Obesity, asthma, and oxidative stress

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Holguín F, Fitzpatrick A. Obesity, asthma, and oxidative stress. J Appl Physiol 108: 754–759, 2010. First published November 19, 2009; doi:10.1152/japplphysiol.00702.2009.—Obesity is associated with increased systemic and airway oxidative stress, which may result from a combination of adipokine imbalance, comorbidities, and reduced antioxidant defenses. While obesity-mediated increased oxidative stress plays an important role in the pathogenesis of vascular disease and nonalcoholic hepatic steatosis, little is known of how it may affect the lung. Contrary to what has previously been thought, the combination of obesity and asthma, both chronic inflammatory diseases, does not necessarily result in a synergistic effect, leading to even greater oxidative stress. However, most available studies have compared the levels of oxidative stress biomarkers on stable asthma patients, and it is possible that the interaction of oxidative stress between obesity and asthma is not readily detectable under basal conditions. We propose that obesity-mediated oxidative stress, which may affect the lung function of asthmatic subjects by increasing airway inflammation and reducing the effectiveness of inhaled corticosteroids, may become evident during exposure to an aggravating factor or during periods of asthma exacerbation. Understanding whether obesity-mediated oxidative stress has a mechanistic role in the association between obesity and asthma will help in the formation of public health policies and increase our capacity to develop therapeutic interventions that improve the life of obese asthmatic subjects.

8-isoprostanes; adipokines

OXIDATIVE STRESS, GENERAL CONCEPTS

Reactive Oxygen Species (ROS) are highly reactive molecules with unpaired electrons that can quickly react with other chemical compounds, potentially altering their structure and function (49, 52). However, production of ROS occurs as part of the normal metabolism, and indeed some degree of ROS formation is required to maintain normal physiology. A very fine balance is maintained between ROS production and protection from oxidative injury by antioxidants, which include nonenzymatic (dietary antioxidants, such as vitamins and thiols) and enzymatic (including superoxide dismutases, catalase, and glutathione peroxidase) mechanisms.

During conditions of oxidative stress, either an increased ROS production and/or reduced antioxidant defenses create an imbalance, allowing for oxidative injury to occur, which can worsen inflammation and injury by enhancing proinflammatory cytokine release and altering enzymatic function (52). However, in some instances, oxidative stress may stimulate the production of anti-inflammatory cytokines, serving as a negative feedback loop to control the inflammatory response.

Which of these reactions predominates depends on multiple factors, including the degree and timing (acute vs. chronic) of oxidative stress.

To determine the level of oxidative stress, ROS can be measured directly using electron spin resonance; however, this technique is cumbersome and costly. As an alternative, by-products of oxidation are measured as a form of “fingerprints,” indicating that oxidative stress occurred. These biomarkers are more stable and easier to quantify than measuring ROS directly. Some of the most common oxidative stress biomarkers include products of lipid peroxidation, such as malondialdehyde (MDA); thiobarbituric reactive acid reactions, which estimates MDA formation; and nonenzymatic by-products of arachidonic acid oxidation, such as F2-isoprostanes or 8-isoprostanes (8-epi-PGF2α) and 8-hydroxy 2′-deoxyguanosine, which estimates oxidized nucleic acid. There are significant limitations and methodological implications for these oxidative stress biomarkers, which are broadly discussed in other studies (36).

Both obesity and asthma are chronic inflammatory diseases characterized by higher than normal oxidative stress. This review will discuss oxidative stress in both conditions and whether oxidative stress is a potential pathophysiological pathway to explain why, compared with leaner subjects, the obese have a greater risk for asthma and worse asthma severity.
OXIDATIVE STRESS IN OBESITY

In cross-sectional studies, obese subjects have higher levels of oxidative stress biomarkers compared with their leaner counterparts (23). Also, weight gain significantly increases the concentration of these biomarkers (51). There are multiple sources for oxidative stress in relation to obesity. Some of them are inherently related to increased adiposity and fat distribution, whereas others are the result of comorbidities or behavioral changes associated with being obese. Increased adipose tissue and, in particular, visceral adiposity are significantly correlated with systemic levels of oxidative stress biomarkers (12, 16, 48).

