Obese Asthma Syndrome: Multiple Inflammatory Patterns and A Key Solution

Bantulà M[1,2], García A[3], Picado C[2,3], Arismendi E[1,2,3]
[1]*Department of Pulmonology, Hospital Clinic, Universitat de Barcelona, Barcelona, Spain*
[2]*Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Universitat de Barcelona, Barcelona, Spain*
[3]*Centro de Investigaciones Biomédicas en Red de Enfermedades Respiratorias (CIBERES), Madrid, Spain*
**These authors contributed equally as first authors*

J Investig Allergol Clin Immunol 2025; Vol. 35(4)
doi: 10.18176/jiaci.1071

Key words: Asthma. Obesity. Inflammation. Phenotype. Cluster.

Palabras clave: Asma. Obesidad. Inflamación. Fenotipo. Grupo.

Obesity frequently complicates the pathobiology, diagnosis, and management of asthma. Traditionally, obese asthma patients have been classified as presenting either early-onset obese asthma, characterized by atopy and type 2 inflammation, or late-onset, noneosinophilic, obese asthma [1]. Obese asthma syndrome reflects these heterogeneous phenotypes in obesity-associated asthma [2].

In late-onset obesity-associated asthma, dominant non-T2 neutrophilic inflammation is likely driven by cytokines such as IL-17A and TGF-β, key mediators of neutrophilic airway inflammation. However, studies suggest more marked recruitment of eosinophils to the lung in obese asthma patients than in their lean counterparts, with higher eosinophil levels in the airway submucosa despite low sputum eosinophils. Hence, the role of eosinophils in obese asthma syndrome remains unclear [3-6].

Weight loss, either through diet or through bariatric surgery (BS), has a beneficial effect on asthma control, reducing exacerbations and improving lung function in patients with asthma and comorbid obesity [2].

We hypothesized that the beneficial effects of weight loss are independent of the characteristics of the underlying inflammatory pattern. We aimed to evaluate the effect of weight loss on several cytokines and on $CD4^+$ T-cell phenotypes in patients with nonobese asthma (NOA) and patients with obese asthma (OA), before and after BS.

Thirty-five asthma patients (21 OA with body mass index [BMI] ≥30 kg/m^2 and 14 NOA <30 kg/m^2) and 33 age- and sex-matched healthy controls (HCs) (BMI <25 kg/m^2) were included. Patients with biological asthma treatments were excluded. We measured various cytokines and classified patients as having a type 1 helper T cell (T_H1), T_H17 (non-T2 inflammation), or T_H2 (T2 inflammation) inflammatory pattern, according to the presence of each of their most representative cytokines, that is, IFN-γ, IL-4, and IL-17A, respectively. The study was approved by the Ethics Committee of Hospital Clínic, Barcelona, Spain (2018/4015) (See Supplementary Files).

We first analyzed cytokine expression. NOA and OA patients presented higher levels of IFN-γ, IL-17A, and thymic stromal lymphopoietin (TSLP) (all P<.005) than HCs. NOA patients also had higher levels of IL-13 and IL-1b than HCs, and OA patients presented higher levels of IL-8 than both NOA patients and HCs (all P<.005). Significant correlations between BMI, cytokines, and pulmonary function were found (see supplementary files).

Second, we analyzed $CD4^+$ T lymphocyte phenotypes, namely, T_H1, T_H17 (non-T2), and T_H2 (T2), by measuring the median fluorescence intensity of IFN-γ, IL-4, and IL-17A, respectively. A predominantly T_H2 inflammatory profile was observed in asthma groups compared to HCs; the difference was statistically significant only in NOA patients (P=.0260). T_H17-mediated inflammation was more pronounced in OA than in NOA patients (P=.0080). No differences were found in the T_H1 inflammatory signature between HCs, NOA, and OA patients (Figure, A).

Analysis of the levels of IFN-γ, IL-4, and IL-17A in OA patients identified 3 clusters: cluster 1, which comprised patients with high IL-17 but low IL-4 and IFN-γ; cluster 2, which comprised patients with high IL-17 and IL-4 and low IFN-γ levels; and cluster 3, which comprised patients with low IL-17, IL-4, and IFN-γ levels.

Six months after BS, T_H2, and T_H17 inflammation decreased significantly (both P=.0313). T_H1 inflammation remained unchanged (Figure, B).

In this preliminary study, we assessed the inflammatory profiles of OA and NOA patients and report 3 main findings. First, patients with asthma (both OA and NOA) present a high dispersion of cytokine serum levels. Second, in some patients, various cytokine profiles may combine, leading them to be grouped into different asthma clusters. And third, weight loss after BS, reduced inflammation independently of the obese asthma cluster.

Regarding proinflammatory cytokines, INF-γ and IL-17A levels were higher in OA and NOA patients than in HCs, probably reflecting an underlying inflammatory environment with a T_H1 and T_H17 response in all the asthma patients, independently of their BMI [3].

