Review Article

Effects of obesity on inflammatory and oxidative stress markers in asthma

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ABSTRACT

Asthma is influenced by environmental factors and obesity, which triggers inflammatory processes that affect airways and give rise to asthmatic conditions. Obesity is associated with low-grade inflammation with the potential of developing several complications including asthma. The origins of asthma and obesity are complex with genetics and environmental factors and among others implicated. The main constituent of obese tissue comprises fat which is chiefly adipocytes. Reactive adipocytes trigger inflammation that has an adverse effect on lung function. Consequently, airways are clogged with inflammatory components leading to asthma. The inflammatory state cause’s macrophages to produce cytokines such as TNF-α which subsequently affect lung function, trigger insulin resistant diabetes and other cardiovascular complications. The mechanism by which the lung changes are characterized by the inflammatory components which triggers oxidative stress markers and pro-inflammatory mediators such as IL-6 and C-reactive protein (CRP). The presence of high oxidative stress markers and pro-inflammatory products exacerbates asthmatic condition. Therefore asthma and obesity result in inflammation that gives rise to oxidative stress, thus these four pathophysiological phenomena are interrelated. This paper reviews the complex relationship between oxidative stress markers and inflammatory markers, especially with regard to evaluation and monitoring of respiratory diseases by laboratory methods.

Keywords: Obesity, Inflammation, Asthma, Diagnosis and monitoring, Laboratory methods, Oxidative stress

INTRODUCTION

The production of reactive oxygen species (ROS) from tissues is orchestrated by unpaired electrons which are very reactive to various body molecules and potentially alter the physiological structure and function of tissues. These structural and functional changes form the basis of the pathogenesis of disease due to imbalance in the levels of pro-oxidant and anti-oxidants leading to oxidative stress. The level of imbalance for example a pro-oxidant increase as opposed to an anti-oxidant decrease results in synthesis of pro-inflammatory component. Consequently, changes in concentration of inflammatory products initiate oxidative stress, and in obesity, there is a high presence of reactive adipocytes a major constituent of adipose tissue, which triggers inflammatory components that block airway passages as seen in asthmatics, thus there is a correlation between obesity and asthma.

Most respiratory diseases are associated with inflammatory processes that generate toxic ROS and reactive nitrogen species (RNS). Injury to tissues leads to oxidative stress and production of cytokines and growth factors involved in activation of inflammatory cells. The pathogenesis of lung fibrosis is directly or indirectly regulated by ROS. Further, inflammation and oxidative stress are linked and oxidative stress results in accumulation of inflammatory cells in the respiratory tract and these cells produce increased amounts of...
oxygen radicals observed in asthma.\textsuperscript{5,6} Obesity, a metabolic condition of abnormal or excessive fat accumulation in adipose tissue, is a global epidemic with significant adverse impact on public health and studies suggest that obesity is associated with inflammatory products that result in disease.\textsuperscript{7} On the other hand, asthma is a result hyper-responsiveness to inflammatory components and this causes airway obstruction leading to poor lung function.\textsuperscript{8} Further, it has been reported that over-reacting airways are associated with obesity.\textsuperscript{9-12}

**Obesity and oxidative stress**

It has been demonstrated that over-activity of adipocytes stimulates the production of oxidative stress markers in obese and overweight individuals.\textsuperscript{13,14} In addition, oxidative stress has been linked to visceral obesity; and foetuses of obese mothers have been shown to have increased insulin resistance and pro-inflammatory adipocytokines.\textsuperscript{15,18} Overweight and obesity in pregnancy have been demonstrated to have high levels of oxidative stress markers such as plasma malondiadehyde and nitric oxide (NO). Elevated oxidative stress and pro-inflammatory products exacerbates asthmatic condition. The increase of inflammatory cytokines induced by oxidative stress from ROS results in expression of pro-inflammatory cytokine genes.\textsuperscript{19} Chronic oxidative stress related cardiovascular diseases has been reported to cause organ damage; and systemic effect of obesity as consequence of reactive adipocytes has an adverse effect on pulmonary function and therefore precipitates asthmatic condition.\textsuperscript{19-21} Moreover, asthmatic condition is poorly controlled in obese subjects because there is persistent and sustained increase in oxidative stress and pro-inflammatory factors.\textsuperscript{22}

