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Predicting Weight-Loss Effects on Obstructive Sleep Apnea and Cardiometabolic Health

In Search of the Craniofacial "Holy Grail"

In the past 40 years, the prevalence of obesity has increased more than threefold, and if current trends continue, then in 3 years from now, the global prevalence will reach 18% and 21% in men and women, respectively (1). Apart from increasing the risk for type 2 diabetes, metabolic syndrome, cardiovascular disease, and several cancers, obesity is the primary causal factor for development of obstructive sleep apnea (OSA). Numerous studies demonstrate an increase in OSA prevalence and severity with weight gain and a corresponding decrease in both with weight loss (2). Indeed, there is little doubt that the current obesity epidemic is a major driver for the more than 425 million moderate–severe cases of OSA globally (3), with studies suggesting that nearly 60% of these cases are attributable to being overweight or obese (4).

Pathogenic mechanisms linking obesity with OSA are thought to involve excessive fatty tissue in the upper airway walls and tongue, acting to decrease the size of the pharyngeal lumen, which in turn leads to pharyngeal collapse during sleep (5). Other obesity-related factors include lower lung volumes, which act to decrease the airway lumen size (5, 6). In addition, obesity-related leptin resistance has been shown to alter the activity of respiratory motoneurons, which may also predispose to OSA (7). However, although these obesity-related mechanisms play a central role in OSA pathophysiology, there is still marked interindividual heterogeneity in alleviation of OSA with weight loss (8, 9). There is also a wide variability in apnea–hypopnea index (AHI) response across multiple studies using both surgical and nonsurgical interventions, with varying magnitudes of weight loss achieved (10). This heterogeneous response in AHI reduction may be linked to specific variations in upper airway fat loss. However, it is also conceivable that craniofacial size could modulate the effect of weight loss (11, 12). This modulating effect on OSA alleviation may, in turn, impact the magnitude of improvement on cardiometabolic health. This is because OSA alleviation with continuous positive airway pressure (CPAP), of and by itself, has been shown to modestly improve aspects of cardiometabolic health, including blood pressure, lipidemia (13), and glucose intolerance (14). Importantly, the differential impact of CPAP and weight loss on inflammation and cardiometabolic health in obese OSA has previously been explored in a clinical trial in which patients were randomized to CPAP alone, weight loss alone, or combination therapy with CPAP and weight loss (15). In secondary analyses of all patients compliant with both weight loss and CPAP, the combination therapy reduced blood pressure twofold greater than weight loss alone and fourfold greater than CPAP alone and was the only treatment to improve insulin sensitivity. Overall, these findings support the use of weight loss as a primary method for improving cardiometabolic health. However, they also suggest that, in the presence of weight loss, alleviating residual OSA with CPAP could

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confer much larger improvements in cardiometabolic health than with weight loss alone. This leads to the question, should all OSA patients undergoing a weight loss program also then use CPAP? Perhaps not if there was a way to predict the extent of OSA alleviation based on the preintervention assessment of craniofacial size.

In this issue of the *Journal*, Ng and colleagues (pp. 711–720) explored this very concept (16). Their study compared changes in inflammatory and metabolic profiles following 6 months of CPAP treatment or weight loss using a lifestyle modification program (LMP) in a population of obese Chinese patients with moderate–severe OSA. Patients randomized to LMP were stratified into two groups based on craniofacial phenotype measured from computed tomography–derived maxillomandibular volume (MMV). They hypothesized that weight loss in patients with more craniofacial restriction (smaller MMV) would confer a greater reduction in OSA and therefore a greater improvement in insulin sensitivity (Matsuda index) and reduction in subclinical inflammation. Their hypothesis was based on the notion that the interaction between craniofacial skeletal structure and the soft tissue housed within it is an important determinant of upper airway collapsibility and that any reduction in soft tissue volume due to loss of upper airway fat would reduce collapsibility to a greater extent in patients with smaller versus larger MMVs.

Patients were middle-aged (~50 yr) and obese (body mass index ~29 kg/m^2) with moderate–severe OSA and mild sleepiness (Epworth Sleepiness Score ~11). The LMP produced a modest 6.2% (4.7 kg) weight loss and a −25.4% (−11 events/h) reduction in the respiratory event index determined from a validated level three cardiorespiratory device. Sleepiness improved in both the CPAP and LMP groups (Epworth Sleepiness Score fell by 3–4 points); however, only patients in the LMP group reduced inflammation and improved insulin sensitivity (Matsuda index). Contrary to the underlying hypothesis, there was no difference in OSA severity, sleepiness, inflammation, and insulin sensitivity improvements between the stratified LMP groups (small vs. large MMV). These results were unaffected by baseline between-group differences in age, sex, and body weight.