Only NOA patients presented higher IL-13 levels than HCs, suggesting, together with a higher eosinophil count than HCs and OA patients, a T2-driven response, in contrast to the more commonly dominant non-T2 (T_H1 and T_H17) responses found in obesity-related asthma [7]. This is supported by previous findings from our group [8], where IL-5, a crucial marker of T2 inflammation, was only significantly increased in NOA patients.

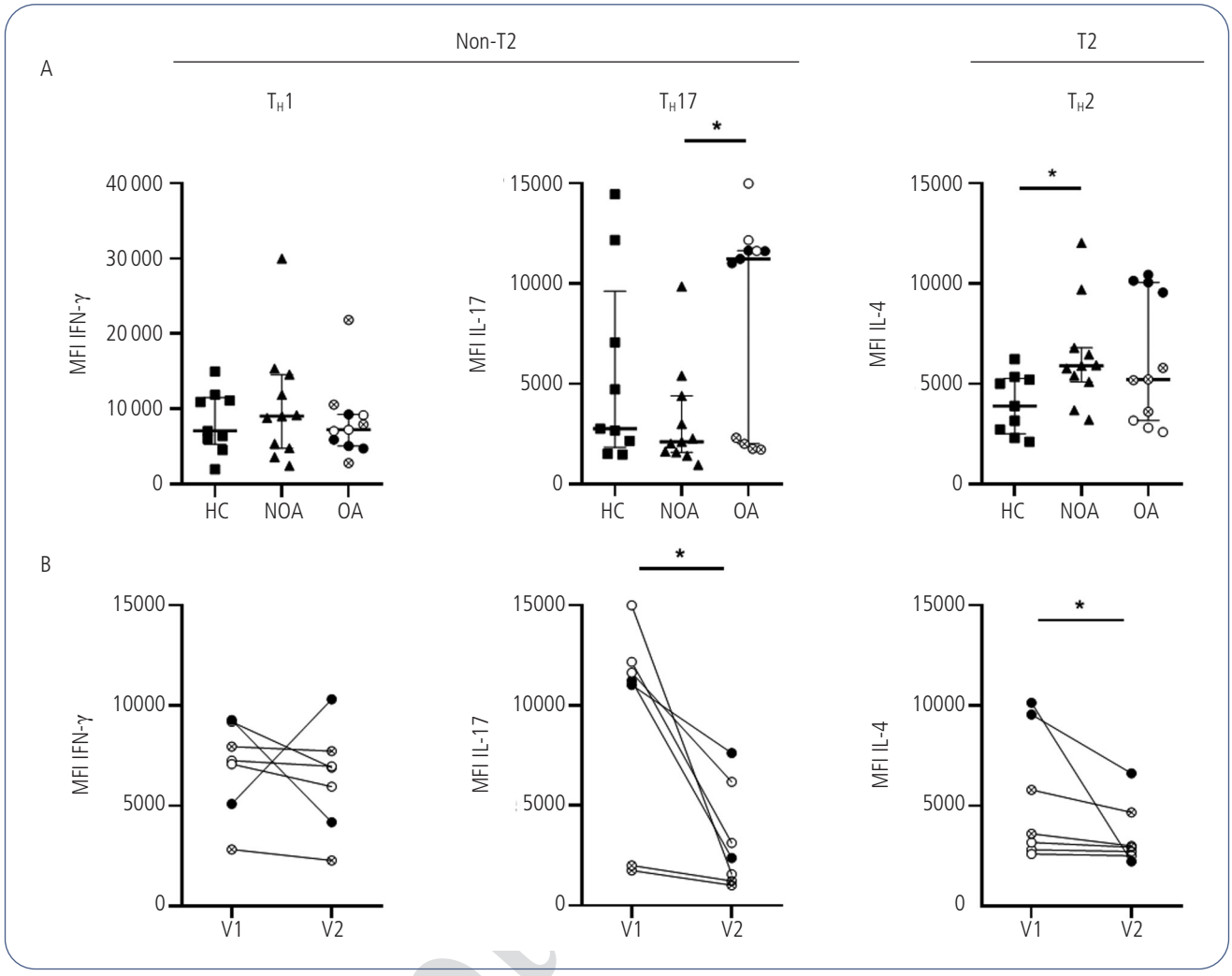

Figure. Median fluorescence intensity (MFI) of IFN-γ, IL-4, and IL-17 median fluorescence intensity (MFI) in $CD4^+$ T-cell subsets. A, Baseline comparison of MFI between healthy controls (HC) (squares), nonobese asthma patients (NOA) (triangles), and obese asthma patients (OA) (circles). OA patients are grouped up into 3 clusters based on their cytokine predominance profile. Cluster 1 (blank circle) patients have high IL-17 but low IL-4 and IFN-γ. Cluster 2 (filled circle) comprises patients with high IL-17 and IL-4 and low IFN-γ. Cluster 3 (crossed circle) comprises patients with low IL-17, IL-4 and IFN-γ. B, MFI in obese asthma patients before (V1) and 6 months after bariatric surgery (V2). T_H indicates helper T. V1, visit 1; V2, visit 2. Data are presented as median (IQR) and individual values..

