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Obstructive Sleep Apnea and the Metabolic Syndrome: The Road to Clinically-Meaningful Phenotyping, Improved Prognosis, and Personalized Treatment

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Summary

Obstructive sleep apnea (OSA) is an increasingly prevalent sleep disorder characterized by upper airway obstruction during sleep, resulting in breathing pauses, intermittent hypoxia, and fragmented sleep. In parallel, the constellation of adverse health outcomes associated with prolonged obesity, such as insulin resistance, elevated blood pressure, triglycerides, and reduced high-density lipoprotein cholesterol – termed metabolic syndrome – raises the risk of cardiovascular morbidity and mortality, type 2 diabetes, and all-cause mortality. Affecting 35–40% of U.S. adults, risk factors for metabolic syndrome, including obesity, middle age, sedentary behavior, and genetics, share considerable overlap with those for OSA. Thus, it has been difficult to disentangle cause, effect, and whether certain treatments, such as CPAP, can improve these outcomes. In this paper, we provide an update to our 2005 review which explored the association between OSA and metabolic syndrome, highlighting visceral obesity as the common etiological factor of both conditions. This update includes (a) recent data on physiological and biochemical mechanisms, (b) new data in nonobese men and women as well as children and adolescents, (c) insight from the latest treatment studies, (d) the role of aging in understanding clinically-meaningful phenotypes of the disorder, and (e) the potential diagnostic/prognostic utility of biomarkers in identifying OSA patients with the strongest cardiometabolic risk.

Keywords

obstructive sleep apnea; metabolic syndrome; inflammation; obesity; biomarkers; phenotypes

Obstructive sleep apnea (OSA) is a prevalent sleep disorder characterized by upper airway obstruction during sleep, resulting in intermittent breathing pauses despite effort, acute

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reductions in hemoglobin oxygen saturation (SpO₂), and fragmented sleep. Importantly, OSA is associated with a number of chronic medical conditions that contribute to poor quality of life, morbidity, and mortality, including hypertension, diabetes, coronary artery disease, and diminished cognitive ability, among others. Patients with untreated OSA have been shown to contribute significantly to increased healthcare costs and resource use, while treatment reduces healthcare use to that of the general population [1]. Population cohort studies over the last two decades have estimated the prevalence of OSA at 17–24% of men and 5–9% of women [2–4], though more recent work emphasizes how rates of OSA have increased between 14% to 55%, depending on the subpopulation studied, in conjunction with the ongoing obesity epidemic [5].

In parallel, adverse health outcomes associated with prolonged obesity – elevated blood pressure, insulin resistance, elevated triglycerides, and reduced high-density lipoprotein (HDL) cholesterol – raise the risk of cardiovascular morbidity and mortality, type 2 diabetes, some cancers, all-cause mortality, and even neurological disorders [6]. Collectively, this constellation of health risks is termed *metabolic syndrome*. Affecting 35–40% of U.S. adults [7], risk factors for metabolic syndrome – including middle age, sedentary behavior, poor diet, and genetics – are similar to those for OSA. The considerable overlap in biomarkers and health outcomes in obese individuals with and without OSA, thus, makes it difficult to disentangle cause, effect, and whether certain treatments, such as continuous positive airway pressure (CPAP), can improve these outcomes.

In this paper, we provide an update to our 2005 review [8], which proposed the argument that both OSA and metabolic syndrome were, largely, manifestations of central obesity, the common etiological factor of both conditions. In that review, we proposed a theoretical model based largely on cross-sectional associations – that metabolic syndrome and OSA represent, essentially, heads of two similar coins, with a bidirectional, feedforward association driven primarily by visceral obesity and insulin resistance (Figure 1). This updated review includes (a) recent data that digs into physiological and biochemical mechanisms underlying the association between OSA and metabolic syndrome, (b) new data in nonobese men and women, as well as children and adolescents, (c) insight from the latest treatment studies, (d) the important role of aging in understanding clinically-meaningful phenotypes of the disorder, and (e) the potential diagnostic and prognostic utility of biomarkers in identifying OSA patients with the strongest cardiometabolic risk.

Obstructive sleep apnea and metabolic syndrome: the chicken or the egg?

