

Inflammatory response of the airway to inhaled endotoxin correlates with body mass index in atopic patients with asthma but not in normal volunteers

To the Editor:

Obesity is a newly appreciated candidate risk factor for both asthma¹⁻³ and adverse effects of air pollutants.⁴ It has been suggested that obesity induces a proinflammatory state that likely plays a role in asthma and other diseases.³ Inflammation is also an underlying feature of the response of the airway to pollutants such as ozone, particulate matter (PM), and endotoxin (which is a component of PM).⁵ Shore and Fredberg² have reported that obesity modifies the response to ozone in rodents. Bennett and Zeman⁶ have also shown that particle deposition in the airway correlates with body mass index (BMI, a marker for obesity) in humans, caused in part by BMI-related differences in breathing pattern. Taken together, these observations suggest that the inflammatory response to endotoxin, a PM component, may be modified by BMI, and that this may be more pronounced in patients with asthma.

We have previously reported that patients with mild allergic asthma and normal volunteers experience a polymorphonuclear neutrophil (PMN) response in the airway after inhalation challenge with endotoxin.⁷ In patients with asthma, we also observe that inhaled endotoxin enhances response to allergen challenge⁸ and that treatment with inhaled corticosteroid decreases the airway PMN response to inhaled endotoxin and coincidentally decreases airway eosinophilia and monocyte CD14 expression.⁹ To determine whether BMI may be a factor in modulating the response to inhaled endotoxin, we re-examined data from our previous studies in which patients with mild allergic asthma and normal volunteers underwent inhaled challenge with either 5 µg endotoxin obtained from Sigma Chemical Co (Milwaukee, Wis) or (more recently) 20,000 EU Clinical Center Reference Endotoxin (CCRE) obtained from the National Institutes of Health.¹⁰ The postendotoxin PMN response (PMNs/mg sputum, mean $\pm$ SEM) was similar across each of the groups studied ($P = .33$, ANOVA), with 1810 ± 277 PMNs/mg recovered from patients with asthma challenged with Sigma LPS ($n = 22$), 1507 ± 666 PMNs/mg from normal volunteers challenged with Sigma LPS ($n = 7$), and 1045 ± 244 PMNs/mg from normal volunteers challenged with CCRE ($n = 9$). To assess the effect of endotoxin in these groups, we calculated the percentage increase in airway sputum PMNs (postchallenge-prechallenge sputum PMN/mg/prechallenge sputum PMN/mg $\times 100$) at 6 hours after endotoxin challenge compared with baseline samples collected within 48 hours before endotoxin challenge. The endotoxin-induced percent increase in PMNs in the patients with asthma ($n = 22$) was $666.9\% \pm 234.1\%$ versus $375.4\% \pm 170.5\%$ in normal volunteers ($n = 16$), in both cases significantly increased above a hypothetical increase over 0, which would be expected if there was

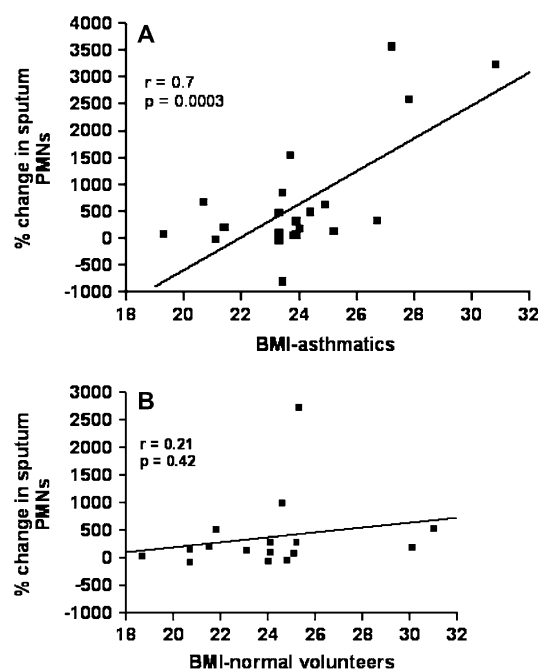


FIG 1. Correlation between airway neutrophil response to inhaled endotoxin (% change in sputum PMNs) and BMI in patients with asthma (A) and normal volunteers (B).

no effect of endotoxin on airway PMN numbers ($P = .01$ and $P = .05$, respectively).