Adipose tissue-mediated systemic oxidative stress and systemic inflammation may be secondary to increased leptin-to-adiponectin ratio and increased levels of other adipokines, such as tumor necrosis factor and plasminogen activator inhibitor-1 (53). Obesity is associated with several comorbidities, including hypertension, insulin resistance, diabetes, and hyperlipidemia; each of these comorbidities alone can increase the oxidative stress burden. However, more often than not, these comorbidities occur simultaneously, as is the case of the metabolic syndrome that is characterized by insulin resistance, hypertension, and hyperlipidemia and is commonly present in adults in the US (44). Compared with obese subjects without metabolic syndrome, those with metabolic syndrome have a greater degree of oxidative stress (23, 40).

Maintaining a healthy lifestyle by eating a balanced diet rich in antioxidants and being physically active is associated with reduced oxidative stress. Unfortunately, this protection is less effective among obese subjects, who are more sedentary, having reduced intake of dietary antioxidants and lower serum vitamin levels (52).

Over time, chronic oxidative stress in obesity has a cumulative effect that favors the development of end-organ damage. This phenomenon has been mostly studied in the cardiovascular system and the liver in which chronic oxidative stress plays a critical role for the development of atherosclerosis and nonalcoholic hepatic steatosis (30, 40, 43). Although it is unknown whether obesity-mediated oxidative stress directly affects the lung, evidence that weight gain, diabetes, and poor glycemic control (both commonly seen in obesity) are associated with reduced lung function and steeper airway function decline raises the possibility that this could be the case (11, 13, 27).

Recently, obesity has been shown to be a risk factor for physician-diagnosed asthma in longitudinal studies (9) and has been associated with reduced asthma control and worse asthma severity (50), increased bronchial hyperresponsiveness, and reduced inhaled corticosteroids effectiveness (28, 37). This review will discuss whether oxidative stress could potentially play a role in mediating these associations.

OXIDATIVE STRESS IN ASTHMA

Compared with nonasthmatic subjects, subjects with asthma have increased systemic oxidative stress (33). In a study by Erkan et al. (14), children with asthma had higher plasma levels of MDA and 8-isoprostanes compared with healthy controls, and the MDA levels were higher in children with more severe asthma. This is partly explained by the fact that acute asthma exacerbations can worsen the degree of oxidative burden. Among patients hospitalized for an acute asthma exacerbation, there is a sixfold increase in the levels of urinary metabolites of F₂-isoprostanes, and total plasma antioxidant capacity is also reduced during these episodes (34, 54). Furthermore, asthmatic subjects with more obstructed airways also have a higher degree of oxidative stress (35).

Nearly 10 years ago, Montuschi et al. (32) showed that airway oxidative stress could be determined by sampling 8-isoprostanes in exhaled breath condensate (EBC). In their study, the EBC concentration of 8-isoprostanes in asthmatic subjects correlated with exhaled nitric oxide, which increased in relation to worsening severity, and the average concentration was higher in asthmatic subjects than in healthy controls (32). Subsequently, other studies have confirmed these results, and some have also shown that steroids are less effective in reducing EBC 8-isoprostanes compared with other EBC biomarkers of inflammation (5, 42, 45, 56). In severe asthmatic subjects, the increased airway concentrations of 8-isoprostanes, hydrogen peroxide, and MDA in bronchoalveolar lavage (BAL) fluid correlate with decreased levels of reduced glutathione (GSH), increased oxidized glutathione (GSSG), and greater oxidation, as measured by the GSH reduct potential (15). Furthermore, an increased intracellular GSH-to-GSSG ratio in murine antigen presenting cells has been shown to tilt the T helper (Th) 2/Th1 toward Th1 through IL-12 production, resulting in less hyperresponsiveness and airway inflammation (24). These results suggest that the GSH airway redox balance may play an important role in the inflammatory response associated with asthma and other allergic-related disorders.