Epidemiological studies have reported that metabolic syndrome is 6 to 9 times more likely to be present in individuals with OSA compared to the general population [9, 10]. The prevalence of OSA peaks around ages 50–59 years for men and 60–69 years for women (Figure 2A) [3, 4]. Particularly in women, OSA is more prevalent following hormonal changes such as menopause, which may explain the delay in peak prevalence compared to men [4]. This quadratic relationship mirrors the prevalence of the metabolic syndrome in U.S. adults according to the Third National Health and Nutrition Examination Survey (NHANES) data collected during the same time frame (1988–1994; Figure 2B) [11].

Just as the prevalence of metabolic syndrome declines in older age (Figure 2A), the cardiometabolic comorbidities associated with OSA also diminish in parallel. Both cross-sectional [Bixler2000, 13] and prospective [14, 15] studies have demonstrated that the relationship between OSA and hypertension, coronary heart disease, heart failure, and mortality is strongest in the youngest, and that OSA is not a significant risk factor for adverse health outcomes in older men and women. Excessive daytime sleepiness (EDS), a cardinal symptom of OSA, is also strongly and independently associated with obesity and metabolic syndrome [16, 17]; similar to cardiometabolic comorbidities, EDS diminishes in frequency and intensity in older patients with OSA. [97]. Together, these findings suggest that cardiometabolic morbidities in the elderly occur independently from OSA, and that OSA in older age is not as strongly associated with the metabolic syndrome as in younger age. These studies are described in greater detail in the section below entitled *Obstructive sleep apnea in the young and middle-aged is a different phenotype than in the elderly*.

Visceral fat is the key predictor of both OSA and metabolic syndrome.

Increased prevalence of OSA has mirrored the surge in obesity over the last two decades. A four-year follow-up study in the Wisconsin Sleep Cohort reported that modest (10%) weight gain predicted a 32% increase in AHI and 6-fold odds of developing moderate-to-severe OSA; on the other hand, 10% weight loss predicted a 26% decrease in AHI [18].

While there are multiple definitions of metabolic syndrome featuring different cut-offs for blood pressure, lipid, and glucose levels [19], the presence of abdominal obesity, specifically – defined by either an elevated waist circumference or waist/hip ratio – is central to all definitions. Waist circumference is largely driven by intra-abdominal, or visceral, adipose tissue in the peritoneal cavity, packed between the stomach, liver, kidneys, intestines, and other internal organs. Higher levels of visceral fat have been observed in obese [20] and, importantly, non-obese [21] men with OSA, even when matched with controls for age and body mass index (BMI). Metabolic parameters including cholesterol, triglycerides, homeostatic model assessment (HOMA, a measure of insulin resistance), and inflammatory markers are also elevated in non-obese men and, for some parameters, women with OSA compared to controls [22]. Visceral fat accounts for 5–8% of total body fat in women and increases during menopause, and up to 10–20% in men [23], which may, in large part, explain the sex dimorphism in OSA prevalence. Of note, longitudinal pediatric studies have also demonstrated that incident OSA in adolescents is most strongly predicted by childhood waist circumference [24], and OSA severity in adolescence is positively associated with a greater increase in waist circumference between childhood and adolescence [25].

The mechanism linking central obesity and OSA is likely the result of interplay between various processes. Excess fat tissue, particularly in the abdominal region, is also associated with accumulation of excess fat in the neck, which contributes to upper airway narrowing [26], increased collapsibility due to caudal traction, decreased efficiency of dilator muscle contraction [27], and sarcopenia, denervation, and skeletal muscle dysfunction due to lipid accumulation [28] and increased inflammatory gene expression [29]. While the mechanisms by which obesity causes OSA remain incompletely understood, we propose that local and

systemic inflammation may be a partially contributory factor, as outlined in the following sections.

Systemic inflammation in OSA is largely derived from visceral fat.

Compared to age- and BMI-matched controls, patients with OSA demonstrate significantly elevated plasma interleukin-6 (IL-6), tumor necrosis factor alpha (TNF α) [20, 30], and C-reactive protein (CRP) levels [31, 32]. Levels of CRP have been positively correlated with AHI, arousal index, and oxygen desaturation [33, 34].

