

Images in Allergy and Immunology

Celine Bergeron, MD, MSc,^a John Kimoff, MD,^{a,b} and Qutayba Hamid, MD, PhD,^a Editors

Obstructive sleep apnea syndrome and inflammation

Editor's note: This feature, Images in allergy and immunology, is designed to highlight current concepts of the immunopathology of allergic diseases and other common immunologically mediated diseases. The presentation will appear as sets of images that involve cross-pathology, histopathology, and molecular pathology and will cover a range of topics of interest to allergists and immunologists.

Obstructive sleep apnea syndrome (OSAS) is a prevalent disease affecting as much as 4% of the North American population.¹ OSAS is characterized by repeated episodes of upper airway obstruction during sleep, resulting in recurrent hypoxemia and sleep fragmentation. These in turn are associated with neurocognitive sequelae, cardiovascular complications, and metabolic syndrome.^{2,3} Current therapies aimed at increasing upper airway caliber during sleep include surgical interventions, oral appliances, and positive airway pressure. Systemic and airway inflammation has been recently linked to OSAS and is hypothesized to contribute to daytime sleepiness and the increased risk of cardiovascular complications and metabolic syndrome.

The underlying inflammation in OSAS has been attributed to upper airway mechanical tissue injury and to systemic hypoxemia. Systemic inflammation in OSAS is characterized by increased plasma levels of TNF- α , IL-6, C-reactive protein, IL-1 β , reactive oxygen species, and adhesion molecules^{4,5} (Table I). Intermittent hypoxemia occurring in OSAS can stimulate transcription factors such as nuclear factor- κ B and

TABLE I. Systemic and local inflammation in obstructive sleep apnea syndrome

Systemic inflammation	Local inflammation
↑ C-reactive protein	↑ IL-6
↑ IL-6	↑ 8-Isopentane
↑ TNF- α	↑ Neutrophils
↑ VEGF	↑ CD4 ⁺ T cells
↑ EPO	↑ CD8 ⁺ T cells
↓ Adiponectin	
↑ Reactive O ₂ species	
↓ Nitric oxide	

VEGF, Vascular endothelial growth factor; EPO, erythropoietin.

increase production of cytokines.⁶ Plasma levels of vascular endothelial growth factor and erythropoietin are increased in OSAS and are suggested to be an adaptive response to reduced blood oxygen through stimulation of erythrocyte production and neovascularization.⁷ There is still controversy over whether plasma adiponectin is elevated or decreased in OSAS.^{8,9} In OSAS, uvulopalatopharyngoplasty reduces plasma levels of TNF- α ,¹⁰ and therapy with continuous positive airway pressure decreases plasma levels of inflammatory mediators.^{11,12} Treatment of OSAS is known not only to improve sleepiness of the subjects but also to decrease the risk of cardiovascular complications. These effects have been hypothesized to be at least in part related to decreases in systemic inflammation associated with treatment. In support of this concept, treatment of patients with OSAS with the TNF- α antagonist (Etanercept; Immunex Corp, Seattle, Wash) was recently demonstrated to improve excessive daytime sleepiness significantly.¹³

Airway inflammation in OSAS has been assessed mainly in surgical specimens obtained from uvulopalatopharyngoplasty and tonsillectomy (Table I). Histological observations of uvular tissue from adult subjects with OSAS show structural alterations such as subepithelial edema,¹⁴ reduction of connective tissue,¹⁵ and excessive inflammatory cell infiltration.¹⁴ This inflammation and edema of the uvula contribute to the upper airway obstruction observed in OSAS. The number of leucocytes (CD45) is significantly higher in upper airway mucosa from OSA; among these plasma cells,¹⁴ CD4⁺ and CD8⁺ T cells¹⁶ predominate. More precisely, CD4⁺ and CD25⁺ T cells are increased in the muscular layer of soft palate and tonsil pillars of patients with OSAS. In upper airway mucosa, activated CD8⁺ T cells prevail¹⁶ (Fig 1-4). In uvula mucosa, higher CD4⁺ and CD8⁺ T cells correlate with body weight in subjects with OSAS,¹⁷ suggesting an influence of obesity (Fig 5).

