IL1R2 Gene Expression Is Downregulated in Obesity-Associated Asthma

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IL-1R2 is the first decoy receptor identified in the IL-1 family. In contrast to other family members, it cannot trigger signal transduction following interaction with its ligands. Regulating IL-1R2 expression helps counterbalance the exacerbated inflammation triggered by endogenous and exogenous stimuli [1].

The NLRP3 inflammasome is an intracellular sensor that detects harmful signals, representing a key component of innate immune responses [2]. Activated NLRP3 interacts with caspase-1, which cleaves IL-1β into its active forms [2].

The NLRP3 inflammasome is involved in the pathogenesis of airway inflammation in asthma [3,4]. IL-1β and caspase-1 are detected at high levels in the sputum and peripheral blood of asthma patients with neutrophilic airway inflammation [3]. Moreover, IL-1β in sputum predicts poor lung function in neutrophilic asthma [5].

Obesity is a risk factor for asthma, and obese asthma patients experience more severe symptoms and decreased responsiveness to existing therapies [6,7]. IL-1β is elevated in obese individuals' blood, resulting, at least in part, from the activation of caspase-1 and its assembly with the NLRP3 inflammasome by fatty acids [8].

Obese asthma patients have increased concentrations of IL-1β and NLRP3 in blood and sputum [9,10]. Activation of the NLRP3 inflammasome owing to a high-fat diet increases IL-1β production and enhances airway hyperreactivity [9]. The role of IL-1R2 in asthma and how obesity affects its expression remain unclear.

Obesity is associated with increased inflammation and oxidative stress, which are closely related and fuel each other [11]. The action of IL-1R2 as a decoy receptor antagonizing IL-1β proinflammatory effects supports the hypothesis that obesity, via IL-1R2 downregulation, may enhance inflammatory responses and oxidative stress in patients with comorbid asthma and obesity.

We recruited 22 obese asthmatic patients (OAs) (body mass index [BMI] ≥30 kg/m^2), 12 nonobese asthmatic patients (NOAs) (BMI <25 kg/m^2), 11 obese nonasthmatic patients (ONAs), and 13 nonobese nonasthmatic controls. The

clinical characteristics of the participants are summarized in Supplementary Table 1. The study was approved by the Ethics Committee of Hospital Clínic of Barcelona (2018/4015), and all patients gave their informed consent to participate.

Ten milliliters of whole blood was collected from each patient, and peripheral blood mononuclear cells (PBMCs) were isolated using Lymphoprep™ (Stem Cell™). One microgram of mRNA isolated from PBMCs using TRIzol (Life Technologies) was converted into cDNA using the High-Capacity cDNA Reverse Transcription Kit (Thermo Fisher). Final cDNA was diluted 10-fold prior to use in qPCR. IL-1R2 expression was analyzed via real-time qPCR in the Viia7 Real-Time PCR system (Applied Biosystems). Specific mRNA expression was normalized against the *18SrRNA* and *GAPDH* genes.

Moreover, 8-isoprostane in serum was analyzed as a marker of oxidative stress using an enzyme-linked immunosorbent assay kit (Cayman Chemical).

The results are expressed as median (IQR). Nonparametric comparisons were performed using the Mann-Whitney test. Statistical analyses were performed using GraphPad Prism (version 8.4) with the α level set at $P<.05$.

We found that expression of the *IL1R2* gene was elevated (almost statistically significant) in NOAs with respect to the controls. In contrast, the expression of *IL1R2* was significantly lower in both OAs and ONAs than in NOAs and controls (Figure, A). *IL1R2* gene expression levels were inversely correlated (r=–0.439, $P<.0006$) with the BMI of all participants (Figure, B). IL-1R2 levels were higher in severe asthma patients, both with and without obesity, than in mild/moderate asthma patients, although the differences were not statistically significant (data not shown).

Serum 8-isoprostane levels were significantly higher in ONAs than in OAs, NOAs, and controls. No differences were found between OAs and NOAs with respect to the controls or between OAs and NOAs (Figure, C).

IL-1R2 expression and serum 8-isoprostane levels were positively correlated (r=0.4081, $P<.002$) (Figure, D).

Patients with comorbid asthma and obesity have more severe disease and are less responsive to therapy [6]. Weight loss results

