

# Continuous positive airway pressure therapy suppresses inflammatory cytokines and improves glucocorticoid responsiveness in patients with obstructive sleep apnea and asthma: A case–control study

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## Abstract:

**CONTEXT:** Asthma and obstructive sleep apnea (OSA) are prevalent respiratory disorders that frequently coexist. Continuous positive airway pressure (CPAP) therapy is the standard treatment for OSA. However, its effects on systemic inflammation and glucocorticoid responsiveness in OSA patients with asthma are largely unknown.

**AIMS:** To examine the potential role of CPAP therapy in reducing systemic inflammation and improving glucocorticoid responsiveness in asthmatic patients with OSA.

**SETTINGS AND DESIGN:** A case–control study was conducted at the respiratory and sleep clinics involving patients with OSA and patients with asthma and OSA.

**METHODS:** The levels of inflammatory asthma biomarkers (interleukin [IL]-4, IL-17A, IL-8, IL-2, and interferon- $\gamma$  [IFN- $\gamma$ ]), and glucocorticoid receptors (GR)- $\alpha$  and GR- $\beta$ , were determined to compare systemic inflammation and glucocorticoid responsiveness between pre- and post-1-month CPAP treatment in both groups.

**STATISTICAL ANALYSIS:** The Wilcoxon signed-rank test was used to compare inflammatory biomarkers before and after CPAP therapy.  $P < 0.05$  considered statistically significant. The analysis was performed using SPSS.

**RESULTS:** Recruited patients ( $n = 47$ ), 51% ( $n = 24$ ) had OSA and 49% ( $n = 23$ ), had OSA with asthma. Interestingly, the blood levels of IL-17 and IL-8 were significantly decreased post-CPAP therapy in OSA patients, whereas IL-4, IL-17, and IFN- $\gamma$  were significantly reduced post-CPAP treatment in OSA patients with asthma. Remarkably, CPAP therapy improved glucocorticoid responsiveness in asthmatic patients with OSA, but not in the OSA group and an increase in the GR- $\alpha$ /GR- $\beta$  ratio was noted post-CPAP therapy.

**CONCLUSIONS:** Continuous positive airway pressure therapy improved responsiveness to glucocorticoid treatment and demonstrated a suppressive effect on proinflammatory cytokines in asthmatics with OSA.

## Keywords:

Asthma, continuous positive airway pressure (CPAP), cytokines, glucocorticoids, inflammation, inflammatory biomarkers, obstructive sleep apnea, systemic

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The global prevalence rate of asthma and obstructive sleep apnea (OSA) has been increasing.<sup>[1-3]</sup> In the (UAE), The prevalence of asthma and OSA was estimated to be 12.1%<sup>[4]</sup> and 20.9%,<sup>[5]</sup> respectively. While asthma therapy, including corticosteroid, may have beneficial effects on OSA patients, especially the pediatric population,<sup>[6-8]</sup> evidence from clinical trials are still lacking.

CPAP therapy, a conventional treatment for OSA, has been demonstrated to enhance clinical outcomes,<sup>[9-11]</sup> and minimize the use of rescue bronchodilators in asthmatic patients with OSA.<sup>[9]</sup> Since asthmatics with OSA exhibit poor response to glucocorticosteroid treatment, this study aimed to examine the potential role of CPAP therapy in reducing systemic inflammation and improving glucocorticoid responsiveness in asthmatic patients with OSA.

## Methods

### Study participants

A case-control study was conducted at the respiratory and sleep clinics at Rashid Hospital, Dubai, UAE. This study was approved by Dubai Scientific Research Ethics Committee (DSREC-10/2015\_02), Rashid Hospital, Dubai Health Authority, UAE. The study was carried out among patients with confirmed OSA with no asthma (Group 1) and patients with confirmed OSA and asthma (Group 2). Potentially suitable patients for the study were identified and recruited by the consulting physicians. They were informed about the study and written informed consent was obtained from all study participants.

Inclusion criteria for patients with OSA alone (Group 1) were: (1) Physician-diagnosed moderate to severe OSA with oxygen desaturation index >10 per hour or apnea-hypopnea index (AHI) of >15 per hour during an overnight sleep study; (2) CPAP naïve subjects or patients who previously received CPAP therapy with 2-week washout period before enrolment. Exclusion criteria included: (1) Current smokers and those who suffer from other chronic respiratory diseases, including asthma; (2) other known significant clinical conditions according to the clinical assessment of respiratory or sleep consultants; and (3) patients regarded unfit for any other clinical reason by their respiratory or sleep physicians and those who refused to participate.

