CHEST

Metabolic Syndrome and the Lung

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A link between metabolic syndrome (MetS) and lung diseases has been observed in several cross-sectional and longitudinal studies. This syndrome has been identified as an independent risk factor for worsening respiratory symptoms, greater lung function impairment, pulmonary hypertension, and asthma. This review will discuss several potential mechanisms to explain these associations, including dietary factors and the effect of adiposity and fat-induced inflammation on the lungs, and the role of other comorbidities that frequently coexist with MetS, such as OSA and obesity. In contrast to the well-known association between asthma and obesity, the recognition that MetS affects the lung is relatively new. Although some controversy remains as to whether MetS is a unique disease entity, its individual components have independently been associated with changes in pulmonary function or lung disease. There is, however, uncertainty as to the relative contribution that each metabolic factor has in adversely affecting the respiratory system; also, it is unclear how much of the MetS-related lung effects occur independently of obesity. In spite of these epidemiological limitations, the proposed mechanistic pathways strongly suggest that this association is likely to be causal. Given the wide prevalence of MetS in the general population, it is imperative that we continue to further understand how this metabolic disorder impacts the lung and how to prevent its complications.

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Metabolic Syndrome and Obstructive Airway Diseases

The definition of metabolic syndrome (MetS) has evolved over time; MetS is currently defined by a grouping of clinical characteristics including abdominal obesity, hyperglycemia, hypertriglyceridemia, hypertension, and low high-density lipoprotein cholesterol levels. Data from the National Health and Nutrition Examination Survey spanning 1999 to 2010 indicate that although the age-adjusted prevalence decreased from 25.5% in 1999 to 2000 to 22.9% in 2009 to 2010 in the United States, MetS is still strikingly common. More than one-fifth of the population and roughly 60% of obese individuals are affected.[1] Several other countries across the world

ABBREVIATIONS: AHI = apnea-hypopnea index; ASM = airway smooth muscle; CARDIA = Coronary Artery Risk Development in Young Adults; CRP = C-reactive protein; CVD = cardiovascular disease; DM = diabetes mellitus; FFA = free fatty acids; HbA1c = glycated hemoglobin; HFpEF = heart failure with preserved ejection fraction; HR = hazard ratio; IGF = insulin-like growth factor; MetS = metabolic syndrome; NF-κB = nuclear factor κB; PRR = pattern recognition receptor; RV = right ventricular; TG = triglyceride

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show as high or even higher percentages in their populations.[2] MetS has been shown in previous studies to be associated with development of diseases, including cardiovascular disease (CVD), diabetes mellitus (DM), hepatic steatosis, and cancer.[3] Mounting evidence indicates that MetS may also be associated with lung function impairment, but the relationship remains unclear.

Several large studies published in the last 10 years show an association between MetS and lung function impairment in adults and children. One of the largest cross-sectional studies in a French population of 121,965 adult subjects showed that MetS was associated with greater lung function impairment (defined as FEV_1 or FVC < lower limit of normal), adjusting for sex, age, smoking status, alcohol consumption, education, BMI, physical activity, or CVD (FEV_1: OR, 1.28; 95% CI, 1.20-1.37; for OR, FVC: 1.41; 95% CI, 1.31-1.51). In addition, individual components of MetS, such as dyslipidemia, fasting hyperglycemia, abdominal obesity, and hypertension, were independently associated with lung function impairment. Among these, abdominal obesity was most strongly related to the outcome.[4] In a Norwegian prospective cohort of 23,191 adults, MetS increased the risk for incident asthma (adjusted OR, 1.57; 95% CI, 1.31-1.87) after adjustment for age, sex, and family history of asthma, smoking, physical activity, education, and socioeconomic differences. Examination of the individual components of MetS showed that waist circumference (adjusted OR, 1.62; 95% CI, 1.36-1.94) and hyperglycemia or DM (adjusted OR, 1.43; 95% CI, 1.01-2.04) remained independent risk factors for asthma.[5] Similar results have been published in a large cross-sectional study of children with asthma. Among 17,994 children 4 to 12 years old from West Virginia compared with children without asthma, those with asthma were more likely to have elevated triglycerides (TGs) and acanthosis nigricans, a marker of insulin resistance, after controlling for BMI, sex, and smoke exposure.[6]

