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ORIGINAL ARTICLE

Leptin and resistin in overweight patients with and without asthma

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Abstract
Background: Excess body mass increases the risk of development of asthmatic symptoms and their severity and decreases the treatment effectiveness. One of the hypotheses explaining the link between the two diseases concerns the adipokines, hormones produced by adipose tissue with a proinflammatory character. The aim of this study was to compare the levels of the adipokines (leptin and resistin) between overweight asthmatic patients, asthmatic patients with normal weight and overweight patients without asthma.
Methods: 80 peripheral blood samples were collected from patients and blood serum extracted. Three groups were selected: overweight asthmatic patients (BMI $\geq$ 25), overweight patients without asthma and asthmatic patients with normal weight (BMI < 25). Waist circumference of the patients was measured (cut-off points were 80 cm for women and over 94 cm for men) and a skin prick test performed. Comparison of adipokine concentration between the 3 groups was made and association between these concentrations and the measurements was performed.
Results: Although the concentrations of both adipokines were slightly higher for overweight asthmatic patients compared to overweight healthy patients, these differences were not significant. A significant association was found between leptin concentration and both BMI ($p < 0.01$) and waist circumference ($p < 0.01$). A difference for this cytokine was also found between asthmatic and non-asthmatic female patients ($p < 0.05$).
Conclusions: As expected overweight patients with BMI $\geq$ 25 and patients with increased waist circumference showed higher leptin levels. We suggest that the studied cytokines, with a stronger indication for leptin, can elicit asthmatic inflammation in obese phenotype of asthma that affects more frequently women.

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Introduction

As defined by the World Health Organization (WHO) asthma is a chronic inflammatory airways disease characterized by recurrent attacks of wheezing and breathlessness.[1] Asthma inflammation involves the recruitment of various cells and cellular elements such as immunoglobulins and cytokines that will result in airways mechanical and physiological changes. Asthmatic patients have narrowed airways due to the bronchi edema and thickening achieved by the hypertrophy and hyperplasia of the smooth muscle cells (result of the VEGF – vascular endothelial growth factor secretion) and their contraction. Additional airflow problems are caused by the increased secretion of mucus.[2]

Obesity and overweight is ''abnormal or excessive fat accumulation that may impair health''.[3] In the last decades the prevalence of asthma and obesity increased significantly in industrialized countries becoming a burden not only for affected patients but also public health systems.[4,5] This convergence captured the interest of researchers and resulted in various studies examining the link between the two conditions. It soon became clear that obesity is a strong risk factor for asthma development, affecting prevalence, severity and treatment effectiveness in obese patients.[6]

Body mass index (BMI) measured in kg per square meter is the most commonly parameter used to assess the excess of weight and obesity. Numerous epidemiological studies found a significant association between BMI and asthma symptoms both in adults[7,8] and children.[9] However, contrary results can also be found.[10,11] BMI, despite being the most frequent, is not the most precise measure of the fat excess. This index describes only the relation of the total body mass to height, not taking into consideration the actual proportion of the fat *versus* lean mass or the fat distribution.

Another commonly used indicator for obesity, examining the fat distribution, is the waist circumference. Central obesity (fat concentration around the waist area) is a strong risk factor for cardiovascular diseases and type 2 diabetes.[12] A study run in the Hunter Medical Research Institute, New Castle, Australia, considered in obesity-related asthma studies not only BMI but also body composition and waist circumference. A significant association was encountered indicating a detrimental impact of increased fat mass and both thoracic and android fat tissue on respiratory health (expiratory reserve volume – ERV) in women. In men the association was found with thoracic and android lean issue and ERV. However, leptin concentration, also included in this analysis, was positively associated with thoracic and android fat tissue in men.[13]

Several studies indicate that obesity-related asthma phenotype is observed more commonly in women. Von Behren et al. used not only BMI but also waist size in the cohort study of 88,304 women and found a positive association between these measurements and current asthma, with waist circumference being independently associated with asthma symptoms, even in the group of women with normal BMI status.[14]

Various hypotheses were presented trying to explain the mechanism causing the association. One explanation focuses on the common environmental factors for both diseases, namely sedentary lifestyle and changes in diet. Other hypotheses implicate the reduced lung capacity caused by the mechanical impact of body mass on the chest, gastroesophageal reflux and sleep-disordered breathing.[15] Recent studies have shown that adipose tissue has not only a passive energy storage role but is also physiologically active having endocrine functions. Hormones secreted by this tissue are called adipokines and their main role is to regulate hunger and satiety, although they are also involved in inflammation processes. The most indicated adipokines suggested to have an impact on asthma development are leptin and resistin.[16] Leptin is a 16 kDa protein of 167 amino acids is a product of ob gene (gene of obesity) in humans. Food intake results in the increased expression of this gene and as a consequence, of leptin serum concentration. The leptin receptor gene (db) is expressed in the lung tissue. The presence of the receptors itself indicates the lungs as the target organ for this hormone.[17] Resistin is a recently discovered 12.5 kDa adipokine belonging to a cysteine-rich secretory protein family. Resistin is expressed in human macrophages, bone marrow, spleen, mononuclear leucocytes and at low levels in adipose tissue. This hormone concentrates around the inflamed tissue, up-grading its own expression and promoting the NF-κB activation and cytokine production *ipso facto* triggering the inflammation. Similarly to leptin, resistin levels increase with increased adipose mass.[18] Both hormones described above are important mediators of the metabolic processes with pro-inflammatory character. Higher serum concentrations of both adipokines were observed in asthmatic patients with an even stronger association for women.[19]

Methods

Questionnaire data collection

The database and sample used in this work is a part of a larger project making part of the Global Allergy and Asthma European Network (GA2LEN).[20] Data collection was carried out in 2010 and centered on the population-based sample of 2200 individuals aged between 18 and 74 years old. As recommended by the GAL2EN protocol, the sample was selected randomly. A short questionnaire including questions about birth date, gender and asthma symptoms was handed to the participants to be filled in and returned by mail. Three attempts were undertaken in order to obtain the best response rate. A skin prick test was conducted on the randomly selected sub-sample of asthmatics. The presence of asthma symptoms was determined using the GINA classification.[21]

Anthropometric measurements

All the individuals participating in the study were measured and weighed (with light clothing and barefoot). BMI was calculated with the formula

$$\mathrm{BMI} = \frac{\text{weight (kg)}}{\text{height (m)} \times \text{height (m)}}$$

Using the cut-off points recommended by the WHO we considered individuals with a BMI value equal to or greater than 25 as overweight and equal to or greater than 30 as