Inclusion criteria for patients with OSA and asthma (Group 2) included: (1) Physician-diagnosed moderate-to-severe asthma defined according to the International ERS/ATS guidelines on definition, evaluation, and treatment of severe asthma<sup>[12]</sup> and OSA; (2) forced expiratory volume in 1 s (FEV1) >70%

predicted; (3) well-controlled asthma symptoms (i.e., Juniper asthma control score <1). Exclusion criteria included: (1) Current smokers and those who suffer from chronic respiratory diseases other than asthma and OSA; (2) asthma exacerbation and/or uncontrolled asthma at the time of recruitment; (3) other known significant clinical conditions according to the clinical assessment of respiratory or sleep consultants; and (4) patients regarded unfit for any other clinical reason by their respiratory or sleep physicians and those who refused to participate.

### Study design

This study comprises different tools to assess OSA symptom control and asthma symptom control, as well as clinical blood tests served as parameters for the comparison between pre- and post-CPAP treatment groups to document the efficacy of CPAP therapy in both patient groups. Patients were recruited from consultants' clinics after consultants' approval and after performing the routine checkup in the pulmonary/sleep clinic for their asthma and/or sleep control and symptoms. At the beginning of the study, the patients in all arms of the study were advised to adhere to the medications prescribed by their consultants. This in turn helped the research team to assure that any post CPAP improvement will be due to the CPAP and not to the prescribed medications. At the time of recruitment, 4 ml of blood sample was obtained from each study participant after consent for the measurement of inflammatory biomarkers and glucocorticoid responsiveness assessment. All OSA patients (with and without asthma) underwent 1 month of home treatment with CPAP at night. CPAP compliance was reinforced at regular intervals by a nurse from pulmonary/sleep clinic contacting patients and encouraging them to adhere to CPAP use not <4-h per night after a month of home CPAP treatment, patients visited the pulmonary/sleep clinic for follow-up after a month CPAP usage. CPAP adherence was checked by downloading the flashcard data for each participant. All patients in our study adhered to CPAP usage of more than 4 h/night. The asthmatic patients were continued on asthma treatment based on their severity of asthma as per GINA guidelines and as per the consultants' opinion<sup>[13-16]</sup> Then, a blood sampling was repeated in all participants to assess inflammatory biomarkers and glucocorticoid responsiveness post 1-month CPAP treatment.

### Multiplex enzyme-linked immunosorbent assay

The inflammatory biomarkers, interleukin (IL)-4, IL-17A, IL-8, IL-2, interferon- $\gamma$  (IFN- $\gamma$ ), and glucocorticoid receptors (GR- $\alpha$  and GR- $\beta$ ), were used to compare systemic inflammation and glucocorticoid responsiveness before and after CPAP therapy. These markers were

quantified in blood serum samples using the multiplex assay kit (Bio-rad) and the Bio-Plex workstation based on Luminex technology, Meakins-Christie Laboratories, Montreal, Canada.

### Statistical analysis

The sample size was determined based on previous OSA and asthma studies<sup>[9,10,17]</sup> Continuous variables were presented as mean  $\pm$  standard deviation (SD), and categorical variables were reported as counts and percentages.<sup>[18]</sup> Wilcoxon signed-rank test was used to compare the inflammatory biomarkers before and after CPAP therapy separately for OSA and OSA with asthma groups. All analyses were two-sided, with a  $P < 0.05$  considered statistically significant. The analysis was performed using SPSS Version 26 (IBM Corporation, Chicago, USA) and GraphPad Prism 8 (GraphPad Software Inc., San Diego, USA) software.

## Results

### Clinical characteristics

Between January 2016 and September 2019, a total of 85 patients were admitted to the respiratory and sleep clinics at Rashid Hospital. Of these, 47 patients met the inclusion criteria and agreed to participate in the study and thus were recruited. Among these patients, 51% ( $n = 24$ ) had OSA, while 49% ( $n = 23$ ) had OSA with

asthma. The study sample included 30% ( $n = 14$ ) males and 70% ( $n = 33$ ) females, and the mean age ( $\pm$  SD) of these patients was 55 years ( $\pm 11$ ) (range 26–72 years). Table 1 displays patient demographics across Group 1 and Group 2. There was no significant difference in age and body mass index between the two groups [Table 1].