This relationship between MetS and lung function impairment and asthma risk appears to be robust, as several other studies have yielded similar results (Table 1).[7-10,12] However, the extent to which MetS confounds or modifies the asthma-obesity association remains controversial. In the aforementioned Norwegian cohort, BMI was not included as a confounder in the model evaluating the risk in asthma incidence afforded by MetS, whereas in a secondary analysis of the Coronary Artery Risk Development in Young Adults (CARDIA) cohort study, this association was confounded by obesity. In it, there was a stronger association between MetS (as a whole or related to its individual components) and incident asthma in females (hazard ratio [HR], 1.5; 95% CI, 1.10-2.05) than in males (HR, 1.24; 95% CI, 0.95-1.61). However, after adjustment for BMI as a continuous variable, the HR in women was attenuated (HR, 1.16; 95% CI, 0.79-1.7).[20] In contrast, obesity predicted asthma incidence in women after adjustment for MetS. Given these results, it would be interesting to determine the asthma incidence risk for nonobese women diagnosed with MetS. Unfortunately, the number of CARDIA participants with these characteristics was very small.

MetS has also been evaluated as a risk factor for other chronic lung diseases, such as COPD and restrictive lung disease. Mirrakhimov[21] summarized the current literature on COPD, MetS, and DM, and affirmed that MetS may increase the risk of a COPD exacerbation with associated hyperglycemia, hypertriglyceridemia, and C-reactive protein (CRP) elevation. Hyperglycemia may also be associated with worse outcomes after an exacerbation. The author suggested that these findings may be attributed to low levels of systemic inflammation.[21] In contrast, a few studies have shown an association between lung restriction and MetS or components of MetS (Table 1).[11,13-17] In summary, abundant epidemiological and clinical evidence exists to support the important link between MetS and lung function impairment, but the exact nature of this relationship remains unknown, and therefore deserves further investigation.

Mechanisms of MetS-Induced Lung Impairment

Insulin and Airway Smooth Muscle. Evidence linking MetS and lung impairment or lung disease, including asthma and COPD, continues to grow, and several mechanisms have been proposed to explain why these associations exist. These include the complex effects of insulin and insulin receptors on the lung and the airways, whose interplay begins early in life given their role for normal lung development.[22] Fetal lung richly expresses insulin receptors during early development, while later they are suppressed; therefore maternal glycemic levels during the early gestational period may affect lung maturation.[23] It is possible that maternal hyperglycemia leads to fetal hyperglycemia and hyperinsulinemia. Excess fetal insulin may affect insulin receptor expression and therefore disturb normal fetal lung maturation. However, the exact mechanism by