OSA-associated inflammation is thought to arise from two major sources. For one, mechanical damage due to snoring, breathing effort, and upper airway obstruction is associated with elevated immune cells in nasal and oropharyngeal mucosa, breath condensate, and sputum [35–38]. A study by Sériès and colleagues [39] comparing OSA patients and age-/BMI-matched controls, however, demonstrated that inflammation in the uvula is correlated with BMI, but not with AHI, suggesting that obesity per se produces tissue inflammation in structures subject to mechanical damage. Second, OSA patients experience a unique pattern of oxygen deficiency – termed intermittent hypoxia (IH) – in which short, repetitive cycles of oxygen desaturation are followed by rapid reoxygenation of tissue. In an in-vitro model, Ryan and colleagues [40] have described how IH, but not sustained hypoxia (SH), preferentially activates inflammatory pathways mediated by the transcription factor nuclear factor kappa B (NF- κ B) which increase the transcription of genes coding for TNF α , interleukins, and other immune proteins.

While OSA is an independent predictor of elevated proinflammatory cytokines, there is considerable evidence in adult and child literature, however, suggesting that central obesity largely precedes systemic inflammation, metabolic dysfunction, and subsequent development of OSA. Obesity per se is recognized as a chronic, low-grade inflammatory state. In addition to adipocytes, fibroblasts, and vascular endothelial cells, adipose tissue contains immune cells such as mast cells, eosinophils, B cells, T cells, and macrophages [41]. Compared to subcutaneous fat, visceral fat contains proportionally more adipocytes that are capable of growing quite large before dividing [42]; as the size of these lipid droplets increases with weight gain, the adipocytes themselves begin secreting low levels of TNF α . In turn, TNF α stimulates preadipocytes and surrounding endothelial cells to produce monocyte chemoattract protein-1 (MCP-1), promoting macrophage recruitment and adhesion to endothelial cells [43]. As adipocytes continue to grow and divide, endothelial damage due to oxidative stress and cell crowding recruits additional macrophages [44], which secrete TNF α , IL-6, IL-1 β , and other proinflammatory cytokines. As a result, plasma levels of acute-phase reactant proteins, such as CRP, become elevated. Taken together, obesity – particularly visceral obesity – creates a proinflammatory state that perpetuates a vicious cycle of macrophage recruitment, impaired adipocyte functioning, and activation of transcription factors for genes encoding proinflammatory proteins [44].

Examining OSA in children and adolescents presents a unique vantage point into the early pathophysiology of the disorder, as the cases are new-onset and are often not confounded by multiple diseases. In a recent study of the Penn State Child Cohort, we demonstrated that visceral fat area is significantly elevated in adolescents with new-onset OSA (AHI ≥ 5).

Importantly, mediation analysis revealed that 82% of the association between visceral fat and OSA in adolescents was mediated by CRP levels, while 42% was mediated by IL-6 (Figure 3A). Although the model cannot account for other potentially important factors that were not included, our findings suggest that the release of proinflammatory cytokines by visceral adipocytes may explain, to some degree, the association between central obesity and incident OSA [45]. In a longitudinal subsample of the Cohort, we also demonstrated that greater increases in waist circumferences from childhood to adolescence (waist) predicted higher adolescent AHI, and that this association may be accounted for by increases in CRP from childhood to adolescence (CRP) [25; Figure 3B]. Interestingly, pre- and perinatal factors such as chorioamnionitis, maternal smoking, weight gain during pregnancy, gestational diabetes, and prematurity have also been associated with childhood OSA [46–48], with inflammation during this critical period hypothesized as a possible mechanism.

Obstructive sleep apnea prevalence is higher in disorders of insulin resistance.

Visceral fat tissue is rich in vasculature and readily contributes adipokines into the bloodstream and nervous system [42]; compared to subcutaneous fat, the proximity of visceral fat to vasculature, central nerves, and critical organs such as the liver make this tissue type relatively more dangerous to overall health. Visceral adipose tissue also has a relatively high concentration of glucocorticoid, androgen, and adrenergic receptors, making the tissue more susceptible to stress hormone, catecholamine, and testosterone signaling [49, 50]. Furthermore, as visceral adipocytes accumulate larger lipid droplets with weight gain, they become dysfunctional, adopting a higher rate of glucose uptake and developing insulin resistance [51]. Through these pathways, increased waist circumference and elevated visceral fat have been strongly linked to metabolic syndrome, cardiovascular events, and cardiovascular and all-cause mortality, particularly in men [52, 53].