### Continuous positive airway pressure therapy suppresses inflammatory cytokines in obstructive sleep apnea patients with or without asthma

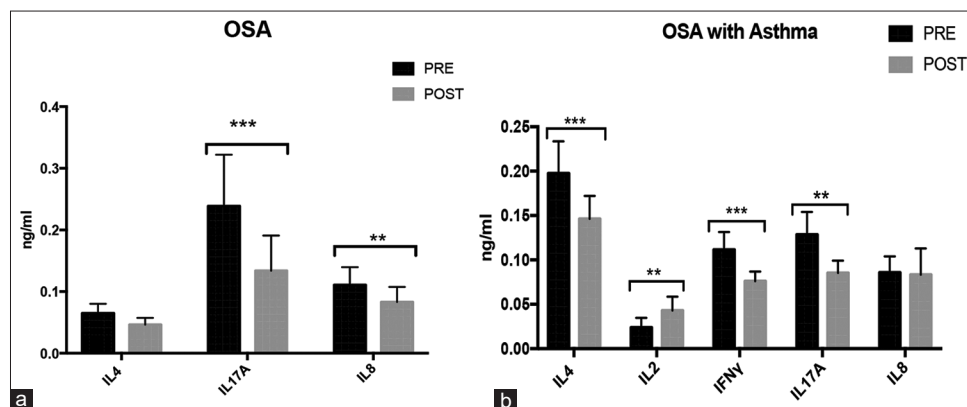
The inflammatory cytokine profile of patients with OSA [Figure 1a] and OSA with asthma [Figure 1b] was assessed before and following CPAP therapy. Serum levels of IL-2, IL-4, IL-17A, IL-8, and IFN- $\gamma$  were determined using enzyme-linked immunosorbent assay. The levels of IL-17 and IL-8 were significantly decreased post-CPAP therapy in OSA patients. IL-4 levels also decreased upon treatment; however, not to a significant extent [Figure 1a]. The pre- and post-CPAP data for IL-4, IL-17A and IL-8 in OSA patients were: IL-4: 0.04 ng/mL versus 0.02 ng/mL ( $P = 0.058$ ); IL-17: 0.03 ng/mL versus 0.02 ng/mL ( $P = 0.0002$ ); and IL-8: 0.07 ng/mL versus 0.05 ng/mL ( $P = 0.005$ ), respectively.

The levels of IL-4, IFN- $\gamma$ , and IL-17 were significantly reduced post-CPAP treatment in patients with OSA and asthma, while that of IL-2 was significantly increased [Figure 1b]. No change in the expression levels of IL-8 was noted upon CPAP therapy. The pre- and post-CPAP data for IL-4, IL-2, IFN- $\gamma$ , IL-17A, and IL-8 in OSA with asthma patients were: IL-4: 0.13 ng/mL versus 0.01 ng/mL ( $P = 0.0003$ ); IL-2: 0.006 ng/mL versus 0.011 ng/mL ( $P = 0.002$ ); IFN- $\gamma$ : 0.085 ng/mL versus 0.07 ng/mL ( $P = 0.0002$ ); IL-17A: 0.1 ng/mL versus 0.08 ng/mL ( $P = 0.004$ ); and IL-8: 0.047 ng/mL versus 0.045 ng/mL ( $P = 0.117$ ), respectively.

**Table 1: Patient demographics for groups 1 and 2**

	Group 1, OSA ( $n=24$ )	Group 2, OSA with Asthma ( $n=23$ )	$P$
Age (years), mean $\pm$ SD	52 $\pm$ 13	58 $\pm$ 8	0.105
Female, $n$ (%)	10 (44)	23 (96)	0.001
BMI (kg/m <sup>2</sup> ), mean $\pm$ SD	36 $\pm$ 7	41 $\pm$ 13	0.180

Student's  $t$ -test was used to compare the continuous data, and Chi-square test was performed for the categorical data. BMI=Body mass index, OSA=Obstructive sleep apnea, SD: Standard deviation



