Fatty airways: a source of good and bad fats?

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Adipose tissue is increased around the airway in asthma and is associated with BMI, airway inflammation and disease severity. Fat in the airway might contribute both positively and negatively to the immunobiology of asthma. http://bit.ly/2CgOGsY

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There is a constant and consistent message in the medical and lay press that obesity is a modern epidemic affecting the developed world. It causes and exacerbates multiple diseases including cardio-metabolic, musculoskeletal, cancer and respiratory diseases [1]. There is no doubt that improving diet and lifestyle to eliminate obesity has positive health benefits [1]. Although this truism is well-known and accepted, the impact of obesity on the immunobiology of disease [1–4] is only beginning to be unravelled and this might reveal more subtle, albeit profound, effects of obesity on chronic inflammatory diseases.

Obesity is a major risk factor for the development of asthma [5]. Prospective epidemiological studies demonstrate consistently that obesity can antedate a diagnosis of asthma [6]. As body mass index (BMI) and fat mass increases, the relative risk of developing asthma increases, asthma-related health status and symptoms worsen and exacerbations become more frequent [7]. Obesity-associated asthma may represent a distinct clinical phenotype, characterised by later onset, female preponderance and greater symptomatology than classic atopic asthma with a relatively low degree of eosinophilic inflammation measured by sputum cytology [8, 9]. Obesity is more common in severe asthma with, strikingly, the majority of severe asthmatics in many developed countries now living with obesity as a major comorbidity [9].

Obesity will cause extrathoracic restriction and is reported to promote airway hyperresponsiveness, most likely *via* increased airway closure [10]. This is related to obesity but not waist circumference [11], suggesting the effects might not simply be due to poor inspiratory effort due to diaphragmatic splinting but could be due to additional factors. Several studies have demonstrated that weight reduction by diet and exercise or bariatric surgery improve asthma outcomes, including symptoms, airway hyperresponsiveness and exacerbation frequency [12–15]. Even though these benefits are considered to be predominantly *via* reduction of extrathoracic restriction some, but not others, suggest an impact on airway inflammation [12–14], highlighting the possibility that the impact upon asthma outcomes might be partly *via* the effect of obesity upon the immunobiology of the disease [2–4].

As noted above obese asthmatics typically have low eosinophil numbers in their airway measured by sputum analysis. However, obesity itself is associated with a small increase in blood eosinophils [16]. Interestingly, bronchial tissue eosinophils are increased in obesity in spite of a lack of sputum eosinophils [17]. An explanation for this apparent paradox has begun to be revealed by human *in vivo* tracking of eosinophils [18].

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Using radiolabelled eosinophils coupled with SPECT/CT to quantify eosinophilic inflammation in patients with asthma revealed important differences in eosinophil kinetics between obese and non-obese asthmatic subjects. Eosinophil retention in the airway is prolonged in obese asthmatics, suggesting that there is altered behaviour of eosinophils in asthma subjects with obesity. In this issue of the *European Respiratory Journal*, Elliot *et al.* [19] report that adipose tissue lies in the outer airway wall and is increased in fatal asthma and those that died with asthma of other causes compared to non-asthmatics. The granulocytic inflammation, both neutrophilic and eosinophilic, was related to the amount of adipose tissue in the airway. The adiposity in the airway was associated with BMI. This adipose tissue in the airway could be an epiphenomenon but perhaps represents an important source of local cytokines and adipokines, such as leptin, that impact on inflammatory cell trafficking and survival and consequently enhance airway inflammation and possibly remodelling.

Many metabolic products, including fatty acids of varying chain length, modulate homeostatic control by activating members of the G protein-coupled receptor (GPCR) superfamily. A pair of receptors, FFA1 and FFA4 (also designated GPR40 and GPR120, respectively) is activated by many distinct long chain fatty acids (>12 carbon atoms) [20] that are stored within adipose tissue as triglycerides and, given the expression of these receptors in many metabolically active tissues and in a wide range of immune cells, there has been considerable interest in targeting either FFA1 and/or FFA4 to treat conditions such as type II diabetes [21]. However, although high level expression of FFA4 in the lung, and potentially by club cells, was identified more than 10 years ago [22] few studies have explored its potential to regulate airway contraction. FFA1 and FFA4 are expressed in human and guinea pig airway smooth muscle, and FFA1 agonists potentiated acetylcholine-induced contraction of guinea pig tracheal rings [23]. Although FFA4 is sometimes described erroneously as a receptor for polyunsaturated omega-3 fatty acids [24], efforts to directly link the effects of such fatty acids to the biology of FFA4 is hampered by their conversion to resolvins which play key roles in resolving lung inflammation [25]. There is clearly a need to better understand the contribution of adipose tissue, fatty acids, and both FFA1 and FFA4 in both normal and diseased lung.

Beyond the local effects within the airway, obesity is associated with increased low-grade systemic inflammation characterised by increases in systemic levels of inflammatory cytokines, such as interleukin (IL)-6, IL-1 and tumour necrosis factor, and adipokines, such as leptin [26]. These mediators originate in adipocytes and activated macrophages in adipose tissue, and together with hyperinsulinaemia and insulin resistance [27] contribute to mechanisms of metabolic dysfunction and metabolic syndrome in asthmatics with obesity. Obese patients with high IL-6 levels have more severe asthma than obese patients with low IL-6 levels [28]. This asthma metabolic syndrome might be amenable to treatments targeting insulin resistance and inflammation, such as anti-IL-6 biological therapies.

Whilst weight reduction *via* diet and lifestyle must remain the mainstay of management for asthmatics with obesity, it is important to consider the varied role of adiposity in the immunobiology of asthma. Systemic anti-inflammatory strategies to target metabolic syndrome might be valuable especially in those with elevated blood IL-6. Eosinophil and T2-directed therapies might be beneficial even in the absence of sputum eosinophilia due to altered eosinophil cell trafficking and retention in the airway. Consideration of lipids in particular triglycerides as immunomodulatory bioactive lipid mediators that impact on airway inflammation and remodelling might make us reconsider the role of "fat" in the airway, with some fats possibly having a beneficial role as "good fats", whereas other "bad fats" are deleterious for asthma.

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