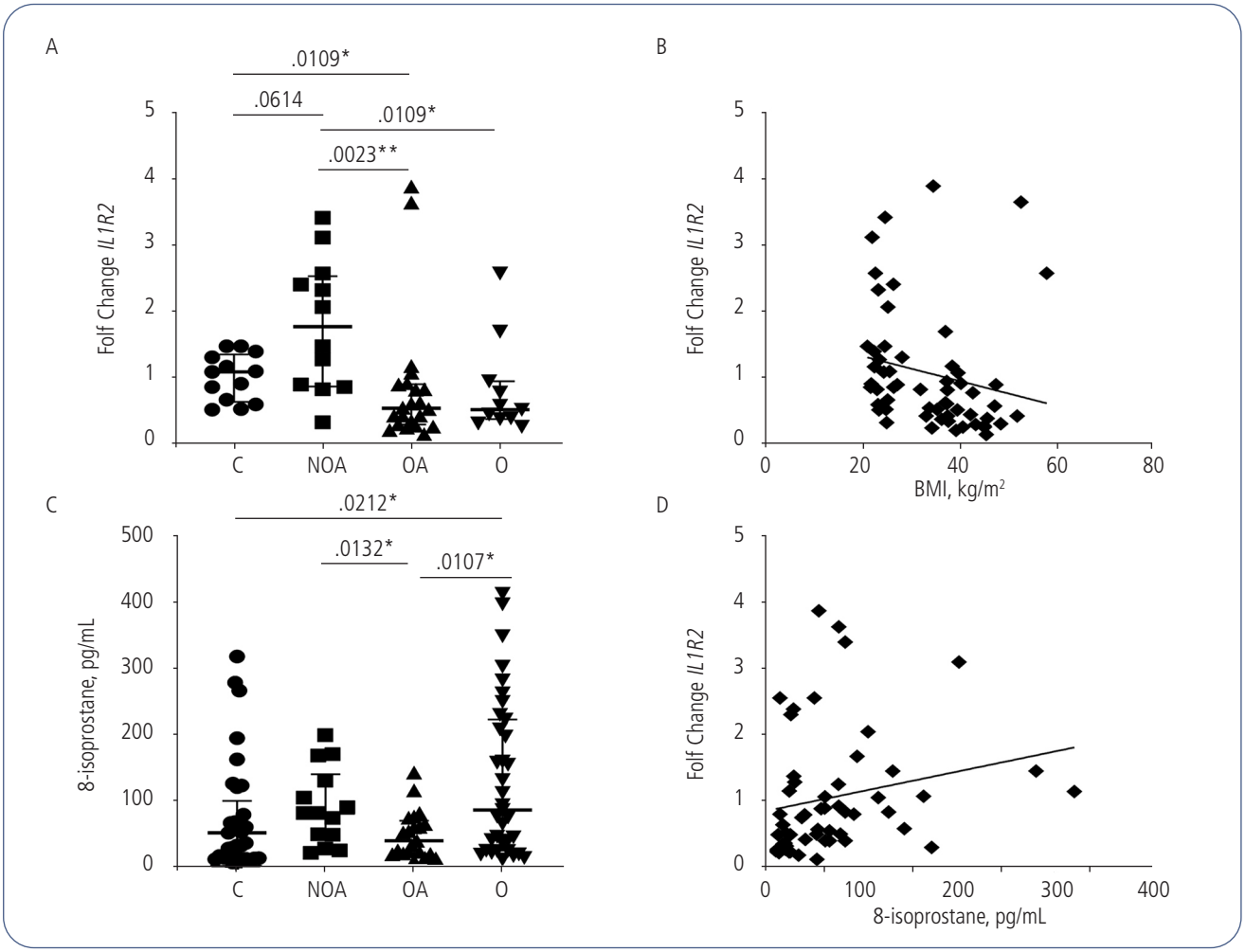

Figure. *IL1R2* gene expression and serum 8-isoprostane levels. A, Differences in *IL1R2* expression expressed as fold change (FC) between nonasthmatic nonobese controls (C), nonobese asthmatic patients (NOA), obese asthmatic patients (OA), and nonasthmatic obese (O) patients. B, Negative correlation (r=–0.439, $P<.0006$) between *IL1R2* expression and body mass index (BMI). C, Comparison of serum 8-isoprostane levels between nonasthmatic nonobese (C) controls, nonobese asthmatic patients (NOA), obese asthmatic patients (OA), and nonasthmatic obese patients (O). D, Positive correlation (r=0.4081, $P<.002$) between serum 8-isoprostane levels and *IL1R2* gene expression. Data presented as individual values and median (IQR). Mann-Whitney test for differences between groups and Spearman rank method for correlation data.

in improved clinical and lung function and better response to corticosteroid therapy [6,12]. Given the potentially relevant role that the NLRP3 inflammasome seems to play in asthma and obesity [3,5,6,9,10], we investigated expression of IL-1R2, a decoy receptor with an important role in counterbalancing IL-1β–related exacerbated inflammatory responses [1,2].

Our data show that obesity markedly downregulates *IL1R2* expression in asthmatic and nonasthmatic individuals. To our knowledge, this work is the first study to implicate *IL1R2* in the mechanisms potentially linking asthma and obesity-related inflammation. However, it is unclear whether the combination of obesity and asthma necessarily causes a synergistic effect, leading to even greater oxidative stress [13]. The results of the present study show that systemic oxidative stress differs significantly between obesity and asthma.

Although both diseases are often considered inflammatory diseases, in asthma, the inflammatory process predominantly affects the airways, with limited systemic involvement, whereas the impact of obesity-dependent inflammation spreads widely from adipose tissue to affect other organs and systems, seriously altering whole-body homeostasis. Elevated 8-isoprostane levels have been found in samples of exhaled breath condensate and induced sputum from asthma patients, revealing that, in contrast to obesity, the inflammatory process in asthma is predominantly local rather than systemic [14,15].

Interestingly, the finding of lower serum levels of 8-isoprostane in OAs than in ONAs suggests that asthma helps downregulate the intensity of obesity-dependent systemic oxidative stress. We are tempted to speculate that the mechanisms that contribute to regulating excessive ROS release in the airways of asthma patients counteract the systemic oxidative stress associated with obesity.

Our study has several limitations, including the relatively small number of patients evaluated: the results need to be tested in a larger cohort. Similarly, we did not use induced sputum to analyze the possible differences that distinct asthma phenotypes may have for the variables studied.

With all these limitations in mind, the results of this study reveal the complex interrelation between asthma and obesity. On the one hand, obesity downregulates the expression of the anti-inflammatory IL-1R2 receptor in asthma patients, while on the other, asthma contributes to reducing 8-isoprostane levels in obese asthma patients.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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