OXIDATIVE STRESS AS A COMMON PATHWAY BETWEEN OBESITY AND ASTHMA

Based on the fact that obesity and asthma are both chronic inflammatory diseases characterized by increased oxidative stress, it would stand to reason that their combination could result in even greater airway or systemic oxidative stress. If such were the case, it would have important implications for the pathophysiology of asthma, as oxidative stress could propagate airway inflammation through redox-sensitive sites in nuclear transcription pathways (39), by promoting epigenetic changes that impair the activity of histone deacetylases (7) and by favoring a Th2-mediated cytokine response (24).

The question of whether an interaction between obesity and asthma on systemic oxidative stress exists was recently evaluated by Sood et al. (47). In this study, researchers performed a cross-sectional study to evaluate the association between plasma levels of 8-isoprostanes with body mass index (BMI) and the percentage of fat and lean mass index using dual-energy X-ray absorptiometry among 2,865 eligible participants (of which 8.1% had an asthma diagnosis) from the Coronary Artery Risk Development in Young Adults (CARDIA) study. In the CARDIA study, BMI was positively associated with 8-isoprostanes, but only in women. Asthma was significantly associated with increased 8-isoprostanes across all subjects, yet this association became nonsignificant after adjusting for BMI. Among women, there was a significant association between increasing BMI with asthma; however, there was no interaction with 8-isoprostanes. These results suggest that obesity is associated with asthma, yet this association is not explained by increased systemic 8-isoprostanes. It should be noted, however, that, without any severity or control information (both of
which may influence 8-isoprostane levels), some limitations of the study must be considered. For example, the study cannot address whether obese asthmatic subjects with more severe disease or difficulty controlling asthma have higher levels of 8-isoprostanes compared with leaner asthmatic subjects of similar severity.

Airway oxidative stress determined by using exhaled 8-isoprostanes has been shown to correlate proportionately with asthma severity and airway inflammation and to be inversely related to lung function. Furthermore, because exhaled 8-isoprostanes are not markedly influenced by treatment with inhaled corticosteroids, it suggests that oxidative stress may play a role in mediating reduced corticosteroid effectiveness. Whether or not exhaled 8-isoprostane levels in asthmatic subjects are correlated with BMI was recently evaluated in the study by Komakula et al. (25), which showed a linear association between BMI and exhaled 8-isoprostanes in 67 moderate to severe adult asthmatic subjects, but not in 47 healthy controls. However, no test for interaction was provided, and the average levels of exhaled 8-isoprostanes were not different between asthmatic subjects and controls.

To further understand whether obesity increases airway oxidative stress at the expense of systemic oxidative stress, we simultaneously measured the concentration of exhaled and serum 8-isoprostanes in moderate to severe adult asthmatic subjects free from an asthma exacerbation, as previously described (25). The study population included a total of 67 nonsmoking asthmatic subjects of whom 79% were women, age range from 18 to 69 yr, and with an average BMI of 33 (95% confidence interval: 30–33); healthy controls were 77% women, age range from 20 to 63 yr, with an average BMI of 30 (95% confidence interval: 28–32). As shown in Fig. 1, obese asthmatic subjects and controls had larger concentrations of exhaled 8-isoprostanes compared with lean asthmatic subjects, and no difference was observed between asthmatic subjects and controls in each weight category. In contrast, as shown in Fig. 2, plasma 8-isoprostanes were higher in asthmatic subjects than in controls and were not different across BMI categories. The exhaled breath and plasma concentrations of 8-isoprostanes were not correlated in asthmatic subjects ($r = 0.27, P = 0.5$) or in controls ($r = -0.26, P = 0.4$). Overall, these results show that, while obesity does appear to increase airway oxidative stress and asthma increase systemic oxidative stress, there is no interaction between the two of them; that is, there is no synergism regarding 8-isoprostanes levels. Furthermore, based on the lack of correlation between the EBC and plasma, it can be speculated that airway and systemic oxidative stress determined by 8-isoprostanes are a separate phenomenon.