TABLE 1] MetS and Lung-Related Outcomes

Outcome	Authors	Study Type, Year	Population	Exposure	Outcome/Results
Lung function	Fimognari et al[11]	Cross-sectional study, 2007	159 nondiabetic elderly persons from two social centers in Rome, Italy, Oct 2002-June 2003	MetS and its components	Restrictive pattern is associated with MetS and insulin resistance (OR, 3.23; 95% CI, 1.23-8.48; $P = .01$).
	Hsaio et al[12]	Prospective cohort study, 2009	450 middle-aged adults from Taipei MJ Health Screening Center, >2-y follow-up	MetS	Reduction in FEV_1 is a predictor of MetS ($P = .036$; adjusted for age, sex, BMI, cigarette smoking, alcohol, physical activity). WBC counts and CRP correlated negatively with FEV_1.
	Lee et al[8]	Population-based cohort study, 2009	9,942 Korean adults, ages 40-69 y	MetS	Asthmalike symptoms (wheeze, resting dyspnea, and postexercise dyspnea) higher in MetS group ($P < .05$). Those with asthmalike symptoms had decreased lung function. Abdominal obesity (OR, 1.63; 95% CI, 1.16-1.54) and hypertension (OR, 1.34; 95% CI, 1.43-1.86) are risk factors for asthmalike symptoms.
	Leone et al[4]	Cross-sectional population-based study, 2009	121,965 French adults, ages 16-96 y	MetS	Lung function impairment, FEV_1 (OR, 1.28; 95% CI, 1.20-1.37) and FVC (OR, 1.41; 95% CI, 1.31-1.51) associated with MetS (independent of age, sex, smoking, alcohol use, education, BMI, physical activity, and CVD history). Lipids, glucose, blood pressure, and abdominal obesity inversely related to lung function. Abdominal obesity the strongest predictor of lung function impairment.
	Lin et al[13]	Cross-sectional study, 2006	46,514 Taiwanese adults from 1998-2000, ages >20 y	MetS	Restrictive lung impairment independently associated with MetS (OR, 1.22; 95% CI, 1.086-1.372) for NCEP criteria and (OR, 1.15; 95% CI, 1.047-1.264) for AHA/NHLBI criteria.
	Bae et al[7]	Cross-sectional population study, 2012	1,370 Korean adults, ages 20-70 y, Jan-Aug 2008	MetS	Men with MetS experienced more lung function impairment. MetS components in men associated with pulmonary function impairment; the more MetS components the patients had, the worse the pulmonary function. This trend was not present in women.
	Rogliani et al[14]	Cross-sectional, population study, 2009	237 patients with MetS	Pulmonary function impairment	Nonsmokers with MetS had lower spirometric (FEV_1, FVC) values with trend toward ventilatory restriction. FEV_1/FVC unchanged. HDL strongest predictor of FEV_1 and FVC with an inverse association in smokers and nonsmokers.
	Nakajima et al[15]	Cross-sectional study, 2008	2,396 healthy Japanese adults, ages 30-80 y	MetS	CRP and FVC % predicted (but not FEV_1/FVC ratio) correlated with metabolic abnormalities after adjustment for confounders. Restrictive pattern (defined as low FVC and FEV_1/FVC ratio ≥85%) associated with MetS.

(Continued)

TABLE 1] *(Continued)*

Outcome	Authors	Study Type, Year	Population	Exposure	Outcome/Results
	Park et al[10]	Retrospective review, 2008	4,905 Korean male patients, age >40 y	MetS; CACS	MetS and CACS increased as the FVC and FEV_1 (% predicted) decreased. Obesity, CRP, HOMA-IR, and presence of coronary artery calcium were independent risk predictors for impaired lung function.
	Paek et al[16]	Cross-sectional study, 2009	4,001 Korean adults, >18 y	MetS and its components	Waist girth, systolic BP, and TGs were associated with FVC. Only TG was associated with FEV_1.
Asthma	Brumpton et al[5]	Prospective cohort study, 2013	23,191 Nord-Trondelag Health Study participants from 1995-2008, ages 19-55 y	MetS	MetS is a risk factor for incident asthma (adj OR, 1.57; 95% CI, 1.31-1.87). Two MetS components remained associated when adjusted for other components: high waist circumference (adj OR, 1.62; 95% CI, 1.36-1.94) and elevated glucose or DM (adj OR, 1.43; 95% CI, 1.01-2.04).
COPD	Breyer et al[17]	Prospective cohort study, 2014	228 COPD and 156 healthy adult subjects from 2007-2012, the Netherlands	MetS	MetS is more prevalent in overweight and obese subjects with COPD compared with BMI-matched healthy control subjects. Functional status and lung function was unaffected by MetS, but prevalence of comorbidities was higher in those with COPD and MetS.
OSA	Parish et al[18]	Retrospective review, 2007	250 consecutive patients referred for PSG for OSA evaluation with 228 included in review	MetS	Of 146 patients with OSA, 60% had MetS, whereas 40% without OSA had MetS ($P = .004$). Higher prevalence of hypertension in OSA group ($P = .001$). Dyslipidemia and DM not different between groups. When data were analyzed by age, OSA primarily associated with MetS and hypertension in males > 50 y.
Pulmonary hypertension	Robbins et al[19]	Prospective study, 2009	122 consecutive at Vanderbilt Pulmonary Vascular Center, Sept 2004-Dec 2005	MetS	PVH patients had higher frequency of hypertension, obesity, DM, and hyperlipidemia. Two or more features of MetS in 94.1% of those with PVH compared with 34.3% of those with PAH ($P < .001$)

adj OR = adjusted OR; AHA/NHLBI = American Heart Association/National Heart, Lung, and Blood Institute; CACS = coronary artery calcification score; CRP = C-reactive protein; CVD = cardiovascular disease; DM = diabetes mellitus; HDL = high-density lipoprotein; HOMA-IR = homoeostasis model assessment–estimated insulin resistance; MetS = metabolic syndrome; NCEP = National Cholesterol Education Program; PAH = pulmonary artery hypertension; PSG = polysomnography; PVH = pulmonary venous hypertension; TG = triglyceride.