**Figure 1:** Effect of continuous positive airway pressure therapy on inflammatory cytokines in obstructive sleep apnea and obstructive sleep apnea with asthma groups. (a) In the obstructive sleep apnea group, there was a significant reduction in the expression levels of interleukin - 17A and interleukin-8 postcontinuous positive airway pressure therapy (interleukin-17A,  $P = 0.0002$  and interleukin-8,  $P = 0.005$ ). (b) In asthma with obstructive sleep apnea group, there was a significant reduction in the expression levels of interleukin-4, interleukin-17A, and interferon- $\gamma$  postcontinuous positive airway pressure therapy (interleukin-4,  $P = 0.0003$ ; interleukin-17A,  $P = 0.004$ ; interferon- $\gamma$ ,  $P = 0.0002$ ). However, the expression of interleukin-2 showed a significant increase postcontinuous positive airway pressure treatment ( $P = 0.002$ )

## Continuous positive airway pressure therapy improves glucocorticoid responsiveness in obstructive sleep apnea patients with asthma

The expression levels of GR, GR- $\alpha$  and GR- $\beta$ , can influence glucocorticoid responsiveness in patients. In OSA patients, the levels of GR- $\alpha$  were reduced after 1 month of CPAP therapy, with no change in GR- $\beta$  levels [Figure 2a]. Consequently, a trend of lower GR- $\alpha$ /GR- $\beta$  ratio was noted, but with no statistical significance. The serum levels of GR- $\alpha$  and GR- $\beta$  in OSA patients pre- and post-CPAP treatment were as follows: GR- $\alpha$ : 3.1 ng/ml versus 2.1 ng/ml ( $P = 0.0124$ ) and GR- $\beta$  0.2 ng/ml versus 0.22 ng/ml ( $P = 0.89$ ), respectively.

Interestingly, CPAP therapy showed the potential in improving glucocorticoid responsiveness in OSA patients with asthma. The levels of GR- $\alpha$  were significantly higher than that of GR- $\beta$  in this group of patients. Post-CPAP treatment, the expression of GR- $\alpha$  increased with no change in GR- $\beta$  levels [Figure 2b]. Consequently, an increase in the GR- $\alpha$ /GR- $\beta$  ratio was noted with CPAP therapy. The pre- and post-CPAP data for GR- $\alpha$  and GR- $\beta$  in OSA with asthma patients were: GR- $\alpha$ : 3.8 ng/ml versus 3.9 ng/ml ( $P = 0.0215$ ) GR- $\beta$ : 0.215 ng/ml versus 0.139 ng/ml ( $P = 0.29$ ), respectively. This indicates that CPAP therapy may improve steroid responsiveness in the OSA with asthma group, but not in the OSA group.

## Discussion

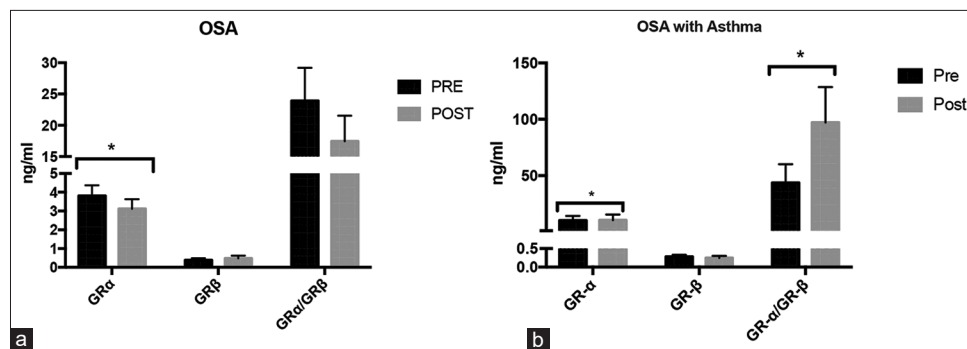
CPAP has been used in clinical practice to act as a pneumatic splint to treat upper airway obstruction in patients with OSA. Although CPAP therapy has been shown to improve asthma symptoms and response to steroid treatment,<sup>[19]</sup> nothing is known about the

potential mechanisms underlying this observation. To our knowledge, this is the first report to suggest the ability of CPAP therapy to suppress proinflammatory cytokines associated with asthma pathogenesis and to improve responsiveness to steroid therapy.

Our findings suggest that CPAP therapy reduces systemic inflammation in patients with OSA alone and those with asthma and OSA. IL-4, a key Th2 cytokine involved in asthma pathogenesis, was higher at baseline in the OSA with asthma group compared to the OSA group. Its levels were significantly reduced in the OSA with asthma group following CPAP treatment.