TNF α levels have been associated with insulin resistance in individuals both with and without type 2 diabetes [54, 55]. Given the well-known association between obesity and inflammation with insulin resistance, it is unsurprising that many studies have reported associations between OSA severity and degree of insulin resistance [20, 56, 57], even in non-obese subjects [22, 58]. Several experimental [59, 60] and observational [61, 62] studies in both humans and animals have demonstrated that hypoxic stress contributes to acute and long-term elevations in glucose, insulin, and/or hemoglobin A1c (HbA1c) levels.

At the same time, while many studies have explored the hypothesis that OSA causes chronic insulin resistance and diabetes, the relative contribution of OSA per se, compared to obesity and other metabolic factors, is not as strong. For instance, in the Wisconsin Sleep Cohort, Reichmuth and colleagues demonstrated that although the prevalence of type 2 diabetes was significantly higher in subjects with OSA, the risk of developing diabetes over a four-year follow-up period was not, suggesting that OSA may be only weakly causal in the development of the disorder [63]. Furthermore, a more recent prospective study reported that baseline fasting insulin, HOMA, and triglycerides significantly predicted OSA six years later, even after adjusting for age, sex, and waist circumference; interestingly, however, baseline OSA did not predict elevated insulin levels at follow-up. Unsurprisingly, baseline waist circumference was the strongest predictor of incident OSA in this study [64]. A recent

study in patients with moderate-to-severe OSA reported that CPAP withdrawal caused dynamic increases in nocturnal glucose levels; however, this was observed primarily in those who were already diabetic [60]. While the hypoxemia, sleep fragmentation, and sympathetic nervous system activation associated with OSA undoubtedly exacerbate metabolic aberrations, considerable data suggest that metabolic factors largely precede the development of the disorder.

As we and others have demonstrated, OSA is very frequent in disorders in which insulin resistance is a primary pathophysiologic abnormality. Polycystic ovarian syndrome (PCOS) is the most common endocrine disorder in women of reproductive age, characterized by oligoovulation, hyperandrogenism, obesity, and insulin resistance. Compared to pre-menopausal women without PCOS, we have reported that those with PCOS are 30.6 times more likely to also suffer from sleep-disordered breathing (SDB), including snoring, and 28.7 times more likely to have OSA (AHI ≥ 10) [65]; later studies have confirmed this finding [66–68]. Obese women with PCOS have significantly higher fasting insulin levels than non-obese women with PCOS [69]; we have reported that insulin resistance is the strongest risk factor for OSA in women with PCOS – stronger than even BMI or testosterone [65].

The association between insulin resistance states and OSA severity has even been demonstrated as young as childhood. We have previously demonstrated that the frequency of EDS increases with increasing BMI and OSA severity in children aged 5–17 years, with significant linear increases in IL-6, TNF receptor-1 (TNFR1), CRP, and leptin, and decreases in adiponectin [70]. Interestingly, just as elevations in inflammation from childhood to adolescence predict OSA in adolescence [25], a recent prospective study demonstrated that metabolic exposures in mid-childhood (age 9) – including adiposity, leptin, HOMA, CRP, and global metabolic risk – predicted SDB just four years later at the early teenage visit (mean age 13.2 years), even after adjusting for age, sex, BMI, race, and other confounders [71].

Insight from treatment studies

As the gold-standard treatment for OSA, CPAP devices apply continuous mild air pressure to keep airways open, allowing patients to breathe spontaneously on their own. CPAP use has been consistently associated with higher sleep efficiency, fewer arousals, lower AHI, improved oxygen saturation, and decreased daytime sleepiness [72].