Upper airway inflammation assessed by induced sputum shows a higher percentage of neutrophils and a lower percentage of macrophages in subjects with OSAS,¹⁸ whereas eosinophils and lymphocytes were not different from those in subjects without OSAS.

From ^athe Meakins-Christie Laboratories, McGill University; and ^bthe Respiratory Division, McGill University Health Center, McGill University.

Received for publication October 7, 2005; accepted for publication October 11, 2005.

Reprint requests: Qutayba Hamid, MD, PhD, McGill University, Meakins-Christie Laboratory, 3626 St Urbain Street, Montreal, H2X 2P2, Canada. E-mail: qutayba.hamid@mcgill.ca; maria.makroyanni@mcgill.ca.

J Allergy Clin Immunol 2005;116:1393-6.
0091-6749/\$30.00

© 2005 American Academy of Allergy, Asthma and Immunology
doi:10.1016/j.jaci.2005.10.008

1393

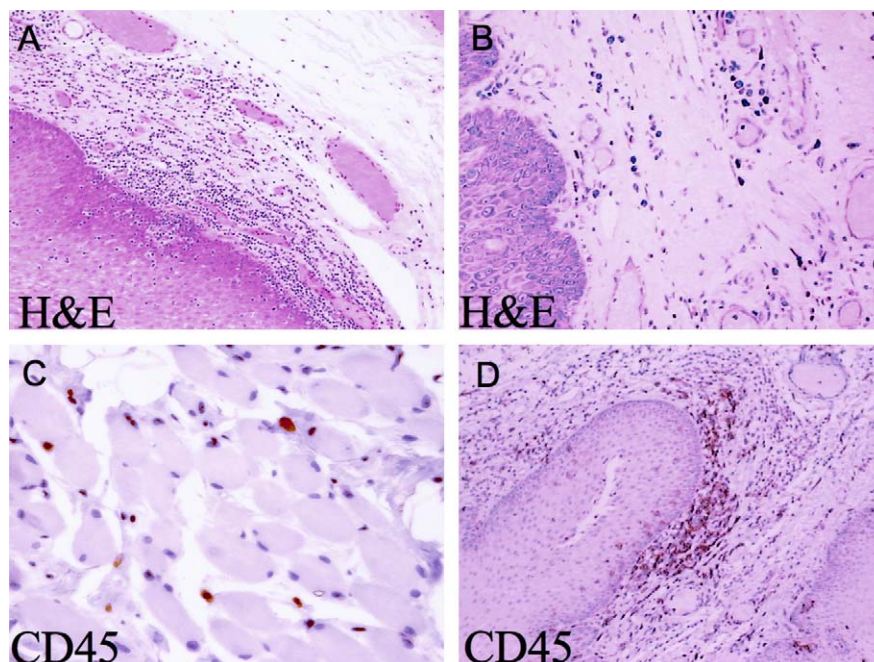


FIG 1. Inflammatory cells infiltration of the upper airway of OSAS. **A and B,** H&E of section from upper airways showing significant inflammatory cells infiltration of the mucosa and submucosa of subjects with OSAS. **C,** Representative example of CD45 immunostaining showing upper airway muscle infiltrated by leucocytes in subjects with OSAS. **D,** Immunostaining of submucosal infiltration with leucocytes (CD45⁺ cells) in subjects with OSAS.

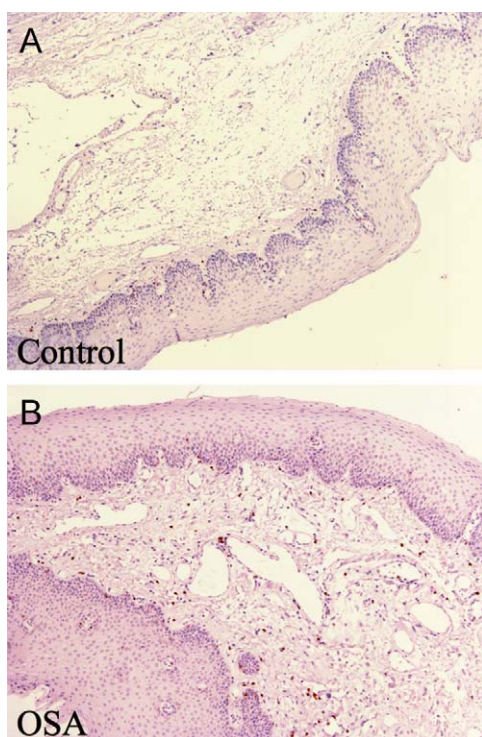


FIG 2. CD8⁺ T-cell infiltration in upper airways. **A,** Control subjects showing absence of CD8⁺ T cells. **B,** OSA subject showing significant infiltration of CD8⁺ T cells in the submucosa of upper airway.

