



Allergologia et immunopathologia

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EDITORIAL

The association between asthma and diabetes: Does it exist?

Asthma, diabetes and obesity are frequent and complex diseases whose prevalence is increasing, particularly among young people.¹ One report which included data from 17 European countries disclosed an annual increase of 5.4, 4.3 and 2.9% among age-groups 0–4, 5–9, and 10–14 years, respectively, during a 15-year period between 1989 and 2003, with an overall increase of 3.9%.² The prevalence of asthma has increased concomitantly. Thus, data from the ISAAC Study disclose asthma prevalence of about 20% in countries such as the USA, United Kingdom or New Zealand, and about 10% in other countries such as Spain, Germany or Sweden.³ However, although epidemiological studies describe a striking concurrence between all three diseases, the relation between them, if it exists, is not yet fully known. Obesity has been recently described as an inflammatory systemic disease, or better, as a pro-inflammatory condition, that could contribute to the increase of the prevalence of asthma (REF). Then, this up-regulation of the inflammatory processes as well as the effects on insulin resistance would play a primary role in the origin of Type-2 diabetes.

Since the description of the paradigm of the TH1/TH2 regulation of the immune system, an academic consensus establishing the incompatibility of the simultaneous coexistence of both patterns has been reached. Thus, for example, patients with Type-1 diabetes with a predominant pattern of Th1 cytokines would be less prone to allergic asthma (with Th2 cytokines).

In the current issue of *Allergologia et Immunopathologia* Tosca et al. publish a study comparing the bronchodilator effect in two well-differentiated groups of children: one including children with allergic rhinitis and diabetes, and the other consisted of children with allergic rhinitis without diabetes. When the authors consider FEV1%, FVC%, and MMEF% no differences were observed, neither in the spirometric pre-bronchodilator study, nor after inhalation of Salbutamol. However, when an intragroup analysis was performed, a statistically significant difference was observed in the pre- and post-bronchodilator MMEF% change (+7% in children with allergic rhinitis and diabetes; 15.94% in children with allergic rhinitis without diabetes). The authors conclude that this lower bronchodilator response might reflect some kind

of protective effect against the development of asthma in children with allergic rhinitis and diabetes. Nevertheless, this study contains some significant flaws, such as the small sample of patients (justified by the limited number of Type-1 diabetes patients), as well as the lack of an appropriate follow-up.⁴

However, these data should be taken cautiously, since observational studies with greater sample sizes also exist in which the opposite is observed: there is an association between asthma and diabetes.⁵ Certainly, these studies also have limitations, like the lack of an appropriate adjustment for confounding variables, the severity of asthma, BMI, tobacco smoke exposure, level of physical activity, or even treatment with corticosteroids — all factors that could be related with the development of diabetes.⁶

Because of its relevance, it is important to mention a study from Kero et al.⁷ that evaluates the prevalence of asthma, Type-1 diabetes, celiac disease and rheumatoid arthritis in a cohort of 60,254 births. The accumulated incidence of asthma among children with celiac disease (24.6%) or rheumatoid arthritis (10%) was significantly higher than among children without celiac disease (3.4%) or rheumatoid arthritis (3.4%) ($p < 0.001$ and $p = 0.016$ respectively). Additionally, there was a non-significant higher trend to have asthma among children with Type-1 diabetes as compared with children without diabetes. Thus, this study suggests that Th1 and Th2 disease can coexist.

There are also studies that demonstrate the association between the decline of lung function and glucose levels or with the diagnosis of diabetes by itself. These studies demonstrate an inferior lung function among diabetic patients in comparison to non-diabetic patients.^{8,9}

Furthermore, longitudinal studies in diabetic patients show a greater drop in lung function when they are poorly controlled or when they have higher figures of HbA1c, as compared with well-controlled diabetic patients.¹⁰ Additionally, it is easier to find asthmatic patients among diabetics with poorer glycaemic figures than among well-controlled diabetics.¹ Nor does it seem that Type-1 diabetes

provides a protective role against the development of allergic sensitisations to aero-allergens.¹¹ Consequently, if poorly controlled diabetes worsens lung function and does not protect against the development of sensitisations to aeroallergens, it seems questionable that it can prevent the appearance of allergic asthma.

On the other hand, lung function in a diabetic patient is inversely proportional to glycaemia, and to the duration and severity of disease, irrespective of other factors like obesity or exposure to tobacco smoke.^{9,12} This deterioration is conditioned by several mechanisms¹³: micro-angiopathy of capillary and arteriolar lung vessels, low-grade inflammation, autonomic neuropathy of the respiratory muscles, loss of the elastic recoil secondary to the glycosylation of the collagen of the lung parenchymal, hypoxia induced by insulin resistance, and low-birth weight.

Adults with Type-2 diabetes have a 3–10% reduction in lung function (FVC more consistently than FEV1) in comparison to adults without diabetes, irrespective of whether they have obesity or exposure to tobacco smoke.¹⁴ This deterioration is even more relevant in Type-2 diabetes than in Type-1 diabetes, and it would supposedly predispose to the trend to develop a restrictive pattern. It has also been speculated that the lung would be a potential target organ in diabetes, in which poor glycaemic control and the duration of the disease would accelerate the physiological deterioration of the lung function as time goes by.

Post-mortem studies in diabetic patients reveal a thickening in the alveolar epithelium and in the basal membrane of the alveolar capillary.¹⁵ The reduction of capillary blood volume found in those patients suggests the presence of a micro-angiopathy, which entails a ventilation/perfusion alteration and the consequent appearance of badly ventilated lung areas. The concomitance of respiratory membrane thickening together with the ventilation/perfusion disturbance suggests an upset in the diffusion capacity in diabetic patients. Furthermore, the addition of anaemia, a quite common problem in diabetic patients with chronic renal failure, would explain the decrease in the DLCO. In addition, the diabetic polyneuropathy potentially affecting the respiratory muscles would worsen the respiratory neuromuscular function. The decrease of the diaphragmatic contractility would be explained by the axonal loss of the phrenic nerve.

The factors related with the rise in the prevalence of Type-1 diabetes and asthma are largely unknown. However, potential common mechanisms have been involved in the pathogenesis of both diseases. For example, it has been suggested that the infestation by extracellular parasites more frequent in developing countries would have some protective effect against asthma and diabetes.¹⁶ The role of Toll-like receptors (TLR) in the stimulation of the innate and acquired immune system, such as, for example, the stimulation of the TLR2 by the P40 protein of the *Klebsiella pneumoniae*, which prevents the appearance of both asthma and diabetes in non-obese prone-diabetic mice (NOD) with a high genetic predisposition to suffer from both diseases, would provide plausible support to the hygienic theory.¹⁷ But we still have a long and winding road ahead

until all mechanisms behind the development of asthma and diabetes have been unravelled. Until then, the possible relation and potential up- or down-regulative interactions between asthma and diabetes should be observed with caution.

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