

Asthma and obesity: are they interrelated?

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Civilizational diseases are an inglorious mark of the present time. This article will focus on two of them: obesity and asthma. These conditions are not only “civilizational” in character, which by definition means a much greater prevalence in highly developed countries, but they also perplex with poorly investigated and thus unclear interrelatedness. The understanding of their concomitance and mutual influence would result in more efficient diagnosis and more optimal treatment of obese asthmatics who represent a distinct case, one of the five main phenotypes of asthma distinguished by an international panel of experts in the 2014 Global Initiative for Asthma guidelines.¹ Apart from the practical aspect, the cognitive one is equally important for a study of factors predisposing to a relationship between both conditions.

It has been proved that obesity affects asthma: pre-existing obesity is considered to be a risk factor for developing asthma in both atopic and non-atopic individuals, a factor hindering satisfactory pharmacological control of asthmatic symptoms and, as a result, a predictor of poor prognosis of asthma.

The former statement can be supported by epidemiological studies showing that asthma prevalence and incidence in obese subjects are significantly higher than in normal-weight population, regardless of the ethnic origin of the population studied.² Numerous observations prove, too, that the management of asthma coexisting with obesity is more difficult and less effective than the treatment of the condition in normal-weight patients. Worse control of asthma in obese subjects may be attributed to: 1) obesity-dependent changes in lung mechanical properties (such as increased work of breathing, hyperinflation, decreased thoracic compliance, lower tidal volumes, reduced total lung capacity with a restrictive pattern, and small airways more prone to closure) and 2) altered responses to asthma medications.³ Peters-Golden et al⁴ and Boulet et al⁵ found an attenuated clinical response to inhaled corticosteroids (ICSs) or a combination of ICSs and long-acting bronchodilators in obese asthmatics. The

causes of weaker response to asthma control medications in obese asthmatic patients are yet unknown. The phenomenon may be accounted for by a lower prevalence of the eosinophilic type of airway inflammation (characterized by good response to ICSs) in this group of patients as well as by an impaired penetration of ICSs to distal airways in obese individuals. Regardless of the possible causes, the observed risk of asthma exacerbation and hospitalization in this group of patients can be a consequence of the above handicaps present in obese asthmatics.⁶

A possible role of a variety of inflammatory cytokines, mediators, and hormones has been suggested to explain the influence of obesity, considered as a low-grade systemic inflammatory condition, on an inflammatory airway disease such as asthma. Proinflammatory cytokines (eg, tumor necrosis factor α [TNF- α], interleukin 6), chemokines (eg, eotaxin), acute phase reactants, as well as increased leptin and reduced adiponectin levels can theoretically have a negative effect on asthma in obese subjects but their actual role in asthma development remains unclear. Adiponectin, an anti-inflammatory hormone, is particularly interesting because its level is significantly low in the obese population.⁷ The deficiency of adiponectin's anti-inflammatory effects may account for the higher prevalence of asthma, an inflammatory disease, in obese subjects.

Searching for possible causes of an interrelation between asthma and obesity, investigators have turned to genetics. Despite much effort, our knowledge about genetic dependencies between asthma and obesity is still poor, most likely because of the polygenic nature of the two conditions. It is hypothesized that shared genetic determinants may play an important role in this interaction. Hallstrand et al,⁸ in a community-based study of American twins, showed that 8% of genetic components are shared by both diseases. Individual studies have identified genetic variants at several loci that have been linked to asthma and obesity: the β_2 -adrenergic receptor gene (*ADRB2*), glucocorticoid receptor gene (*NR3C1*), the human leukocyte antigen gene cluster (*HLA*),

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vitamin D receptor gene (VDR), leptin (*LEP*), protein kinase C alpha (*PRKCA*), and *TNF-α* gene.⁸⁻¹¹ The polymorphism of the *TNF-α* gene was strongly correlated at position 308 (G/A) in the population of asthmatic adults in contrast to asthmatic carriers of the G/G genotype.¹¹ In turn, the polymorphism of the *LEP* gene at position 2549 (T/G) correlated with body mass index [BMI] in asthmatic patients.⁹ However, further analysis of the obesity asthma candidate genes based on a genome-wide association study did not confirm the association between the majority of these genes. Only *PRKCA*, *ROBO1*, and *GNPDA2* seem to influence both conditions.¹²

Recently, polymorphisms in the region of 16p11.2 have been linked to asthma and obesity.¹³ Gonzales et al¹³ showed that 16p11.2 inversion has a strong protective effect on the risk of asthma, especially when coexisting with obesity. The inversion of the genotype was highly correlated with the expression of several genes that are involved in fat accumulation (apolipoprotein B48 macrophage receptor, *APOB48R*), glucocorticoid-resistance (interleukin 27), signaling of leptin (SH2B adapter protein 1, *SH2B1*) both mitochondrial metabolism and interferon α inhibition (TUFM).¹³ A genome-wide association study of the BMI in 23 000 participants with and without asthma helped find candidate genes for asthma and obesity in children.¹⁴ Eventually, only the *DENND1B* gene was strongly associated with asthma and obesity in children.¹⁴

In the context of the above considerations, the paper by Marta Gruchała-Niedoszytko et al¹⁵ included in this issue of the *Polish Archives of Internal Medicine (Pol Arch Med Wewn)* is particularly interesting. The authors compare gene expression profiles (the whole-genome expression was performed in RNA samples isolated from peripheral blood) in 3 groups of patients: obese asthmatic patients, asthmatic patients with normal body mass, and obese patients without asthma. They identified differences in 6 genes between the first two groups and, what was more predictable, in 23 genes between obese patients without asthma and normal-weight patients with asthma. Additionally, comparing the groups of obese patients without asthma and obese patients with asthma, the authors showed differences in gene expression in RNA samples from peripheral blood that they linked to obesity, and based on the results, they created a predictive model allowing for a precise genetic differentiation between the two groups.

Interesting as the outcome of the study is in a broader perspective of the beneficial use of genetics in medicine, as proved by the application of genetics in oncology and hematology, it seems that genetic differentiation between obese non-asthmatic and asthmatic individuals has a limited practical role in diagnosing asthma concomitant with obesity. In everyday medical practice, the differentiation between obesity-related dyspnea and bronchospastic dyspnea rarely causes difficulties, as demonstrated by Parkhale et al,¹⁶

who proved that obesity is not an independent predictor of misdiagnosis in asthma. Then, the study by Gruchała-Niedoszytko et al¹⁵ may find little practical application in asthma diagnosis and management, but, importantly, it was not designed to identify a causal relationship between obesity and asthma. From the perspective of asthma research, the study is inspirational because it prompts the need for further investigation into the possible connections between these two comorbidities in adults.

For all its many strengths, the study has also some limitations. It was conducted in a rather small group of patients and lacked a control group of nonobese subjects without asthma ("supernormals"). It seems that it would be more informative to compare the groups of obese and nonobese asthmatics separately with such a supernormal control group of individuals. Additionally, as the authors admit themselves, there is a need to validate the gene profile in independent groups of all the above populations of patients.

The relationship between asthma and obesity still remains to be elucidated. It is now widely accepted that the concurrence of the two conditions is disadvantageous but questions remain as to how obesity could influence the development of asthma, which genetic and epigenetic factors are involved, what are the biomarkers of airway inflammation in obese asthmatics, and what are the specific therapeutic requirements in this population. In the times of personalized medicine, precise definitions of pheno- and endotypes of asthma are absolutely essential to be able to optimize pharmacological treatment of this type of asthmatics and, in a broader perspective, to provide them with the highest-quality care.

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