The BMI ranged from 19.3 to 30.8 in the patients with asthma (mean $\pm$ SEM, ± 0.5) and 18.7 to 31.0 in normal volunteers (mean $\pm$ SEM, 24.0 ± 0.8 ; $P = .9$ asthma vs normal). After a determination that our data were normally distributed, we used the Pearson correlation and simple linear regression techniques, and observed a significant correlation between BMI and the percent increase in sputum PMNs recovered after endotoxin challenge in patients with asthma ($R = 0.7$; $P = .0003$; $n = 22$; Fig 1, A), but not in normal subjects ($R = 0.21$; $P = .42$; $n = 16$; Fig 1, B). Within the asthma group, 16 of the 22 volunteers were female (72%), and when considered separately, the correlation between BMI and endotoxin-induced PMN response strengthened to $R = 0.8$, $P = .0003$. For normal female subjects ($n = 11$, 68% of the total group), this correlation was $R = 0.26$, $P = .46$. Eosinophil cationic protein and IL-8 levels (pg/mL) in sputum from patients with asthma after endotoxin challenge were also significantly correlated with BMI ($R = 0.9$, $P = .0003$, $N = 10$; and $R = 0.6$, $P = .03$, $N = 18$, respectively), but not so for normal subjects (eosinophil cationic protein: $R = 0.36$, $P = .27$; IL-8: $R = 0.35$, $P = .22$). Taken together, these observations suggest that BMI is an important determinant of acute airways inflammatory response to inhaled endotoxin in patients with asthma, but not in normal volunteers.

There are potential limitations of these analyses that are important to acknowledge. First, within the normal

volunteer group, our data include challenge with 2 different sources of endotoxin. Although the response to each endotoxin source was not statistically different, there were decreased PMNs present in the CCRE versus Sigma groups, which, when both groups are combined, modestly increases the variability of this measure. Because of this increased variability and smaller sample size, we recognize that a larger sample size may have revealed a statistically significant correlation that we did not observe for the normal cohort. Second, the group with asthma had increased PMN responses relative to normal volunteers, but these differences were not statistically significant. Third, our study population was predominantly female, and it is possible that female sex may be important in asthma and response to pollutants. Finally, it is important to note that all of the patients with asthma studied in these protocols had mild intermittent disease and required no chronic controller medication. Nonetheless, within the asthma group (all of whom underwent challenge with the same source of endotoxin), we observed a significant correlation between endotoxin induced increases in airway inflammation and BMI.

To our knowledge, this is the first report examining a relationship between BMI and inflammatory response to inhaled endotoxin in asthma. Endotoxin has been linked to asthma severity in ambient air and domestic and occupational environments and is a good model for acute events associated with asthma exacerbation. There are a number of potential mechanisms by which BMI may be linked to the inflammatory response to inhaled endotoxin in asthma. We have reported that allergic airway inflammation may modify mCD14 expression in airway macrophages and monocytes, which may enhance their response to endotoxin. It is important to note, however, that without allergic and nonatopic controls with asthma, it is presently unclear whether atopy, asthma, or the combination of the 2 is responsible for the differences we observed between our study cohorts. Our group has also observed that even with modest changes in BMI, there is increased particle deposition in the airways. Thus, in patients with asthma, increased deposition of endotoxin related to body mass may allow an increased effective airway dose of endotoxin to interact with primed monocytes and macrophages. It is also possible that increased BMI reflects changes in inflammatory biology reported to occur in obesity, including increased leptin, which has recently been reported to promote eosinophil survival. Thus, obese patients with asthma may have modified response to endotoxin at a cellular level.

Regardless of the precise mechanism, it is important to consider the potential interaction between body mass and asthma exacerbation. Obesity likely represents an important target for intervention in many patients with moderate and severe asthma. Our data demonstrate that in asthma, further examination of both the effect of BMI on airway physiology relative to deposition of inhaled bioactive particles, as well as the effect of obesity on innate and acquired immune responses, is needed to understand the role of obesity in asthma pathogenesis and exacerbation.

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Dominance of human innate immune responses in primary *Francisella tularensis* live vaccine strain vaccination

To the Editor:

Francisella tularensis is the etiologic agent of the zoonotic disease, tularemia. An inoculum as small as 10 bacteria can cause a flulike disease with substantial morbidity and mortality among infected humans.^{1,2} Human tularemia presents in ulceroglandular, oculoglandular, oropharyngeal, pneumonic, and septic forms.^{1,3} Rapid administration of antibiotics prevents mortality in the majority of human cases if exposure doses are low and nonaerosol.²⁻⁴ Without early diagnosis and administration of antibiotics, high-dose aerosol exposure progresses rapidly to life-threatening pleuropneumonitis and systemic infection.³ The relative abundance of *F tularensis* in nature and the relative ease with which it may be administered raise concerns over its exploitation as a biothreat agent.^{1,3,4}