which these receptors can influence the developing lung remains unclear. We speculate that changes in lung development may be implicated in the strong relationship that exists between maternal obesity and wheezing and asthma in the offspring. For example, Forno et al[24] have recently shown the magnitude of this association in a meta-analysis of 108,321 mother-child pairs, which showed that for every unit increase in maternal BMI, there is a corresponding 2% to 3% increase in the risk of asthma in the offspring. In addition, the effect of insulin on airway smooth muscle (ASM) receptors continues as a highly active area of study. Prior data indicates that insulin may induce hypercontractility in ASM through laminin expression in a bovine tracheal smooth muscle model via the phosphoinositide 3-kinase and Rho-kinase-dependent pathways.[25] The interaction between insulin and airway muscarinic receptors may also be important, as a recent investigation using diet-induced obese rats in vivo and human tracheal smooth muscle in vitro showed that hyperinsulinemia (either from obesity or addition of exogenous insulin, respectively) resulted in vagally mediated bronchoconstriction and loss of inhibitory muscarinic receptor 2 functionality on parasympathetic nerves.[26,27] Therefore, insulin dysregulation may negatively affect the airway through multiple routes to cause lung function impairment. Data from a 3-year randomized controlled trial on the safety and direct effects of inhaled human insulin (Exubera) showed that those receiving the drug were more likely to exhibit respiratory symptoms, including cough and mild dyspnea, along with reductions in FEV_1 and diffusing capacity of the lung for carbon monoxide.[28] This trial result lends support to the notion that insulin may exert a direct effect on human airways by influencing ASM or airway epithelial cells. In addition, it may do so circuitously by inhibiting muscarinic receptors or by induction of a secondary effector to induce hypercontractility. Data from the National Health and Nutrition Examination Survey shows further evidence that insulin sensitivity or resistance is related to lung function.[29] Regardless of asthma diagnosis, insulin sensitivity (defined as the fasting glucose to insulin ratio and the insulin sensitivity check index value, or 1/log[fasting insulin] + log[fasting glucose]) was positively associated with FEV_1 and FVC. In contrast, insulin resistance (defined by the homoeostasis model assessment-estimated insulin resistance) was inversely associated with these lung function parameters. MetS was associated with a greater decline in FEV_1/FVC among subjects with asthma (12.6%) vs those without asthma (2.3%). Even in healthy subjects without diagnosed DM, abnormalities in glucose metabolism can be associated with lung function decrements. In the Korean National Health and Nutrition Examination Survey, those with an elevated glycated hemoglobin (HbA1c $>5.7 \leq 6.4$) had reduced FVC, and FEV_1 and were twice as likely to have restriction when compared with those with a HbA1c of 5.3 or greater.[30]

In summary, exposure to elevated insulin levels either during fetal lung maturation or later in life can induce morphological or functional changes in ASM or potentiate airway responsiveness to parasympathetic stimulation, which could reduce lung function or enhance bronchial hyperreactivity. In adults, chronically elevated insulin levels are associated with reduced lung function in patients with or without a diagnosis of DM.