Despite these beneficial effects, however, a recent meta-analysis concluded that CPAP does not significantly improve lipid levels, insulin resistance, inflammatory markers, or the proportion of patients with the metabolic syndrome [73]. Specifically, CPAP does not significantly reduce IL-6, TNF α , TNFR1 [74, 75], CRP [76], leptin [22, 77], nor fasting insulin and glucose [74], even after comparing groups with low versus high CPAP compliance [22]. A sham-controlled study also demonstrated no reversal of metabolic syndrome after 12 weeks of CPAP use [78], and a recent study demonstrated that CPAP did not significantly reduce HbA1 levels in individuals with Type 2 diabetes [79]. While several of these studies have been criticized for short follow-up periods ($\leq$ three months), another

recent paper demonstrates that even one year of CPAP use does not significantly alter levels of CRP, IL-8, or TNF α in patients with OSA and coronary artery disease [80]. Interestingly, in this study, even though IL-6 levels decreased with CPAP use, IL-6 levels had also decreased in parallel in the non-CPAP group, which may have been due to other lifestyle changes (e.g. diet, exercise, and weight reduction), about which the non-CPAP group received education [80]. In another recent randomized trial, improvements in inflammation, insulin resistance, and serum triglycerides were only observed in patients with OSA who combined their CPAP use with weight loss during a 24-week period [81].

On the other hand, while CPAP use largely does not improve metabolic parameters nor reverse metabolic syndrome, there is evidence suggesting that OSA is associated with dynamic increases in cortisol in proportion to OSA severity [60] and elevated 24-hour and nighttime cortisol levels [82] and are, in fact, corrected with CPAP therapy [82–84]. The intermittent hypoxia, subsequent autonomic arousal, and frequent nocturnal awakenings are hypothesized to create a state of sympathetic hyperarousal. Despite little to no effect on other metabolic parameters, longer-term CPAP use (three months) has been associated with modest reductions in blood pressure [74, 85].

Taken together, these treatment studies suggest that metabolic factors (including inflammatory markers, lipids, and markers of insulin resistance) are not reversed by improved AHI and sleep efficiency unless accompanied by long-term weight loss. Sympathetic activation and increased blood pressure as a consequence of intermittent hypoxia, however, may be improved by CPAP therapy. Of note, the relatively high failure rate of upper airway surgeries for patients with OSA, such as uvulopalatopharyngoplasty (UPPP) [86], is even higher in obese patients [87], further suggesting that obesity and metabolic factors may play a contributing role in the pathophysiology of the disorder.

In line with the hypothesis that OSA stems from a systemic cause, several pilot treatment studies employing anti-inflammatory therapy have modestly reduced OSA severity in both children and adults without CPAP treatment or surgical intervention. In a placebo-controlled, double-blind study of eight obese men with severe OSA (AHI = 52.8 ± 9.1 events/h), a three-week trial of the TNF α antagonist etanercept significantly reduced AHI (to 44.3 ± 10.3 events/h), IL-6 levels, and objective daytime sleepiness (as measured by the Multiple sleep latency test [MSLT]) [88]. Several randomized controlled trials in children, spanning across several weeks to months, also report reduced AHI and relative normalization of sleep parameters with intranasal corticosteroid treatment in combination with oral anti-inflammatory medication, despite no significant reductions in adenotonsillar size [89–93]. An emerging body of literature also reports an association between OSA and autoimmune and rheumatic disease populations, particularly rheumatoid arthritis [94, 95]. Common to both conditions are increased levels of circulating proinflammatory cytokines; however, the potential direction of this association has not been explicitly examined. Interestingly, however, a recent study reported a significantly lower prevalence of OSA in patients with spondyloarthritis who take TNF inhibitors compared to those who do not [96].

There are certainly limitations to drawing physiological conclusions from these studies given a lack of rigorous data, mostly due to methodological limitations in being able to conduct

the type of cellular- and molecular-level analyses necessary in human patients with OSA. Future clinical trials, as well as animal studies of obesity-derived OSA, will better shed light on these complex mechanisms. Taken together, however, these studies do lend evidence that systemic inflammation may play some role in the development of OSA, and that anti-inflammatory therapies, as well as therapies designed to reduce visceral adiposity – compared to CPAP, upper airway surgery, or other mechanical treatments – may address the systemic root cause of OSA for many patients.