**POTENTIAL MECHANISMS BY WHICH OBESITY INCREASES AIRWAY OXIDATIVE STRESS**

Obesity may increase airway oxidative stress via several potential mechanisms (See Fig. 3). One possibility relates to obesity-mediated adipokine imbalance, which is characterized by having greater leptin and lower adiponectin levels. This adipokine imbalance has been associated with increased systemic oxidative stress, and it also occurs in the airways, as shown in a study by Holguin et al. (18), in which obese leptin-receptor-deficient mice ($db^{-/-}$) had significantly larger concentration of leptin and reduced adiponectin in the BAL fluid, compared with wild-type lean mice. In humans, BAL leptin increases linearly with BMI, and the plasma and BAL levels are significantly correlated, which suggests that plasma

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**Fig. 1.** Box plots of exhaled breath 8-isoprostanes in asthmatic subjects and controls by body mass index categories. Shaded dots are outlier values.

**Fig. 2.** Box plots of plasma 8-isoprostanes in asthmatic subjects and controls by body mass index categories. Plasma samples were collected from a subset of the patients with exhaled breath condensate 8-isoprostane measurements shown in Fig. 1. Shaded dots are outlier values.

**Fig. 3.** Proposed scheme for obesity and airway oxidative stress.
Obesity-mediated increase in EBC 8-isoprostanes could partly explain why inhaled steroids are less effective among obese asthmatic subjects. Oxidative stress, through epigenetic changes, may propagate and amplify airway inflammation and increased systemic levels of MDA (22). Moreover, treating the repetitive cycle of airway obstruction with continuous positive airway pressure (CPAP) treatment has been shown to reduce 8-isoprostane plasma levels in patients with OSA (4). 

Another mechanism by which obesity may increase airway oxidative stress is through obstructive sleep apnea (OSA), which is a prevalent comorbidity among obese subjects (1). The diagnosis of OSA has been associated with increased systemic and airway oxidative stress. The intermittent hypoxic episodes occurring as a result of repetitive airway obstruction have been correlated with upregulation of NAPDH oxidase and increased systemic levels of MDA (22). Moreover, treating the repetitive cycle of airway obstruction with continuous positive airway pressure (CPAP) treatment has been shown to reduce 8-isoprostane plasma levels in patients with OSA (4). 

OSA patients have been shown to have increased levels of exhaled biomarkers of oxidative stress. Carpagnano et al. (10) reported that OSA patients have higher levels of exhaled 8-isoprostanes, which correlated with the degree of respiratory distress index, which quantifies the number of apnea/hypopnea episodes per hour ($r = 0.8$, $P < 0.01$), and improved after CPAP treatment. Petrosyan et al. (38) also showed that, in addition to having higher exhaled levels of 8-isoprostanes, OSA patients have increased leukotriene LTB4 and hydrogen peroxide, both of which decrease with CPAP treatment. A higher prevalence of OSA has been documented among patients with difficult-to-control asthma, and reduction of respiratory distress index with CPAP has been associated with improved asthma-related quality of life (2, 3, 55). These studies suggest that OSA may be an important comorbidity in obesity and asthma; however, it is unknown whether OSA imposes an extra burden in the airway oxidative stress of asthmatic subjects.