Abdominal Obesity, Adipokines, and Insulin-Like Growth Factor I

Among the MetS components, abdominal obesity has the strongest association with lung function impairment.[4] The basis for this may be twofold, as data exist to support the concept of mechanical as well as metabolic effects from excess truncal adiposity.[4] Compared with obese control subjects, obese patients with asthma have a higher expression and levels of inflammatory markers and adipokines in visceral fat. Of these, leptin and adiponectin[31] are just two of the multiple hormones produced by adipose tissue[32] that may exert metabolic effects on the lung. Leptin levels are increased with obesity and are secreted in direct proportion to adipose tissue mass. Although the functional role of plasma leptin on lung maturation begins early in life, its impact in the lung is not entirely clear. Umbilical cord levels of this adipokine are not associated with increased risk of wheezing during the first 2 years of life.[33,34] Leptin and leptin receptors are present in the airways on bronchial epithelial cells,[35] and elevated leptin levels may modulate the immune reaction in the airways by inciting a robust proinflammatory response[36] or bias the cellular response toward a type 1 helper phenotype.[37] It is also possible that leptin increases greater bronchial hyperreactivity through its airway epithelial cell receptors. Indeed, among obese patients with asthma, airway reactivity has been shown to be strongly correlated with visceral fat leptin expression (rho $= -0.8$; $P < .001$).[31] Adiponectin has also been shown to be expressed by airway epithelial cells.[38] In contrast to leptin, adiponectin levels are decreased with obesity and insulin resistance.[39] Multiple

studies in mice and humans have shown conflicting results regarding the effect of adiponectin levels on lung function,[40-44] including one large cross-sectional study in a subset of the CARDIA participants, which found that after controlling for BMI, adiponectin levels were positively associated with lung function.[44] Hence, further research is needed to understand the interplay between the immune system and adipokines and the ultimate effect on lung function.

Another novel therapeutic approach for asthma that has been described is based on mounting evidence for insulin-like growth factor (IGF) I and IGF binding protein-3 as a cause of subepithelial fibrosis, airway hyperresponsiveness, airway inflammation, and ASM hyperplasia; specifically, IGF-I enhances these pathologic changes, whereas IGF binding protein-3 counteracts them.[26] It is also well understood that obesity induces low levels of growth hormone, by reducing the number of burst secretions, thereby potentially causing upregulation of IGF-I as it functions in a negative feedback loop with growth hormone.[26,39]

In summary, adipokine dysregulation is a potential mechanism for obesity-mediated airway changes in asthma. Given that obese patients with asthma have evidence for increased visceral adipose inflammation, changes in adipokines could also play a role in MetS-mediated effects in lung function.

Fatty Acid-Induced Inflammation

One of the defining features of MetS is hyperlipidemia, which provides another potential mechanism linking MetS and lung function impairment, due to fatty acid-induced inflammation. Circulating levels of fatty acids are regulated by insulin-stimulated uptake and release of TGs and free fatty acids (FFAs) by adipocytes.[45] However, in MetS, adipose tissue is not able to efficiently regulate fat storage, and excess TGs and FFAs remain in circulation.[45] A lipotoxic state can develop[46] as these FFAs can activate innate immune responses via a plethora of inflammatory mechanisms, such as pattern recognition receptor (PRR) activation, intracellular signaling pathways, and endoplasmic reticulum stress.

Fatty acids initiate innate immune responses via activation of PRRs, which stimulate a variety of intracellular signaling pathways, leading to increased activity of transcription factors such as nuclear factor κB (NF-κB) and activator protein 1, which control inflammatory gene expression.[47] The best described PRR in relation to dietary fat is toll-like receptor 4, which is activated by dietary saturated fatty acids, such as lauric and palmitic acids,[48] leading to NF-κB activation and release of proinflammatory mediators such as tumor necrosis factor-alpha (TNF-α) and interleukin (IL) 6.[48] Saturated fatty acids also activate other innate immune receptors, such as NLR family, pyrin domain containing 3 (NLRP3), which leads to the formation of molecular platforms called inflammasomes, which allow maturation of the inflammatory mediators needed to respond to cellular stress, in particular IL-1β.[49] Excess fatty acids can also induce endoplasmic reticulum stress, which triggers the unfolded protein response, activating inflammatory pathways[50] and stimulating production of reactive oxygen species, which further amplify the activity of the transcription factors activator protein 1 and NF-κB, thereby increasing production of inflammatory mediators.[51]