**Inflammation in asthma**

Increased release of cytokines as well as growth factors are involved in the activation of inflammatory cells and pathogenesis of lung fibrosis seen in tissue injury and are regulated by ROS.\textsuperscript{5} Studies report that ROS such as superoxide, H₂O₂; and perhaps hydroxyl radicals contribute to inflammation in asthmatic airways; and an increased NO synthesis has been shown to be associated with pathogenesis of inflammation in asthma.\textsuperscript{4,23,24}

Asthma is associated with inflammation and increased responsiveness in airways of the lungs and this involves secretion of broncho-constrictive, pro-inflammatory products, chemo-attractants mediators, cytokines and ROS.\textsuperscript{4,22} It is suggested that ROS and oxidative stress in asthmatic airways possibly contribute to inflammatory injury and oxidative damage of proteins.\textsuperscript{25} Environmental pollutants and endotoxins from microorganisms have the capacity to prompt neutrophilic airway inflammation thus obstructing the airway and as the lung changes due to over reactivity, this increases oxidative stress and pro-inflammatory mediators such as IL-6 and C-reactive protein.\textsuperscript{9,12}

Pro-inflammatory mediators in serum are therefore higher in asthmatics by comparison with healthy individuals (Table 1). In addition, systemic inflammation is more marked in neutrophilic asthmatic conditions with elevation of Toll-like receptor TLR-2 and TLR-4 as compared to non-asthmatics.\textsuperscript{20} Brian-derived neutropic factor (BDNF) linked to inflammation has also been reported to be increased in circulation in patients with asthma, but its significance is not clear.\textsuperscript{27}

**Table 1: Inflammatory markers in asthma.**

<table>
<thead>
<tr>
<th>Marker</th>
<th>Association with asthma</th>
<th>Lung function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leptin</td>
<td>Increase allergic airway responses</td>
<td>Decrease lung function and increase asthma\textsuperscript{28}</td>
</tr>
<tr>
<td>Ghrelin</td>
<td>Decrease allergic airway responses</td>
<td>Increase lung function\textsuperscript{29}</td>
</tr>
<tr>
<td>Calprotectin</td>
<td>Increase allergic airway response</td>
<td>Decrease lung function and increase asthma\textsuperscript{30}</td>
</tr>
<tr>
<td>Complement components (C3, C4)</td>
<td>Increase allergic airway responses</td>
<td>Decrease lung function\textsuperscript{31}</td>
</tr>
</tbody>
</table>

**Oxidative stress in asthma**

ROS have been reported to contribute to the inflammation in airways in asthma. Indeed, increased levels of ROS and oxidatively modified proteins are observed in asthmatic airways. NO reacts with oxygen and ROS to produce nitrite, nitrate and RNS species such as peroxynitrite, which nitrate proteins and nitration of protein tyrosine is linked to lung diseases. Respiratory antioxidant defences change in asthma and superoxide dismutase an important anti-oxidant that catalyses superoxide radical to H₂O₂ is lower in asthmatics as compared to controls.\textsuperscript{4} Although NO is associated with tissue injury, studies have demonstrated that NO administered exogenously with hyperoxic gas mixtures has a protective effect against lung injury, thus NO has anti-oxidant role and endogenous NO that is elevated in exhaled air of asthmatics perhaps is protective.\textsuperscript{4,32}

