

Sexual dimorphism: Is it relevant to steroid resistance or asthma control?

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Suboptimal asthma control was more prevalent among inhaled corticosteroid users, particularly females from a population of 501 adult subjects with asthma evaluated in a cross-sectional French study published in this issue of the Journal.¹ Optimal asthma control was not achieved in the majority of study participants. Although this study has limitations, its results challenge us to review the potential sources of corticosteroid resistance and to examine the evidence for sexual dimorphism² in steroid responsiveness for asthma and chronic obstructive pulmonary disease (COPD). Limitations of the study include potential confounding by indication, less well validated measures of asthma control, and potential disease misclassification. Subjects with asthma with more persistent or severe symptoms were more likely to be prescribed inhaled corticosteroids (confounding by indication). Classification of asthma control using Global Initiative for Asthma Guidelines³ may not be as well validated an approach as the Asthma Control Test, a tool discussed in the article by Schatz et al that also appears in this issue of the Journal.⁴ In addition, the higher prevalence of cough and phlegm in patients with poorly controlled asthma on inhaled corticosteroids suggests possible disease misclassification or overlap of asthma with COPD⁵ in this population. Finally, this study did not formally assess its participants for steroid resistance. One definition used for asthma research requires a <15% increment in the FEV₁ (percent of predicted value) after 2 weeks of treatment with 40 mg oral prednisolone, despite demonstrating a >15% reversibility to an inhaled β_2 -agonist.⁶ This may be too limiting in evaluating change in FEV₁, in that a steroid response may occur even if the response to β_2 -agonists is suboptimal. In the study by Siroux et al,¹ variable participant compliance or dosage may have influenced symptom responsiveness.

Nevertheless, most⁷⁻¹⁰ but not all¹¹ previous reports agree with the findings of this French study, suggesting that female subjects with asthma may derive less benefit from inhaled steroids. In the study by Siroux et al,¹ the reduced response to inhaled

corticosteroids in females may have been a result of biologic/molecular differences between the sexes, or unmeasured gender differences in the technique of administration of inhalers,¹² medication compliance,¹³ treatment of women by physicians, stress,¹⁴ home allergens, smoke exposure, and/or home cooking exposures.

Much has been written about the molecular basis for steroid resistance,¹⁵ and an exhaustive review is beyond the scope of this editorial. Suggested mechanisms include decreased expression or binding affinity of the glucocorticoid receptor,¹⁶ increased phosphorylation of the glucocorticoid receptor,¹⁷ dysregulation of the transcription factor activator protein 1 (AP-1),¹⁸ reduction and activity of histone deacetylase 2,^{19,20} and vitamin D₃ deficiency resulting in diminished IL-10 production from T-regulatory cells.²¹ Additional epidemiologic associations with steroid resistance include cigarette smoking²² (which can reduce histone deacetylase 2 expression)^{23,24} and obesity²⁵ (which may operate through the mitogen-activated protein kinase pathway).²⁶

There is little doubt that sex has a major impact on age-associated asthma prevalence^{27,28} and asthma severity.^{29,30} Sex appears to influence the heritability of and genetic susceptibility to asthma-related intermediate phenotypes like IgE.^{31,32} Life cycle hormonal changes have been posited to be partially responsible for some of these sex differences,^{33,34} and sex and life cycle-specific changes in glucocorticoid and estrogen metabolism may represent pathways influencing sex-specific asthma expression and steroid responsiveness.³⁵ The degree of glucocorticoid receptor expression has been shown to be sex-dependent in some human studies,^{36,37} consistent with findings suggesting that glucocorticoid responsiveness differs by sex in rodents.^{38,39} Although vitamin D levels have been shown to be lower in female subjects than in male subjects in the general population,⁴⁰ this has not been demonstrated in patients with asthma.⁴¹ However, sex has been shown influence the numbers of IL-10-producing T-regulatory cells, with female subjects having lower counts.⁴² In addition, although little evidence links sex with histone deacetylase 2 expression specifically, histone deacetylase 2 binds to the estrogen receptor α , and 17 β -estradiol results in its disassociation.⁴³ The correlation with obesity and asthma per se has been noted to be stronger among female subjects than male subjects.⁴⁴⁻⁴⁷ In addition, evidence shows that 17 β -estradiol can regulate the mitogen-activated protein kinase pathway in some cell types in female rats only.⁴⁸

The molecular, physiologic, and radiologic evidence for sex differences in COPD expression, and in responsiveness to steroids in COPD, is less consistent.^{49,50} Although female subjects do not typically exhibit increased smoking behavior compared with men, the pathophysiologic response to smoking may differ.^{51,52} It has been posited that women respond to smoke exposure with more airway disease, and men with more emphysema, but the evidence for this is mixed.^{51,53,54} Early-onset severe COPD may be female-predominant.⁵⁵

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Further research is needed to ascertain the relative importance of biology (sex) and behavior (gender) in explaining male:female differences in asthma or COPD, including differences in responsiveness to inhaled corticosteroids. Given the large numbers of patients with airways disease worldwide, therapies tailored to sexual dimorphism in response to diet or pharmacologic therapy could have a major impact.

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