Obstructive sleep apnea in the young and middle-aged is a different phenotype than in the elderly

As mentioned earlier in this review, while the prevalence of OSA based on clinical criteria tends to peak in middle age, the cardiometabolic comorbidities associated with OSA tend to diminish. We have previously reported in the Penn State Adult Cohort that, cross-sectionally, the prevalence of OSA based on AHI criteria alone (i.e. AHI ≥ 10 , with or without accompanying symptoms) continues to increase linearly after 65 years of age; however, the peak prevalence based on comorbid AHI and clinical criteria is around age 55 years for men and 65 years for women (Figure 2A) [3]. Furthermore, oxygen desaturation in older individuals was significantly less in the elderly, suggesting the possibility that OSA in the young and middle-aged is more severe [3].

Subsequent cross-sectional [12, 13] and prospective [14, 15] studies have reported that the associations between AHI and hypertension [12, 13], incident coronary heart disease and heart failure [15], and even mortality [14] are not as strong, or are even non-significant, in the elderly compared to the young and middle-aged. In a recent 10-year follow-up of the Penn State Adult Cohort, we report that both mild (OR = 4.35) and moderate (OR = 3.80) OSA are associated with increased odds for developing incident hypertension; however, this association is only observed in those < 60 years ($p = 0.01$) and lost in the elderly. Furthermore, young and middle-aged subjects with OSA also have higher rates of obesity, increased BMI, and higher fasting blood glucose and triglyceride levels compared to those ≥ 60 years with incident OSA [97]. Together, these findings suggest that cardiometabolic morbidities in the elderly occur independently from OSA, and that OSA in older age is not as strongly associated with the metabolic syndrome as in younger age.

Several physiological mechanisms have been hypothesized to explain this observation. A decade ago, Kirkness and colleagues studied the effects of age on pharyngeal pressure under hypotonic conditions (passive Pcrit) during sleep in men and women with and without OSA. The authors reported that OSA increased in severity when passive Pcrit rose above -5 cmH₂O, with a predictive power of 0.73. Passive Pcrit was significantly higher in men than women, and increased with age [98]. Edwards et al. expanded on these findings in 2014 in a small study of ten young (20–40 years) and old (≥ 60 years) patients with OSA matched for sex and BMI, measuring collapsibility, loop gain, upper airway muscle responsiveness, and respiratory arousal threshold during drops in positive airway pressure. Compared to younger patients with OSA, older patients had, on average, a more collapsible airway, lower ventilation prior to the pressure drop, and a lower loop gain. The authors concluded that

airway anatomy and collapsibility play a relatively greater role in the pathogenesis of OSA in older adults [99]. In line with these studies, a recent longitudinal study of elderly patients with OSA showed no association between dual X-ray absorptiometry (DXA)-measured central obesity and changes in AHI across an 8-year period [100]. Taken together, these findings are in line with the notion that OSA in older age is a distinctly different phenotype than in the young – due to an increasingly independent association with cardiovascular and metabolic comorbidities – and differential diagnosis, prognosis, and treatment options should be considered in this population.

In search of a clinically-useful biomarker of cardiometabolic risk

As detailed throughout this review, (a) markers of metabolic dysfunction, such as inflammation, are highly prevalent in OSA, and (b) OSA treatments, while successful at reducing AHI, do not significantly improve metabolic parameters unless combined with weight loss. While it is clear that treatment should be pursued in more severe cases of OSA (AHI ≥ 30), OSA in the mild ($5 \leq \text{AHI} < 15$) to moderate ($15 \leq \text{AHI} < 30$) range presents a challenge, as AHI alone cannot satisfactorily predict the development of OSA-associated comorbidities – particularly when patients do not complain of excessive daytime sleepiness or other troubling symptoms. Furthermore, the gold-standard treatment, CPAP, has relatively poor compliance; 31% of patients with OSA who are prescribed CPAP never commence therapy after diagnosis and titration, and an additional 15% abandon their machines after 10 months of use [101]. CPAP devices can also be highly disturbing to both the patient and their bed partner due to discomfort and noise [102, 103].