The pathogenic changes in asthma brought about by ROS involve stimulation of lipid peroxidation, alteration of protein structure inclusive of nitration and increment in the release of arachidonic acid from cell membranes, contraction of airway smooth muscles, increment in airway reactivity and secretion as well as increment in vascular permeability. It has been mentioned that inflammatory cells are mobilised to airways in asthma; and eosinophils that infiltrate asthmatic airways generate high levels of superoxide ion (O₂⁻) and NO that ultimately give rise to peroxynitrite, a very reactive metabolite that possibly damages airway epithelium.\textsuperscript{25,33} ROS also affect the respiratory airways through activation of signal transduction pathways and transcription factors via formation of oxidised mediators.
such as isoprostanates and hydroxyl-nonenal.\textsuperscript{34} Although nitrilation of proteins is a feature in normal cells, nitrilation of tyrosine is associated with various diseases; and protein nitrilation is high in asthmatic airways compared to non-asthmatic controls.\textsuperscript{4,35,36}

As mentioned, inflammation leads to accumulation of inflammatory cells in the respiratory tract and these cells synthesise various oxygen radicals whose levels are increased in asthma; thus oxidative stress.\textsuperscript{3,6} Studies reported that ROS contribute to inflammation in asthmatic airways; increased NO synthesis is associated with pathogenesis of inflammation in asthma; NO is elevated in asthmatic exhaled breath as compared to healthy subjects; and exhaled NO levels inversely correlated with airflow measurements.\textsuperscript{3,23,24,32}

Studies also showed that ROS react with peptide bonds or with the side chains of proteins and there is oxidation of amino acids such as lysine, leucine, glutamic acid and valine.\textsuperscript{3-6} The extent and clinical significance of such oxidation in diseases such as asthma need further studying.

**Obesity and inflammation**

Obesity is characterized by the presence of reactive adipocytes which initiate inflammatory processes. It is therefore reported that obese individuals have increased chances of developing asthma than non-obese subjects. Moreover, low grade systemic inflammation in obese subjects occurs as a result of increase reactive adipocytes and resident fats that recruit macrophage activity. This mechanism has an endocrine function, which is linked to regulation of energy metabolism.\textsuperscript{41-43}

Macrophages are attracted to the site of reactive and dying adipocytes, which subsequently clear dead cells. In the process of macrophages activity, inflammatory response is generated due to high concentration of fats in adipocytes.\textsuperscript{45,44} In addition, the macrophage activity stimulates production of cytokines such as tumour necrosis factor-alpha (TNF-\(\alpha\)), which triggers insulin resistance diabetes and cardiovascular disorders. Studies show that diglyceride acyltransferase (DGAT1) in macrophages, which synthesise triglycerides from dietary fats, is responsible for pathological conditions relating to obesity.\textsuperscript{45} Hence, enhancing the capacity of macrophages to store dietary fats might possibly alter the pathological process.\textsuperscript{46}

The over-reaction of adipocytes is linked to obesity and this triggers the production of fibroblasts, endothelial cells and macrophages.\textsuperscript{45} In normal metabolism, there is a resident population of leukocytes, which changes during expansion of fats triggering adipose tissue macrophage.\textsuperscript{44,47} The molecular and cellular mechanisms of TNF-\(\alpha\) in adipose tissue and in the adipocytes were studied in inflammatory cells in obese and lean humans; cytokine TNF-\(\alpha\) was observed to increased in obesity and this was coupled with increases in interleukin (IL)-6, IL-1\(\beta\), and chemokine (C-C motif) ligand 2 (CCL2).

TNF-\(\alpha\) is of interest, because it is highly induced in adipose tissues of obese animals including humans and such induction initiates insulin resistance both in cell culture and in vivo. The TNF-\(\alpha\) and the signalling pathway could be adipose tissue-derived autocrine/paracrine and endocrine factors to generate insulin resistance.\textsuperscript{48}

The dynamics of balance between pro- and anti-inflammatory components in obesity are initiated by adipokines and cytokines via intracellular signalling transduction pathways and the mechanisms involve proteins such as the nuclear factor kappa B (NF-kB); and in the extracellular milieu, proteins involved in regulating the extracellular signal are the mitogen-activated protein kinase.\textsuperscript{49,50}