IL-6 and 8-isopentane, measured in exhaled breath condensate, are elevated in subjects with OSAS compared with obese and healthy subjects.¹⁹ Furthermore, the level of IL-6 and 8-isopentane correlated positively with the apnea-hypopnea index. Nasal lavage fluid from subjects with OSAS compared with healthy controls show an elevated number of neutrophils and higher concentration of bradykinin and vasoactive intestinal peptide.²⁰ Taken together, these findings demonstrate that similar to systemic inflammation, airways in OSAS are characterized by inflammation and oxidative stress.

There are as yet only limited data evaluating the effects of anti-inflammatory therapy on upper airway function in OSAS. However, topical fluticasone produced a beneficial effect on apnea-hypopnea index in pediatric patients with OSAS.²¹ Recent work has also demonstrated increased expression of leukotriene receptors 1 and 2 in tonsillar tissue of children with OSAS compared with nonapneic controls.²² Treatment with a leukotriene antagonist improved measures of sleep-disordered breathing in this group.²³

Obstructive sleep apnea syndrome is associated with important neurocognitive sequelae and is a risk factor for cardiovascular disorders and metabolic syndrome.^{2,3} The high level of inflammatory mediators in OSAS has a potential role in the development of these complications. Local airway tissue inflammation is also present and likely contributes to upper airway mechanical and neuromuscular dysfunction, and may contribute to other processes including destabilization

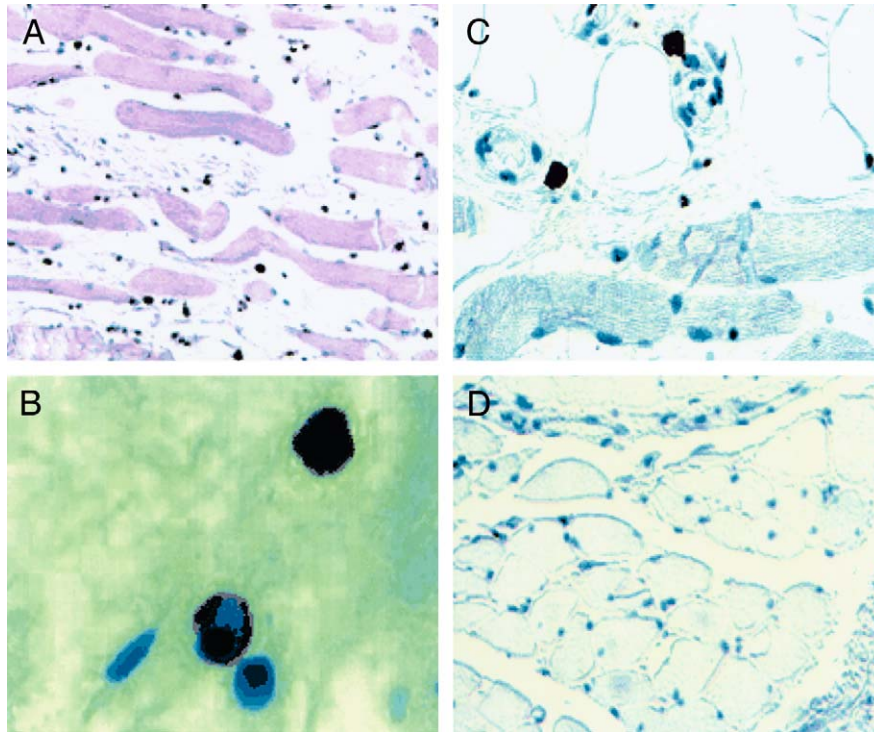


FIG 3. Inflammatory cells infiltration of the upper airway. **A**, CD4⁺ T-cell infiltration in the muscle layer in a subject with OSAS. **B**, High magnification of CD4⁺ T cells. **C**, CD25⁺ T cells in muscle layer of a subject with OSAS. **D**, CD4 staining in healthy subject. Reprinted with permission.¹⁶