Various studies have reported a relationship between hyperlipidemia and worsened respiratory outcomes. Two recent large cross-sectional studies have reported that hyperlipidemia was associated with lung function impairment in adults[4] and asthma risk in children.[6] Other studies have shown that elevated TG levels were associated with airway hyperresponsiveness[52] and adult-onset wheezing.[53] In addition, in male patients with asthma, sputum neutrophil percentage was found to be positively associated with plasma saturated fatty acid levels,[54] consistent with the hypothesis that excess FFAs stimulate airway innate immune responses. Only one intervention study has directly examined the effect of fatty acids on innate immune responses in asthmatic airways. Consumption of a single high-fat meal led to increased circulating fatty acid levels at 4 hours, corresponding with an increase in airway neutrophil percentage and toll-like receptor 4 mRNA expression in sputum cells.[55] These studies highlight the potential for hyperlipidemia to induce inflammation through a variety of mechanisms, which may contribute to the link between MetS and airways disease.

In summary, a variety of mechanisms may be at play between components of MetS and lung function impairment and likely involves the interplay between adiposity-induced alterations at multiple levels and airways in the lung (Fig 1).

MetS and OSA

There is a robust association between OSA and MetS, either as a whole or with its individual components.[18,56] The prevalence of MetS in patients with OSA is 60%, which is considerably higher than in the general population.[57] This association is partly explained by the

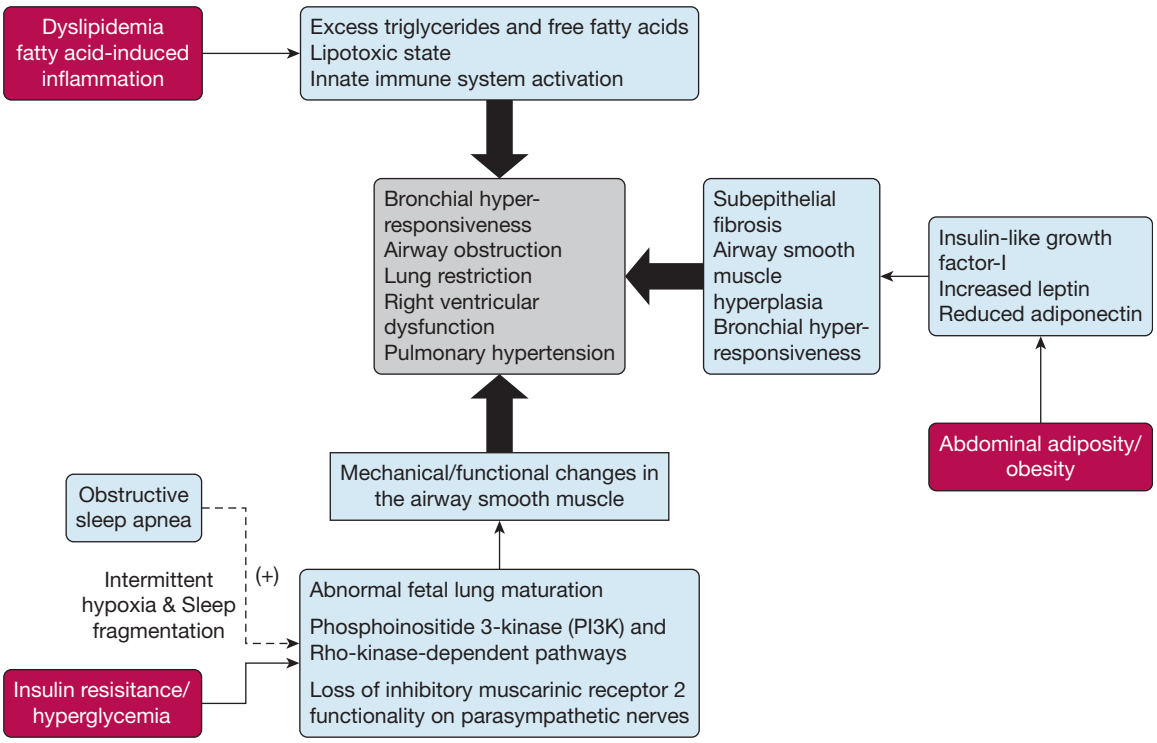

Figure 1 – *Potential mechanisms of the effect of metabolic syndrome on lung function are shown. Based on current data, multiple pathways related to metabolic syndrome may affect lung function, including changes in leptin and adiponectin, dietary effects of excess obesity, alterations in circulating growth hormone and subsequently insulin-like growth factor I, the effect of hyperglycemia and hyperinsulinemia, and the mechanical effect of abdominal obesity.*