**Obesity and asthma**

Obesity and asthma are associated and studies showed that obesity increases the risk of developing asthma.\textsuperscript{51} In addition, a strong correlation between body mass index (BMI) and airway hyper-responsiveness is observed.\textsuperscript{52-54} Symptoms of asthma include wheezing, shortness of breath, chest tightness, cough and sputum production that clogs air flow.\textsuperscript{55} Asthma is an allergic disease, involving activation of the acquired inflammatory interleukin (IL)-5-mediated eosinophilic airway.\textsuperscript{56}

The inflammatory mechanism is triggered by allergen activated Th2 helper T cells and mast cells through immunoglobulin IgE as a result of histamine release.\textsuperscript{51} There is evidence associating BMI and changes in air ways.\textsuperscript{52-54} Various markers are associated with inflammation and obesity in asthma and examples of these are shown in Table 2.

**Table 2: Inflammatory markers in obesity and asthma.**

<table>
<thead>
<tr>
<th>Inflammatory markers in obesity</th>
<th>Effects of Obesity</th>
<th>Effects of Asthma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leptin</td>
<td>Increase\textsuperscript{62}</td>
<td>Increase\textsuperscript{58,63}</td>
</tr>
<tr>
<td>Adiponectin</td>
<td>Increase\textsuperscript{57,63}</td>
<td>Increase\textsuperscript{57,63}</td>
</tr>
<tr>
<td>Resistin</td>
<td>Increase\textsuperscript{64}</td>
<td>Decrease\textsuperscript{65}</td>
</tr>
<tr>
<td>Visfatin</td>
<td>Increase\textsuperscript{61}</td>
<td>Increase\textsuperscript{63}</td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>Increase\textsuperscript{66}</td>
<td>Increase\textsuperscript{66}</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>Increase\textsuperscript{67,68}</td>
<td>Increase\textsuperscript{67,68}</td>
</tr>
<tr>
<td>Serum amyloid A</td>
<td>Increase\textsuperscript{64}</td>
<td>Increase\textsuperscript{69}</td>
</tr>
<tr>
<td>Cytokines- IL-6, IL-8, IL-18, IL-10 &amp; TNF-(\alpha)</td>
<td>Increase\textsuperscript{64}</td>
<td>Increase\textsuperscript{70}</td>
</tr>
</tbody>
</table>

Adipokines such as leptin and adiponectin are worth mentioning since obese and asthmatic conditions are associated with high levels of blood leptin levels.\textsuperscript{57} Leptin stimulates neutrophilic airway inflammation in asthma and...
thus increasing the activity of TNF-α. This process inhibits apoptotic actions in neutrophil thereby expanding the concentration and action of neutrophils thus aggravating neutrophilic airway inflammation.\textsuperscript{59-61}

**Environmental and dietary factors**

Asthma has been shown to associate with various factors including environmental allergens; and some dietary factors are also known to mitigate oxidative stress.\textsuperscript{71,72} Ozone (O₃) is an oxidising environmental pollutant hence contributes to respiratory health; for instance high level of ozone exacerbates symptoms of asthma and inflammation.\textsuperscript{73-76} Indeed dietary factors with anti-oxidant activity have been reported to be beneficial in alleviating oxidative stress. Studies show that reduction in consumption of fruits and vegetables, sources of vitamins C and E and carotene perhaps contribute to decreased pulmonary anti-oxidant defences making them susceptible to inhaled allergens and irritants thus giving rise to asthma.\textsuperscript{25,72} Studies by Alcala et al; in mice showed that vitamin E reduced oxidative stress, cytokine and improved insulin sensitivity.\textsuperscript{72}

**Oxidative stress markers: monitoring by laboratory methods**

The variety of oxidative stress markers is an interesting dilemma; there are methods for the various markers, some simple while others technically complex. Most routine laboratories can measure these markers using immunoassays and routine equipment such as spectrophotometers on samples such as blood and urine that are easy to collect. The various markers measured include asthmatic urine, blood, sputum lung tissue and bronchoalveolar lavage fluid and the concentrations of these metabolites in some cases correlate with disease severity.\textsuperscript{73} Other techniques for measurement include a variety of chromatographic techniques; and a summary of the oxidative markers and measurements are summarised in Table 3.\textsuperscript{78}

