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EDITORIAL

# Visceral adipose tissue: A clue to the obesity-asthma endotype(s)?

Obesity and asthma are both prevalent chronic pathological conditions throughout the world, representing today a serious global economic and social burden to health care systems and patient's quality of life.[1,2] Overweight and obesity are defined as abnormal or excessive fat accumulation that presents a risk to health. The worldwide prevalence of obesity more than doubled between 1980 and in 2014, when more than 1.9 billion adults were overweight and over 600 million of these were obese. Overall, about 39% of the world's adult population (40% of women and 38% of men) are overweight, and 13% are obese (15% of women and 11% of men).[3]

The National Health and Nutrition Examination Survey (NHANES) data has indicated that in the USA almost one in three asthma patients are obese and that the prevalence of obesity between subjects with current asthma has increased in a 23 years span from 21.3% (NHANES I) to 32.8% (NHANES III).[4] A recent meta-analysis showed that weight gain *per se*, almost doubled the odds of incident asthma.[5] Studying a representative sample of 32,644 adults (52.6% females) from the 4th Portuguese National Health Survey, we also recently found that obesity more than quadrupled the odds of incident asthma, increasing also the odds of a more persistent and severe asthma phenotype.[6] On the other hand, in the same meta-analysis, weight loss was associated with significant improvements in mean scores for symptoms, rescue medication, and asthma exacerbations, in an included randomized controlled trial.[5] Additional evidence, gathered from observational studies, also showed improvements in asthma control-related outcomes with weight loss.

Asthma is nowadays seen not as a single disease entity but a syndrome that associates characteristic recurrent symptoms, variable airflow obstruction and underlying airways inflammation. It is now recognized that asthma encompass different driving biomechanical and cellular pathways that translate into different clinical expressions (e.g. phenotypes) but also different pathophysiological mechanisms (e.g. endotypes) and, for some of those, unfavourable response to standard, guideline-oriented, pharmacological treatments.[7] In fact, obesity can negatively influence the response to standard asthma medication, as overweight or obese adults with severe asthma exacerbations have longer durations of treatment in the emergency room (and also more in-hospital admissions), and increasing body mass index (BMI) has been associated with decreased response to inhaled corticosteroid, but not leukotriene-antagonist.[5]

Obesity-related/associated asthma is more and more seen at our clinics, especially in women, and as one of the exacerbation-prone asthma phenotypes.[6,7] Therefore, identified the underling mechanisms of a particular asthma-phenotype – i.e. the corresponding endotype(s) – is nowadays crucial for its effective and tailored care. Neurogenic inflammation may be one these mechanisms, as shown in an experimental model of high fat diet-induced obesity and allergen-challenged sensitized mice.[8] In this model, metabolic and allergic inflammation parameters independently increased Substance-P (SP) and the presence of both conditions further increased SP levels. In a follow-up study, the same group showed that a SP-antagonist improved both metabolic biomarkers and the allergic inflammation, supporting this common pathway in the obese–asthma phenotype, and identifying SP as a potential therapeutic target in this endotype.[9]

In this issue of the journal, Capelo et al. explore, in a cohort of 83 asthmatic women, the associations between the abdominal adiposity distribution, asthma control, lung function and cytokines (adiponectin and interleukin-6).[10] In this cross-sectional study, the authors addressed the association between subcutaneous (SAT) and visceral (VAT) adipose tissues, measured by ultrasound, and asthma control, according to Global Initiative for Asthma (GINA) criteria. The analyses were adjusted for important confounders such as age, BMI, education level, rhinitis, hypertension, diabetes, and asthma onset and disease duration.

Their results showed that women with uncontrolled asthma have significant higher VAT (cm), VAT/SAT ratio and a tendency for higher waist circumference (cm), than women with controlled or partially controlled asthma. Additionally, a negative association between VAT and VAT/SAT with asthma control was found in these women, after adjusting

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for confounders. Considering the association with cytokine levels, VAT associated with interleukin-6, while BMI and SAT were inversely associated with the ''anti-inflammatory'' adiponectin serum levels.

The link between obesity and asthma has been partially explained by mechanical factors, inflammatory conditions and stress triggers.[11,12] Obesity causes a reduction in respiratory system compliance, lung volumes, and peripheral airway diameter, as well as an increase in airways responsiveness.[13] On the other hand, obesity is known to be associated with chronic low-grade systemic inflammation, with an imbalance between pro- (leptin, plasminogen activator inhibitor, IL-6) and anti-inflammatory (adiponectin) cytokines,[14] in line with Capelo et al. findings. However, we have previously reported a negative association between BMI and airways inflammation, measured by exhaled nitric oxide (FeNO) in overweight and obese asthmatics, providing support to the mechanical hypothesis linking obesity and asthma.[15] Nonetheless, Capelo et al. hypothesizes that it is the visceral adipose tissue (VAT), and not subcutaneous adiposity or BMI that relates to the pro-inflammatory signals and asthma control in obese asthmatic women. Therefore, future studies evaluating the relation of VAT to airways inflammation (e.g. FeNO) in the obsess-asthma endotype(s) are warranted.

The cornerstone for obesity treatment is a multicomponent lifestyle intervention, with lifestyle or behavioural training, dietary change to reduce energy intake, and an increase in physical activity to increase energy expenditure.[16] Likewise, some dietary patterns seem to have health benefits. We have previously described a protective link between a Mediterranean diet[17] and $n-3$ polyunsaturated fatty acids[18] and asthma control, and between a ''fish, vegetables and fruit'' dietary pattern and current persistent asthma prevalence, while a detrimental association between a ''high fat, sugar and salt'' dietary pattern and severe asthma prevalence was observed.[19]

Taken together, these results reinforce the relevance of investigating the relationships between asthma and obesity, indicating that body weight, waist circumference and/or visceral adiposity assessment should be considered and integrated in day-today clinical asthma care, and that adequate body weight maintenance may also be a preventive step to minimize the burden of asthma in the global health care system. These studies also provide rational for lifestyle interventions in the obesity-asthma endotype(s), to better understand which nutritional intervention, dietary modification and exercise prescription will be able to optimise not only weight reduction, but also the asthma control and patient's quality of life.

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