**WHAT CLINICAL CONSEQUENCES COULD OBESITY-MEDIATED INCREASED IN OXIDATIVE STRESS HAVE ON ASTHOMATIC SUBJECTS?**

Obesity-mediated increase in EBC 8-isoprostanes could partly explain why inhaled steroids are less effective among obese asthmatic subjects. Oxidative stress, through epigenetic changes, may propagate and amplify airway inflammation and has been postulated as a potential mechanism for reduced steroid effectiveness among COPD and severe asthma patients (6). Reduced inhaled steroid responsiveness among obese asthmatic subjects, based on asthma control, has been shown in some studies, yet it is unknown whether airway oxidative stress plays a role. In a post hoc analysis of 3,073 moderate asthmatic subjects, Peters-Golden et al. (37) showed that increasing BMI was associated with a reduced percentage of symptom-free days among asthmatic subjects randomized to inhaled corticosteroids and the placebo, whereas increasing BMI was less influential in subjects randomized to leukotriene blockers. Prospectively, Saint-Pierre et al. (41) have followed 400 asthmatic subjects longitudinally for a median of 186 days to estimate the transition from acceptable to unacceptable asthma control based on Canadian asthma guidelines. Using a Markov probability model, the authors showed that overweight subjects were less likely to transition from unacceptable to acceptable control (relative risk 0.43, $P < 0.01$), despite optimal pharmacological management.

**OBESITY, ASThma, AND OXIDATIVE STRESS, A SHIFTING PARADIGM**

Given the fact that both asthma and obesity are chronic inflammatory diseases that are characterized by increased oxidative stress, it was logically expected that the combination of both diseases would result in synergy; however, so far this does not appear to be the case. During baseline conditions, obese asthmatic subjects do not appear to have more airway inflammation or airway oxidative stress than nonasthmatic obese subjects. However, it is possible that, if oxidative stress does play a pathophysiological role between these two diseases, it may not be readily evident by contrasting levels of oxidative stress biomarkers during baseline conditions.

For example, airway oxidative stress may not be different between obese asthmatic subjects and obese nonasthmatic subjects during baseline conditions, yet, upon exposure to an aggravating factor, obese asthmatic subjects would respond with a much greater degree of airway (and possibly systemic) oxidative stress (See Fig. 3). An analogy to this rationale could be the airway oxidative stress induced by chronic alcohol intake. The alcoholic lung is characterized, among other things, by severe impairment of the glutathione antioxidant system with reduction of GSH and increased GSSG (21). These changes, although severe, do not lead to any major lung function impairment; however, upon exposure to a major stressor, such as sepsis, because of the underlying impairment in glutathione homeostasis, the alcoholic lung is more likely to develop more severe diffuse alveolar damage and acute respiratory distress syndrome.

It is also possible that, during acute exacerbations, the acute inflammatory response in asthmatic subjects leads to a greater degree of oxidative stress. For example, diet-induced obesity in animals leads to a macrophage polarization shift from an M-2 state into a more proinflammatory or activated state M-1 phase, which contributes to insulin resistance (29). It could be reasonable to speculate that a similar phenomenon may occur in other circulating inflammatory cells that could eventually be recruited to the lung during acute processes.

To better address these possibilities, well-characterized obese and nonobese asthmatic subjects and controls should be exposed to allergens or other triggers of airway inflammation (including ambient pollutants) in a controlled environment to determine if BMI and or the preexposure level of airway oxidative stress can modify the response to the exposure. As an example of how BMI can modify the pulmonary effects during acute exposure, Bennett et al. (8) have shown that higher BMI among young, nonasthmatic adults is associated with steeper acute exposure during intermittent exercise. Future studies should determine whether changes in the inverse relationship between BMI and forced exhaled volume in 1 s with ozone exposure during intermittent exercise. Future studies should determine whether changes in the inverse relationship between BMI and forced exhaled volume in 1 s with ozone exposure can be explained by the baseline levels of airway and/or systemic biomarkers of oxidative stress.
CONCLUDING REMARKS

The association between obesity and airway oxidative stress needs to be confirmed using other biomarkers of oxidation and in the context of different clinical obesity and asthma phenotypes. For example, is the degree of airway oxidative stress similar among obese adult vs. child-onset asthmatic subjects? Does obesity-mediated oxidative stress differ in atopic vs. nonatopic asthmatic subjects? Does airway oxidative damage explain why some obese asthmatic subjects do not fully achieve control with inhaled steroids? If so, is there a role for antioxidant supplementation to improve inhaled steroid responsiveness in lean and obese controls and asthmatics (Abstract). Am J Respir Crit Care Med 179: A2510, 2009.