fact that patients with OSA are more likely to have greater visceral adiposity, in addition to abnormal glucose metabolism. In the Wisconsin sleep study the OR for having a diagnosis of DM increased in relation to the degree of OSA severity. Compared with those with a mild apnea-hypopnea index (AHI), those with an AHI of at least 15 events/h or greater than 30 events/h had an OR for DM of 2.3 (95% CI, 1.3-4) and 3.5 (95% CI, 1.7-7), respectively.[58] The mechanisms by which OSA increases the risk for DM may depend on intermittent hypoxia and fragmented sleep.[59,60] Intermittent hypoxia leads to a broad array of physiologic changes including sympathetic and hypothalamic-pituitary axis activation that result in abnormal metabolism characterized by hyperglycemia and insulin resistance.[61] On the other hand, sleep fragmentation, defined as the number of sleep arousals, has been associated with higher fasting insulin levels and greater adiposity.[62,63]

CPAP reduces systemic biomarkers of oxidative stress but has shown only modest and inconsistent improvement in improving glucose control in patients with MetS.[64-66] In contrast, this therapy has been effective in reducing blood pressure in patients with resistant hypertension and OSA.[67]

In summary, there is ample evidence suggesting that OSA can induce or exacerbate most, if not all, of the MetS components. Some of these effects can be ameliorated by the use of CPAP; however, the modest and inconsistent benefits suggest that other factors besides intermittent hypoxia or the degree of AHI are at play.

MetS and Pulmonary Hypertension

MetS, advancing age, and female sex are strongly associated with the development of pulmonary venous hypertension (group II pulmonary hypertension classification), defined by an increase in mean pulmonary artery pressures (≥25 mm Hg) but with high left ventricular filling pressures (pulmonary artery occlusion pressures >15 mm Hg).[19]

Pulmonary venous hypertension most commonly occurs in the setting of left ventricular diastolic dysfunction with preserved left heart systolic function, referred to as heart failure with preserved ejection fraction (HFpEF).[19,68,69] In patients with HFpEF, the precapillary pulmonary arterioles can undergo vasoconstriction and remodeling as a consequence of chronic elevations in pulmonary venous pressure, leading to an increase in pulmonary vascular resistance, even in the setting of

increased left ventricular diastolic pressure. This disease is now referred to as PH-HFpEF and is one of the most common forms of pulmonary hypertension seen in pulmonary hypertension and heart failure clinics.[70]

It is now appreciated that features of MetS, including systemic hypertension, obesity, DM, and hyperlipidemia, represent risk factors for the development of all forms of pulmonary vascular disease and right ventricular (RV) dysfunction.[71] This association is also observed in murine models of MetS, such as the apo E knockout mouse that develops pulmonary hypertension when fed a high-fat diet.[72]

Also, patients with pulmonary arterial hypertension exhibit an increased prevalence of glucose intolerance (increased HbA1c levels) and insulin resistance, which is associated with changes in RV structure and function. Potential mechanisms by which MetS causes RV dysfunction include mitochondrial dysfunction with a shift in cardiomyocyte energy utilization from fatty acid oxidation to glucose. This reduces the mitochondrial use of lipids, leading to cytoplasmic deposition of lipid intermediaries, a condition known as "lipotoxic cardiomyopathy."[71,73]

There are no currently approved therapies for PH-HFpEF, and most medications approved for group I pulmonary arterial hypertension have been shown to be ineffective in patients with left heart disease. New therapies that target both MetS and the pulmonary vasculature are being tested in preclinical models and in patients, including peroxisome proliferator-activated receptor-G activators, metformin, and nitrates and nitrites.[72,74-77]

Conclusions

Each MetS component contributes to lung disease. It is unclear whether treating MetS will reduce its effects on the respiratory system. Despite this uncertainty, optimally treating each component of MetS is a sensible way to minimize the risk of respiratory comorbidity.

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