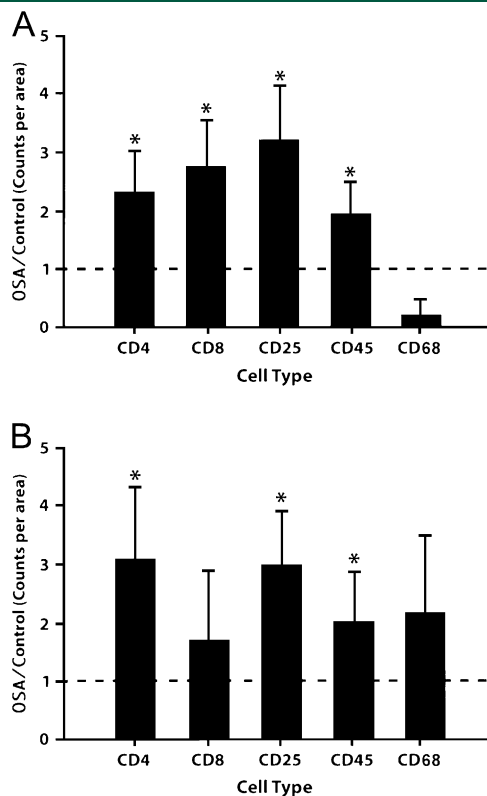


FIG 4. Ratio of inflammatory cells infiltration in subjects with OSAS and healthy subjects. **A**, Upper airway mucosa. **B**, Muscular layer of the upper airway. Reprinted with permission.¹⁶ * $P < .01$ OSAS vs control.

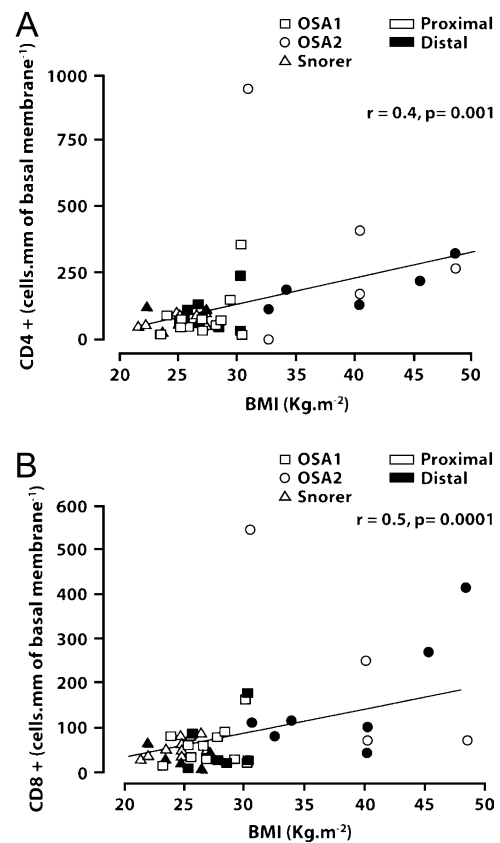


FIG 5. Correlation of CD4⁺ (**A**) and CD8⁺ (**B**) T cells with body mass index (BMI). Reprinted with permission.¹⁷

of asthma control. Further research is required to evaluate the relationship between systemic and airway inflammation and the mechanisms by which these contribute to the pathophysiology of OSAS, and to determine the therapeutic potential for anti-inflammatory treatment in this important condition.