<table>
<thead>
<tr>
<th>Metabolite</th>
<th>Oxidation/nitration product</th>
<th>Technique</th>
<th>Inference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein</td>
<td>Protein carbonyls</td>
<td>Spectrophotometry</td>
<td>Oxidative damage and disease-derived protein dysfunction \textsuperscript{79,80}</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ELISA</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Electrophoresis</td>
<td></td>
</tr>
<tr>
<td>Tyrosine nitration</td>
<td></td>
<td>ELISA</td>
<td>Oxidative damage \textsuperscript{79,80}</td>
</tr>
<tr>
<td>Lipid</td>
<td>Malondialdehyde</td>
<td>Spectrophotometry</td>
<td>Protects from oxidative stress \textsuperscript{81-82}</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GC-MS</td>
<td></td>
</tr>
<tr>
<td>F₂-isoprostanes</td>
<td></td>
<td>Immunoassays</td>
<td>Oxidative damage \textsuperscript{83}</td>
</tr>
<tr>
<td>DNA</td>
<td>8-hydroxy-2'-deoxyguanosine</td>
<td>HPLC, GC-MS, GC-MS/MS, LC-MS</td>
<td>Oxidative stress and DNA damage \textsuperscript{84-86}</td>
</tr>
<tr>
<td></td>
<td>8-nitroguanine</td>
<td>HPLC, GC-MS, GC-MS/MS, LC-MS</td>
<td>DNA damage \textsuperscript{85}</td>
</tr>
<tr>
<td>Carbohydrates</td>
<td>Advanced glycation end products (carboxymethyllysine, pentosine)</td>
<td>HPLC, GC-MS, ELISA, Immunohistochemistry</td>
<td>Oxidative stress and cellular dysfunction \textsuperscript{87,88}</td>
</tr>
</tbody>
</table>

Studies have reported nitrotyrosine (a product of peroxynitrite mediated oxidative damage) in airway epithelium and inflammatory cells in bronchial biopsies of asthmatic patients.\textsuperscript{79}

The F₂-Isoprostanes urine metabolites are elevated in acute asthma attack, which is aggravated compared to stable asthmatics.\textsuperscript{90} Although some reports showed an increase in plasma lipid peroxidase as well as total anti-oxidant capacity in hospitalized patients with acute asthma is different compared to stable asthmatics, other markers such as plasma glutathione peroxidase, total nitrates appear not changed between acute asthmatics and stable subject, possibly due to compensatory changes.\textsuperscript{91}

Increased levels of H₂O₂ and NO levels have been observed in exhaled air in steroid-naïve asthmatics as compared to normal subjects and H₂O₂ in exhaled breath condensate has also been reported high in asthma.\textsuperscript{83} In a non-evasive study using exhaled breath condensate, levels of H₂O₂ were higher in asthmatics by comparison...
with control.\textsuperscript{32} Lu et al in their studies in humans reported that the association of obesity and asthma were not fully explained by systemic inflammation, i.e. plasma levels of CRP, IL-6 and TNF-\(\alpha\), adiponectin and neuropeptide Y thus other factors make be involved. However the authors reported high levels of adiponectin by comparison with non-asthmatics.\textsuperscript{41}

**CONCLUSION**

Although asthma is influenced by environmental factors, obesity comes as a result of adipocytes which could trigger inflammatory cells, potentially affect airways and give rise to asthmatic conditions. Obesity is likely to increase the severity of asthmatic condition. Obesity results in inflammation, which give rise to oxidative stress and on the other hand oxidative stress leads to inflammation. Studies therefore need to focus on relationship between oxidative stress markers and inflammatory markers.

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**REFERENCES**


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