A recent joint biomarker workshop sponsored by the National Heart Lung and Blood Institute, National Institute on Aging, and the Sleep Research Society advised that the sleep field lacks a “unique biomarker signature that is context -relevant, simple and easy to use” that can help clinicians determine a patient’s long-term prognosis [104]. Furthermore, a recent editorial highlights the importance of identifying precise, cost-effective biomarkers for cardiometabolic risk that allow clinicians to identify OSA patients who are most likely to benefit from therapy [105]. We have previously demonstrated that inflammation (specifically, CRP) is elevated in a dose-response manner across OSA patients with hypertension, OSA patients without hypertension, and controls, suggesting that inflammation may be a clinically useful marker of OSA severity and comorbid cardiovascular problems [106]. We recently demonstrated that objectively-measured daytime sleepiness (via MSLT), but not subjectively-measured sleepiness (Epworth sleepiness scale), correlates with 24-hour IL-6 [107]. Furthermore, CRP has been shown to partially mediate the association between AHI and incident type 2 diabetes [108], suggesting its potential efficacy in discriminating which OSA patients may have a worse prognosis.

In a new study [109], we compared the relative utility of AHI versus CRP in identifying the presence and severity of hypertension and hyperglycemia in 60 middle-aged adults with mild-to-moderate OSA ($5 \leq \text{AHI} < 30$). We found that CRP levels were associated with greater odds for having hypertension (OR = 1.42, $p = 0.08$) and hyperglycemia (OR = 1.83, $p = 0.01$) compared to AHI (both $p > 0.12$). Furthermore, receiver-operating characteristics (ROC) curves demonstrated that adding a measure of CRP to standard clinical factors (age,

sex, and BMI) yielded moderately good to strong risk prediction models for the disorders (AUC = 0.72 and AUC = 0.81, respectively), while adding AHI did not (both AUC < 0.69). According to these models, a “typical” obese (BMI = 30 kg/m²), middle-aged (50 years) man with AHI = 15 has a 36.6% probability of having hypertension and 25.7% probability of having hyperglycemia if their CRP = 0.5 mg/L (healthy levels); these probabilities increase to 58.1% and 60.2%, respectively, if their CRP levels are increased to 3.0 mg/L (“at risk” levels; Figure 4A). Similarly, an obese, middle-aged woman with AHI = 10 has a 15.3% and 8.3% probability of hypertension and hyperglycemia, respectively, if their CRP = 0.5 mg/L; these probabilities increase to 30.2% and 28.4% if their CRP = 3.0 mg/L (Figure 4B). Our findings are also interesting given the results of another recent study [110] showing that a combination of elevated CRP, hemoglobin A1c (HbA1c, a measure of plasma glucose levels), and erythropoietin (a cytokine released in response to cellular hypoxia) levels provided the greatest predictive power for the presence of moderate-to-severe OSA (AUC = 0.84), with high sensitivity (85%) and specificity (79%). No current test for detecting OSA, however, can replace the gold-standard polysomnography.

Although CRP represents a nonspecific marker of inflammation, we propose that incorporating a patient’s CRP levels through routine bloodwork – along with other standard clinical sleep measures – may enhance the ability for clinicians to detect cases of mild-to-moderate OSA with true cardiometabolic risk, thus improving the accuracy of prognosis and clarifying which treatment option may be most beneficial to the patient. Future studies should follow up patients over a period of several years to explore whether CRP levels at baseline predict the severity of future cardiometabolic sequelae, more so than AHI alone.

Conclusions

At the time that our 2005 review [8] was published, our proposed heuristic model (Figure 1) was largely theoretical – based primarily on cross-sectional associations and astute clinical observation of patients with OSA who did and did not present with comorbid metabolic syndrome. Our proposed research agenda at the time detailed the need to examine the association of OSA and metabolic syndrome in non-obese populations and children; explore the potential for anti-inflammatory agents in reducing OSA severity; and a need for prospective studies on the mechanisms underlying the consequences of lifestyle changes, such as weight gain and weight loss, on OSA prevalence, incidence, and severity.

In the past decade, we and others have been able to better unravel these complex mechanisms via in-vitro and animal models, studies in children and adolescents, and prospective observational and treatment studies. And our conclusions largely remain the same: there is a bi-directional, feedforward association between metabolic syndrome and OSA.