REFERENCES

- Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. *N Engl J Med* 1993;328:1230-5.
- Phillips BG, Somers VK. Sleep disordered breathing and risk factors for cardiovascular disease. *Curr Opin Pulm Med* 2002;8:516-20.
- Vgontzas AN, Bixler EO, Chrousos GP. Sleep apnea is a manifestation of the metabolic syndrome. *Sleep Med Rev* 2005;9:211-24.
- Hatipoglu U, Rubinstein I. Inflammation and obstructive sleep apnea syndrome pathogenesis: a working hypothesis. *Respiration* 2003;70:665-71.
- Lavie L. Obstructive sleep apnoea syndrome—an oxidative stress disorder. *Sleep Med Rev* 2003;7:35-51.
- Semenza GL. Hypoxia-inducible factor 1: control of oxygen homeostasis in health and disease. *Pediatr Res* 2001;49:614-7.
- Imagawa S, Yamaguchi Y, Higuchi M, Neichi T, Hasegawa Y, Mukai HY, et al. Levels of vascular endothelial growth factor are elevated in patients with obstructive sleep apnea-hypopnea syndrome. *Blood* 2001;98:1255-7.
- Wolk R, Svatikova A, Nelson CA, Gami AS, Govender K, Winnicki M, et al. Plasma levels of adiponectin, a novel adipocyte-derived hormone, in sleep apnea. *Obes Res* 2005;13:186-90.
- Zhang XL, Yin KS, Mao H, Wang H, Yang Y. Serum adiponectin level in patients with obstructive sleep apnea hypopnea syndrome. *Chin Med J (Engl)* 2004;117:1603-6.
- Kataoka T, Enomoto F, Kim R, Yokoi H, Fujimori M, Sakai Y, et al. The effect of surgical treatment of obstructive sleep apnea syndrome on the plasma TNF-alpha levels. *Tohoku J Exp Med* 2004;204:267-72.
- Dyugovskaya L, Lavie P, Lavie L. Increased adhesion molecules expression and production of reactive oxygen species in leukocytes of sleep apnea patients. *Am J Respir Crit Care Med* 2002;165:934-9.
- Yokoe T, Minoguchi K, Matsuo H, Oda N, Minoguchi H, Yoshino G, et al. Elevated levels of C-reactive protein and interleukin-6 in patients with obstructive sleep apnea syndrome are decreased by nasal continuous positive airway pressure. *Circulation* 2003;107:1129-34.
- Vgontzas AN, Zoumakis E, Lin HM, Bixler EO, Trakada G, Chrousos GP. Marked decrease in sleepiness in patients with sleep apnea by etanercept, a tumor necrosis factor-alpha antagonist. *J Clin Endocrinol Metab* 2004;89:4409-13.
- Sekosan M, Zakkar M, Wenig BL, Olopade CO, Rubinstein I. Inflammation in the uvula mucosa of patients with obstructive sleep apnea. *Laryngoscope* 1996;106:1018-20.
- Paulsen FP, Steven P, Tsokos M, Jungmann K, Muller A, Verse T, et al. Upper airway epithelial structural changes in obstructive sleep-disordered breathing. *Am J Respir Crit Care Med* 2002;166:501-9.
- Boyd JH, Petrof BJ, Hamid Q, Fraser R, Kimoff RJ. Upper airway muscle inflammation and denervation changes in obstructive sleep apnea. *Am J Respir Crit Care Med* 2004;170:541-6.
- Series F, Chakir J, Boivin D. Influence of weight and sleep apnea status on immunologic and structural features of the uvula. *Am J Respir Crit Care Med* 2004;170:1114-9.
- Salerno FG, Carpagnano E, Guido P, Bonsignore MR, Roberti A, Aliani M, et al. Airway inflammation in patients affected by obstructive sleep apnea syndrome. *Respir Med* 2004;98:25-8.
- Carpagnano GE, Kharitonov SA, Resta O, Foschino-Barbaro MP, Gramiccioni E, Barnes PJ. Increased 8-isoprostane and interleukin-6 in breath condensate of obstructive sleep apnea patients. *Chest* 2002;122:1162-7.
- Rubinstein I. Nasal inflammation in patients with obstructive sleep apnea. *Laryngoscope* 1995;105:175-7.
- Brouillette RT, Manoukian JJ, Ducharme FM, Oudjhane K, Earle LG, Ladan S, et al. Efficacy of fluticasone nasal spray for pediatric obstructive sleep apnea. *J Pediatr* 2001;138:838-44.
- Goldbart AD, Goldman JL, Li RC, Brittan KR, Tauman R, Gozal D. Differential expression of cysteinyl leukotriene receptors 1 and 2 in tonsils of children with obstructive sleep apnea syndrome or recurrent infection. *Chest* 2004;126:13-8.
- Goldbart AD, Goldman JL, Veling MC, Gozal D. Leukotriene modifier therapy for mild sleep-disordered breathing in children. *Am J Respir Crit Care Med* 2005;172:364-70.