IL-17 is another proinflammatory cytokine involved in asthma pathogenesis. Elevated IL-17 levels have been implicated in the pathogenesis of both OSA<sup>[20,21]</sup> and asthma.<sup>[22,23]</sup> In fact, IL-17A was higher in the OSA group at baseline and was significantly reduced in both groups following CPAP treatment. CPAP therapy may thus contribute to reducing the inflammatory burden in these patients and improving their disease prognosis. The inhibitory effect of CPAP therapy on IL-4 and IL-17 expression in OSA patients with asthma might also suggest its ability to target both Th2-high and Th2-low/Th17 phenotypes of asthma and thereby regulate asthma pathogenesis.

Furthermore, CPAP also significantly inhibited the expression of IFN- $\gamma$  in OSA patients with asthma. Asthma patients were found to have elevated levels of IFN- $\gamma$ , with significantly higher concentrations in patients with uncontrolled asthma when compared to those with partially or fully controlled disease.<sup>[24]</sup> The reduction in IFN- $\gamma$  levels with CPAP therapy may contribute to better asthma control in patients with OSA and asthma. The expression of IL-2 showed a significant increase post-CPAP treatment. IL-2 is a marker for Th-1



**Figure 2:** Effect of continuous positive airway pressure therapy on glucocorticoid responsiveness in obstructive sleep apnea and obstructive sleep apnea with asthma groups. (a) In obstructive sleep apnea patients, there was a significant reduction in the levels of glucocorticoid receptors- $\alpha$ , with no change in glucocorticoid receptors- $\beta$  levels postcontinuous positive airway pressure therapy (glucocorticoid receptors- $\alpha$ ,  $P = 0.0124$ ; and glucocorticoid receptors- $\beta$ ,  $P = 0.89$ ). A reduced trend in glucocorticoid receptors- $\alpha$ /glucocorticoid receptors- $\beta$  ratio was noted but without statistical significance ( $P = 0.075$ ). (b) In asthma with obstructive sleep apnea patients, glucocorticoid receptors- $\alpha$  levels were much higher than that of glucocorticoid receptors- $\beta$ . The expression of glucocorticoid receptors- $\alpha$  showed a significant increase with no change in glucocorticoid receptors- $\beta$  levels postcontinuous positive airway pressure treatment (glucocorticoid receptors- $\alpha$ ,  $P = 0.0215$ ; and glucocorticoid receptors- $\beta$ ,  $P = 0.29$ ). Consequently, an increase in glucocorticoid receptors  $\alpha$ /glucocorticoid receptors- $\beta$  was noted with continuous positive airway pressure therapy ( $P = 0.021$ )



inflammation and the fact that it is increased in response to CPAP therapy may indicate switch from Th2 to Th1 immune profile.

The GR are responsible for mediating the widespread activity of glucocorticoids.<sup>[25]</sup> While GR $\alpha$  mediates the role of a ligand-dependent transcription factor, GR $\beta$  acts as a dominant-negative inhibitor of GR $\alpha$ -mediated transactivation. The expression levels of GR $\alpha$  are much higher than GR $\beta$  in most tissues.<sup>[26]</sup> However, increased GR $\beta$  expression has been associated with glucocorticoid resistance or hyporesponsiveness in diseases, such as asthma.<sup>[27]</sup> Therefore, the ratio of the expression of GR $\alpha$  to GR $\beta$  is one among the various parameters used to determine glucocorticoid responsiveness.<sup>[28]</sup> Interestingly, in asthma patients with OSA, the GR- $\alpha$  levels were significantly higher than GR- $\beta$ . CPAP therapy further boosted GR- $\alpha$  expression which may explain the improved glucocorticoid responsiveness observed in these patients upon CPAP therapy. Since asthma patients with OSA are associated with poor asthma control and steroid hyporesponsiveness, the ability of CPAP therapy to improve glucocorticoid sensitivity in this subset of patients may contribute to better disease management and improved quality of life. IL-17 is often associated with steroid hyporesponsiveness as well.<sup>[27]</sup> Obese asthmatics represent a phenotype similar to asthmatics with OSA in terms of their poor response to glucocorticoid therapy, and IL-17A induced a decrease in GR $\alpha$ /GR $\beta$  ratio in obese adipocytes.<sup>[29]</sup> Therefore, the ability of CPAP to reduce IL-17 levels in both OSA and OSA with asthma groups indicates its therapeutic potential in improving glucocorticoid responsiveness in addition to improving the inflammatory burden.