OA and NOA patients had higher levels of the alarmin TSLP. In addition, a positive correlation was observed between TSLP and BMI, consistent with TSLP playing its role higher up in the inflammatory cascade than other cytokines and, therefore, being present in different asthma clusters.

Analysis of $CD4^+$ T_H profiles and the different asthma clusters in the study population reveals interesting results. First, we found 3 clusters that group patients with different inflammatory profiles. Cluster 1 comprised patients with high IL-17 but low IL-4 and IFN-γ levels, suggesting a predominance of T_H17 inflammation, as reported elsewhere for obese asthma patients [3,9]. Cluster 2 comprised patients with high IL-17 and IL-4 and low IFN-γ levels, thus revealing a mixed T_H17 and T_H2 inflammatory profile. Consequently, different inflammatory patterns may coexist in the same individual, with both T_H2 and T_H17 cytokines playing a role in the pathogenesis of obesity-related asthma. Finally, patients with low IL-17, IL-4, and IFN-γ levels made up Cluster 3, where other cytokines may have been responsible for the underlying inflammation. This lack of representation of a T_H1 profile may be a potential limitation of the study. However, all these results reflect the complexity of obese asthma syndrome [2,10].

The effect of BS was studied at 6 months in OA patients. Although IFN-γ values remained unchanged, IL-4 and IL-17A levels decreased significantly after BS. Weight loss, achieved through lifestyle changes, GLP-1 agonists, or BS reduces asthma exacerbations, airway hyperresponsiveness, and systemic inflammation, improving obesity-related asthma regardless of the predominant endotype [2,11,12]. In summary, despite the limited number of patients included, our results lay the foundation for further research and emphasize that different endotypes may coexist in the same patient, potentially explaining variability in response to treatment.

Most importantly, regardless of the cluster an obese asthma patient belongs to, weight loss improves their inflammatory profile.

Acknowledgments

We thank Helena Kruyer for her help in the translation of the paper.

Funding

The authors declare that no funding was received for the present study.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

References

1. Dixon AE, Que LG. Obesity and Asthma. Semin Respir Crit Care Med. 2022;43(5):662-74.
2. Peters U, Dixon AE, Forno E. Obesity and asthma. J Allergy Clin Immunol. 2018;141(4):1169-79.
3. Maggi E, Parronchi P, Azzarone BG, Moretta L. A pathogenic integrated view explaining the different endotypes of asthma and allergic disorders. Allergy. 2022;77(11):3267-92.
4. Cosmi L, Liotta F, Maggi E, Romagnani S, Annunziato F. Th17 cells: new players in asthma pathogenesis. Allergy. 2011;66(8):989-98.
5. Lessard A, Turcotte H, Cormier Y, Boulet LP. Obesity and asthma: a specific phenotype? Chest. 2008;134:317-23.
6. Desai D, Newby C, Symon FA, Haldar P, Shah S, Gupta S, et al. Elevated sputum interleukin-5 and submucosal eosinophilia in obese individuals with severe asthma. Am J Respir Crit Care Med. 2013;188(6):657-63.
7. Kuruvilla ME, Lee FE, Lee GB. Understanding Asthma Phenotypes, Endotypes, and Mechanisms of Disease. Clin Rev Allergy Immunol. 2019;56(2):219-33.
8. Bantula M, Tubita V, Roca-Ferrer J, Mullol J, Valero A, Bobolea I, et al. Differences in inflammatory cytokine profile in obesity-associated asthma: effects of weight loss. J Clin Med. 2022;11:1-19.
9. Jackson DJ, Busby J, Pfeffer PE, Menzies-Gow A, Brown T, Gore R, et al. Characterisation of patients with severe asthma in the UK Severe Asthma Registry in the biologic era. Thorax. 2021;76:220-7.
10. Arismendi E, Bantulà M, Picado C. Obese Asthma Syndrome: Much Work to Do. Arch Bronconeumol. 2023;59(8):473-5.
11. Marantos G, Daskalakis M, Karkavitsas N, Matalliotakis I, Papadakis JA, Melissas J. Changes in metabolic profile and adipoinsular axis in morbidly obese premenopausal females treated with restrictive bariatric surgery. World J Surg. 2011;35(9):2022-30.
12. Nguyen DV, Linderholm A, Haczku A, Kenyon N. Obesity-related, metabolic asthma: a new role for glucagon-like peptide 1 agonists. Lancet Respir Med. 2017;5(3):162-4.

Manuscript received September 26, 2024; accepted for publication January 30, 2025.

Ebymar Arismendi
C/Villarroel, 170
08036 Barcelona, Spain
E-mail: earismen@clinic.cat