This study has several strengths. It is the first to explore the potential modulatory role of craniofacial phenotypes on weight loss–induced OSA reduction and improvements in cardiometabolic health in a large, well-characterized Chinese ethnic population. Patient retention and adherence to the study protocol was excellent, with only 5 of 194 randomized patients not completing follow-up. Also, despite the modest loss of weight with the LMP, there were clinically important improvements in subclinical inflammation by approximately −30% and an increase in insulin sensitivity by more than 25%. This result is a clear demonstration that even a modest reduction of 10–20% in daily energy intake can produce important improvements in health.

The study also has several limitations. As acknowledged by the authors, although the large sample size enabled a robust analysis of outcomes between LMP and CPAP, the stratification of the LMP group into small and large MMV may have reduced the statistical power to explore differences between these latter groups. Furthermore, although objective CPAP use was enhanced by excluding patients who were unwilling to accept CPAP therapy based on a prerandomization 30-minute acclimatization test, overall objective compliance was still suboptimal at 4 hours. The study results may not be consistently generalizable, as it was conducted in an exclusively Chinese population. Finally, although the LMP was effective, the intensity of the intervention with weekly dietary consultation in the first 4 months poses a high patient burden in terms of time and financial commitment in clinical settings. Furthermore, an economically viable solution to stopping weight regain after 6 months remains largely elusive for obesity researchers (17).

It could also be argued that the search for a reliable craniofacial phenotype to predict those patients who will be "cured" of their OSA through weight loss is the "holy grail." If found, this will greatly advance the field to triage patients to the most viable and effective therapy to treat their OSA. Although on this occasion, the authors have not found the answer, they should be commended for providing invaluable data on which to base further research in this important area of sleep medicine. ■

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A Good Fit versus One Size for All: Alternatives to Race in the Interpretation of Pulmonary Function Tests

Reference equations facilitate interpretation of pulmonary function test (PFT) results by accounting for major sources of population variation and providing a range of expected values for a specific age, height, and sex. Unlike most other tests in medicine, reference equations for PFTs are also indexed to self-identified race, a standard practice endorsed by guidelines. Based on observations in large nonsmoking populations without a history of chronic pulmonary disease or symptoms, reference equations yield lower values for non-White compared with White groups. These differences are taught as immutable, with race often portrayed as a biomedical proxy for genetic differences rather than the shifting social construct it is (1). Race shapes society in profound ways and can capture the biological consequences of inequality related to unmeasured risk factors, including exposures to a disproportionate burden of environmental hazards as well as to individual and structural racism. However, the premise that using race in PFT interpretation is helpful to patients in the clinical setting or in research has been challenged, given the risks of norming lower pulmonary function in non-White groups, masking modifiable social risk factors, and contributing to health disparities (2, 3). Alternative ways of interpreting PFT results are understudied.

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Two articles in this issue of the *Journal* investigate contrasting approaches that move our understanding forward and force us to ask how and for what we use pulmonary function testing.

One use of pulmonary function testing is to assess prognosis based on how far a measured value is outside the expected range. McCormack and colleagues (pp. 723–726) used spirometry data from NHANES III (third National Health and Nutrition Survey, conducted from 1988 to 1994) to ask whether measured values normalized to reference values more accurately assess risk of subsequent mortality with or without consideration of race (4). NHANES III is a nationally representative sample that includes adults with and without respiratory and other symptoms and diseases, as well as former and current smokers. Mortality predictions using the Global Lung Initiative (GLI) race-specific and multiracial composite (labeled "other" in the initial GLI publication) reference equations were compared (5). Regardless of the choice of reference equations, a lower normalized FEV_1 or FVC was strongly associated with increased mortality after adjustment for age, sex, smoking, and income. Predicted survival was better matched between White and Black populations at the same normalized FEV_1 or FVC when using multiracial rather than race-specific reference equations, a finding that extends prior work and is supported by another analysis of NHANES III (6, 7).

The mechanism by which lower measured spirometric values in Black individuals are associated with similar mortality to White individuals with higher spirometric values at the same age, sex, and standing height remains to be determined. Lower spirometric values may either be a result of the same factors that independently