Bouloukaki *et al.* have previously reported that inflammatory markers (such as high-sensitivity C-reactive protein [hs-CRP], fibrinogen, erythrocyte sedimentation rate [ESR], and uric acid) significantly increased in patients with OSA without any known comorbidities and correlated with OSA severity.<sup>[30]</sup> In another study by Vicente *et al.*, they showed that CD4<sup>+</sup> T cells, IL-6, and IL-8 were higher in pharyngeal lavage (PHAL) of OSA patients than in snorers or healthy controls ( $P < 0.05$ ).<sup>[31]</sup> The AHI also correlated with CD4<sup>+</sup>, IL-6, and IL-8 in PHAL (all  $P < 0.05$ ). There were no differences in plasma inflammatory biomarkers between the study groups and no relationship between plasma and PHAL biomarkers. Furthermore, these biomarkers decreased significantly in PHAL but not in plasma after 1 year of CPAP therapy or surgery. On the other hand, Msaad *et al.* showed that markers of systemic inflammation, including hsCRP TLC and ESR, decreased significantly after 6 months of standardized treatment ( $P < 0.001$  for all comparisons).<sup>[32]</sup> Our study further reinforces a faster reduction in systemic

inflammation in OSA patients receiving CPAP therapy for 1 month.

Lafond *et al.* reported that the quality of life in asthma patients treated with CPAP improved from  $5.0 \pm 1.2$  at baseline to  $5.8 \pm 0.9$ .<sup>[17]</sup> In this study, nocturnal CPAP treatment did not alter airway responsiveness or FEV1 in subjects with stable mild-to-moderate asthma and newly diagnosed OSA. Literature suggests that CPAP helps in better control of asthma symptoms and hence, may explain the improved quality of life in OSA with asthma patients.<sup>[9-11]</sup> Based on our study results, another hypothesis could be postulated to explain the benefits of CPAP in patients with OSA and asthma, in that CPAP aids in better drug delivery to the peripheral lung which is the site of maximal inflammation and improved drug effectiveness through regulating the GR. Nevertheless, this hypothesis would need to be confirmed in large case-control trials.

In this study, we have introduced a distinct phenotype of asthma and sleep apnea which could benefit from alternative treatments including CPAP. This translation study presented the OSA as an independent inflammatory burden to asthma for which the inflammatory mediators are higher than asthma alone, hence then, treatment of OSA with CPAP not only improves OSA but also decreases the burden of inflammation on Asthma.

### Limitations

This study has several limitations. The follow-up period was relatively short, the patients sample size was limited, and the gender distribution was not uniform across study arms. However, patients were carefully selected to fulfill the study inclusion and exclusion criteria and the number was sufficient to detect differences between the groups. Future studies with a larger cohort, a third control group, and longer follow-up are needed to further validate the current study findings.

### Conclusions

This is the first report to show that CPAP therapy improved glucocorticoid responsiveness and might have a regulatory effect on the inflammatory profile of patients having coexistent asthma and OSA. Patients with OSA and asthma had a high inflammatory burden as compared to OSA patients; and application of CPAP therapy significantly reduced the inflammatory markers in this group. The observed reduction in inflammatory cytokines is mostly attributable to the regular use of CPAP since the treatment regimens for asthma patients were similar and as per the standard recommendation by GINA guidelines.

CPAP therapy also improved glucocorticoid responsiveness in the OSA with asthma group as it

increased the GR- $\alpha$  levels. Our study results prompt a larger sample size study involving similar groups but with a follow-up for a longer period of CPAP treatment to confirm the observed anti-inflammatory effect of CPAP and to better understand the mechanisms regulating the anti-inflammatory effect of CPAP treatment as well as its ability to regulate steroid receptors.

### Statement of significance

This study reveals for the first time that the use of CPAP therapy reduces systemic inflammation and improves glucocorticoid responsiveness in asthmatic patients with OSA. Our results have demonstrated a suppressive effect of CPAP therapy on proinflammatory cytokine expression as well as a regulatory effect on glucocorticoid receptor expression, suggesting a potential promising line of treatment.

### Preparation of the manuscript

This Manuscripts is prepared in accordance with "Uniform requirements for Manuscripts submitted to Biomedical Journals" developed by the International Committee of Medical Journal Editors.

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### Conflicts of interest

There are no conflicts of interest.

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