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Weight Loss and Obstructive Sleep Apnea: What Lies AHEAD?

Commentary on Kuna et al. Long-term effect of weight loss on obstructive sleep apnea severity in obese patients with type 2 diabetes. SLEEP 2013;36:641-649.

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Obesity is a well-established risk factor in the development of obstructive sleep apnea (OSA).[1] Weight loss is recommended in clinical guidelines as an effective treatment of OSA,[2] particularly after three recent randomized controlled trials were published in 2009.[3-5] Less established is whether the benefits of initial weight loss on OSA severity are sustained once an intervention has ended or when weight regain occurs. In the current issue of SLEEP, Kuna and colleagues[6] report findings from the Sleep AHEAD (Action for Health in Diabetes) trial, demonstrating that among overweight and obese patients with type 2 diabetes mellitus (T2DM) and OSA, the improvement in AHI at one year with weight loss through an intensive lifestyle intervention (ILI) persisted at four years despite a 50% weight regain. At year four, 44% of participants demonstrated an improvement in OSA severity category, compared to only 18% of participants given diabetes support and education (DSE). Moreover, nearly 21% of ILI participants had complete remission of OSA, compared to only 3.6% of DSE participants.

Tuomilehto et al.[4] also reported reduced OSA severity (-4.4 events/hour) with a 12-month lifestyle intervention that resulted in an 11 kg weight loss. The improvement was sustained for an additional year despite a 32% weight regain following the termination of the supervised program.[7] Johannson and colleagues[5] randomized obese men with moderate to severe OSA to either a very low energy diet combined with lifestyle counseling or a weight maintenance group. The initial improvement in AHI of 21 events/h (18 kg weight loss) after 9 weeks of intervention was mostly sustained at 1 year despite a 31% weight regain.[8] Collectively, these studies demonstrate that improvements in OSA severity with weight loss interventions are dose-dependent and sustained over a 1- to 4-year period despite a 30% to 50% weight regain.

Why might improvements in OSA severity persist when weight and OSA are thought to be so intricately connected? OSA is more closely linked to abdominal adiposity than general measures of obesity.[9] Abdominal adiposity is associated with reductions in lung volumes,[10] which leads to a loss of caudal traction on the upper airway, an increase in pharyngeal collapsibility,[11-14] increased oxyhemoglobin desaturations,[15] and greater OSA severity.[16] Abdominal visceral fat is also an abundant source of pro-inflammatory cytokines and hormones, such as TNF-α and IL-6.[17,18] Their purported somnogenic activity[19] might lead to depression of upper airway neuromuscular control.[20] Furthermore, OSA may increase visceral adiposity based on small studies, where treatment of OSA with CPAP resulted in an 8% to 16% reduction in visceral adipose tissue independent of changes in subcutaneous adipose tissue and changes in weight.[21,22] Thus, sustained improvements in OSA severity may be due to relative improvements in body fat distribution despite the weight regain. Although waist circumference was not independently associated with improvements in AHI in Sleep AHEAD,[6] the measure is insensitive relative to imaging modalities in assessing visceral adiposity and it is subject to measurement variability that can exceed 3%,[23] which may explain the absence of an independent association in Sleep AHEAD.

An additional intriguing finding of the Kuna et al.[6] Sleep AHEAD report was that the ILI intervention, consisting of dietary modification, physical activity, and education, was associated with an improvement in AHI by 4.8 events/hour, independent of weight loss and waist circumference. Disentangling the effects of dietary change, improved fitness and increased physical activity, however, is not possible from the available data. Nevertheless, considering that physical activity was a major component of the Sleep AHEAD intervention, increased physical activity—as acknowledged by the authors—may have accounted for this finding. Indeed, a recent analysis revealed that hours of exercise were associated with a reduced incidence of mild-moderate OSA, whereas a decrease in exercise duration was associated with worsening OSA.[24] Moreover, Kline et al. reported a nearly 33% reduction in AHI following twelve weeks of exercise training (4 times/week) without weight loss in a group of overweight adults with moderate OSA.[25]

Several mechanisms have been hypothesized to explain how exercise may modulate OSA severity,[26] including improved visceral adiposity, pharyngeal muscle tone, sleep quality, and shifts in peripheral fluid accumulation.[25] Exercise training, independent of weight loss, leads to significant reductions in abdominal adiposity[27-29] and may be required for visceral fat reduction in those with diabetes.[30] Acute bouts of exercise increase the level of catecholamines,[31] which, in turn, stimulate adipocyte lipolysis through α-adrenergic receptors.[32] Catecholamines have been shown to be more lipolytically active in visceral fat, compared with subcutaneous fat,[33] and α-receptor sensitivity to catecholamines may be enhanced through increased physical activity. To our knowledge, the comparative effectiveness of diet or exercise alone versus a combined diet and exercise intervention on improvements in central obesity and OSA is not known and is an important area for future research.

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An additional consideration, noted by Kuna et al.[6] is that improvements in OSA severity, despite weight regain, may translate into improved cardiovascular outcomes. OSA is closely linked to cardiovascular disease, with several intermediate links postulated, including endothelial dysfunction,[34] inflammation,[35] and increased sympathetic activity.[36] Abdominal adiposity is an established risk factor for both OSA and cardiovascular disease. Could improvements in OSA with a weight loss regimen that includes moderate exercise, therefore, mediate the associations between reduced abdominal obesity and improved cardiovascular risk profiles? Currently, little if any data are available to answer this question, however, exercise has been hypothesized to have direct beneficial effects on cardiovascular health, which extends beyond traditional cardiovascular risk factors (e.g., blood pressure, blood lipids, and T2DM). This apparent "risk factor gap" may be at least partly filled by the independent protective effect of exercise on endothelial health.[37-42] Testing these hypotheses are especially important in light of the recent decision by the NIH to halt the Look AHEAD trial (the parent trial of Sleep AHEAD) two years prior of planned completion, due to interim analyses demonstrating no differences between ILI and DSE for reductions in non-fatal MI, non-fatal stroke, death, or hospitalization for angina. Considering that 86% of Sleep AHEAD participants had established OSA,[43] might the lack of apparent benefit in the larger trial be explained by the high likelihood that most individuals had underlying OSA at baseline, and despite measurable changes in OSA severity, a majority still had underlying OSA at 4 years follow up?

Sleep AHEAD[6] and the studies by Johannson et al.[8] and Tuomilheto et al.[7] expand our understanding of the long-term effects of behaviorally induced weight loss on OSA and set the stage for continued research designed to explore the most effective treatment strategies for reducing OSA with regard to exercise programming. Specifically, the mechanisms by which an intensive lifestyle intervention improves OSA, whether through increased physical activity or other components needs to be understood. Addressing this would undoubtedly have major implications for how we design and implement therapies for reducing cardiovascular disease risk among OSA patients.

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DISCLOSURE STATEMENT

The authors have indicated no financial conflicts of interest.

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