to interpret these with caution.

CPAP treatment for 3 months did not appreciably change the levels of incretins

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or, for that matter, HOMA-IR or HbA1c. A case is made for essentially having the same participants serving as their own controls by comparing fasting GLP-1 in the 43 CPAP-treated patients with the baseline fasting GLP-1 levels of those studied earlier ( $N > 43$ ) with  $AHI < 20$ . There are, however, some caveats to this approach. First, a comparison of those with residual  $AHI \leq 5$  (treated with CPAP) with those with  $AHI < 20$  would not be fair. A second caveat is that if  $AHI$  was found to have a significant association with incretins, then one would expect much lower fasting incretins post-CPAP.

It is possible that the effect was not observed because of the relatively short follow-up of patients, a common limitation in the literature, which has yielded inconsistent results. For example, in a randomized double-blind crossover study by Weinstock and colleagues (8), 8 weeks of CPAP did not normalize impaired glucose tolerance in prediabetics with sleep apnea and obesity, whereas insulin sensitivity (a reciprocal of insulin resistance) was

improved (in the 2-h oral glucose tolerance test) in those with  $AHI > 30$ , a finding that contrasts with that of Matsumoto and colleagues. However, a subtle similarity exists between the two studies: Matsumoto and colleagues found a significant difference in incretins and HOMA-IR only when an  $AHI$  cut-off of 50 was used, and Weinstock and colleagues similarly found that only those with severe OSA had improvement in glucose tolerance.

These findings could have important clinical implications. Perhaps, short-term treatment with CPAP in those with only mild to moderate OSA may be inadequate for improving indices of glucose metabolism. Although the current literature on studies (9–11) evaluating whether treatment of OSA with CPAP reverses the metabolic dysfunction in specific HbA1c are largely inconclusive, two recent meta-analyses (3, 12) provide sufficient evidence that even 3 months of CPAP treatment is effective in reducing HOMA-IR in nondiabetics. Lack of a change in incretins and HOMA-IR in the

current study may have to do with short duration of follow-up (3 mo) and a 37% attrition rate at the time of final sleep study, which reduces the power of a subgroup analysis. Also, as mentioned earlier, because the effect is likely to be seen in those with severe OSA, perhaps pooling the results of the entire study population (with wide-ranging  $AHIs$ ) diluted the overall effect.

In addition to these limitations, the predominantly Asian male study cohort limits the generalizability of the study findings. Also, although this study provides evidence for an association between elevated fasting incretins and OSA in nondiabetics, one cannot entirely conclude whether elevated fasting incretins are a cause or consequence of insulin resistance in these patients. Despite these limitations, the new data provide a rationale to consider other possible mechanistic links to insulin resistance in these patients. ■

**Author disclosures** are available with the text of this article at [www.atsjournals.org](http://www.atsjournals.org).

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