Visceral obesity and insulin resistance – determined by genetic, constitutional, and environmental factors – are the principal culprits leading to OSA, and these associations may be driven by a chronic, low-grade inflammatory state. In turn, central obesity and inflammation may lead to upper airway narrowing, respiratory muscle fatigue, and decreased dilator muscle contraction. Furthermore, these mechanisms may explain why mechanical treatments, such as CPAP or upper airway surgeries, are often unsuccessful at reversing

metabolic syndrome unless combined with weight loss. Given our significant progress in better understanding these mechanisms over the last decade, it is certainly a worthwhile endeavor for future studies to focus on the use of biomarkers for improving the accuracy of OSA diagnosis and prognosis, and for clarifying which treatment option may be most beneficial to the patient.

But in the meantime, our recommendations remain the same: for the average patient with OSA, weight management, healthy eating habits, and regular exercise should obvious, complement to treatment for any patient with OSA.

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Abbreviations

AHI	apnea-hypopnea index
BMI	body mass index
CPAP	continuous positive airway pressure
CRP	C-reactive protein
DXA	dual X-ray absorptiometry
EDS	excessive daytime sleepiness
HbA1c	hemoglobin A1c
HDL	high-density lipoprotein
HOMA	homeostatic model assessment
IH	intermittent hypoxia
IL-6	interleukin-6
MSLT	Multiple sleep latency test
OSA	obstructive sleep apnea
SDB	sleep-disordered breathing
SpO₂	blood oxygen saturation
TNFα	tumor necrosis factor alpha
TNFR1	tumor necrosis factor receptor-1

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Practice Points:

1. The relationship between age and OSA across the lifespan mirrors that of age and metabolic syndrome.
2. The increased prevalence of OSA has followed the surge in obesity over the last two decades.
3. Visceral fat is the key predictor for both metabolic syndrome and OSA, even in non-obese and younger populations.
4. Increased systemic inflammation and insulin resistance in patients with OSA are largely derived from visceral adiposity.
5. Continuous positive airway pressure does not reverse inflammation, insulin resistance, or elevated lipid levels, but lowers cortisol and has a modest effect on blood pressure.
6. OSA in the elderly is more strongly associated with upper airway collapsibility, not metabolic abnormalities, and may represent a different phenotype.
7. C-reactive protein may be a useful biomarker for improving the accuracy of diagnosis and prognosis of mild-to-moderate OSA, and for clarifying which treatment option may be most beneficial to the patient.

Research Agenda:

Future studies should:

1. Follow up patients of a wide age spectrum over a period of several years to explore whether biomarker levels at baseline, such as CRP, can predict the severity of future cardiometabolic sequelae.
2. Explore the characteristics and mechanisms that delineate OSA phenotypes (for example, in young and middle-aged vs. older individuals).
3. Study how inflammatory and metabolic molecules affect central and peripheral breathing mechanisms in animals and humans.
4. Assess the impact of lifestyle or pharmacological therapies that reduce inflammation or metabolic syndrome (alone, or in combination with existing treatments such as CPAP), on OSA and associated adverse health outcomes.

Figure 1. A heuristic model of the feedforward associations between visceral fat, insulin resistance, inflammatory cytokines, stress hormones, excessive daytime sleepiness (EDS) and fatigue, and obstructive sleep apnea (OSA). Adapted from Vgontzas et al., 2005 [8].

Figure 2.

The prevalence of clinically-defined OSA in men and women (**A**), and metabolic syndrome in U.S. men and women (**B**; National Health and Nutrition Examination Survey [NHANES] 1988–1994). From Ford et al., 2002 and Vgontzas et al., 2005 [8, 11].

Figure 3. Model (A) for the association between visceral adiposity and moderate OSA, as mediated by IL-6 and CRP, in adolescents with incident OSA. Scatterplot (B) depicting the association of increased CRP from childhood to adolescence (ΔCRP) with adolescent AHI in boys. Adapted from Gaines et al., 2016 and Gaines et al., 2017a [25, 45].

Figure 4.

Probabilities of hypertension and hyperglycemia in “typical” obese, middle-aged men (A) and women (B) with mild-to-moderate OSA when CRP levels are in the healthy (0.5 mg/L) vs. “at-risk” (3.0 mg/L) range. From Gaines et al., 2017b [108].