Dehydroepiandrosterone Supplementation May Benefit Women with Asthma Who Have Low Androgen Levels: A Pilot Study

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ABSTRACT

Introduction: Among individuals with severe asthma, FEV₁ is low in individuals with low dehydroepiandrosterone (DHEA) sulfate (DHEAS) levels. In the Severe Asthma Research Program (SARP), no women with DHEAS \(< 200 \mu g/dL\) had an FEV₁ \(< 60\%\) predicted. DHEA has benefited patients with COPD and pulmonary hypertension in small trials. Therefore, we hypothesized that DHEA supplementation may improve FEV₁ in asthmatic women with low DHEAS.

Methods: Premenopausal, nonsmoking, otherwise healthy women, 18-50 years old, with mild or moderate asthma and baseline FEV₁ \(> 60\%\) predicted received 100 mg DHEA orally every 12 h for 2 weeks. Spirometry and DHEAS were measured at the initial visit and 2 weeks later, after completion of DHEA treatment. Based on our previous work, the primary outcome variable for this pilot study was post-albuterol spirometry in the low-DHEAS group. Subjects also continued their other routine asthma management.

Results: Serum DHEAS increased with DHEA treatment in women with starting DHEAS \(< 200 \mu g/dL\): this increase was from 71 \(±\) 23 to 725 \(±\) 295 \(\mu g/dL\) (\(n = 10; \ p = 0.0001\)). The increase in the high-DHEAS group was smaller. Post-albuterol FEV₁ increased by 51 mL, from 3.026 \(±\) 0.5 to 3.077 \(±\) 0.49 L (\(n = 10; \ p = 0.0001\)). The increase in the high-DHEAS group was smaller. Post-albuterol FEV₁ increased by 51 mL, from 3.026 \(±\) 0.5 to 3.077 \(±\) 0.49 L (\(n = 10; \ p = 0.034\) by paired \(t\) test, significant after Bonferroni), in women with low DHEAS. In the high-DHEAS group (baseline DHEAS \(\geq 200 \mu g/dL\)), post-albuterol FEV₁ did not change significantly (\(n = 3, \ p = NS\)). Three subjects were excluded: one had comorbid COPD, one could not perform spirometry, and one did not take the DHEA. There were no adverse effects of DHEA treatment in this trial.

Conclusions: Endocrine treatments (corticosteroids) are a mainstay of anti-inflammatory management for moderate and severe asthma. Their use has improved asthma outcomes. Androgens also reduce airway inflammation and promote airway smooth muscle relaxation, but are rarely used clinically for asthma treatment. Our results suggest that the over-the-counter steroid DHEA may improve lung function in asthma outcomes among women with DHEAS < 200 \(\mu g/dL\).
Keywords: Asthma; Dehydroepiandrosterone (DHEA); Lung function

Key Summary Points

Endocrine treatments (corticosteroids) are a mainstay of anti-inflammatory management for moderate and severe asthma.

Their use has improved asthma outcomes.

Androgens also reduce airway inflammation and promote airway smooth muscle relaxation, but are rarely used clinically.

Our results suggest that the over-the-counter steroid DHEA may also improve lung function in asthma outcomes among women with DHEAS < 200 µg/dL.

INTRODUCTION

Background and Significance Regarding Androgens for Patients with Asthma Who Have Low Circulating Androgen Levels

In the United States, asthma affects over 8% of the population, leading to annual healthcare expenditures in excess of $20 billion [1–5]. In severe asthma, chronic symptoms and exacerbation-prone disease persist despite the use of corticosteroids and other interventions in established management protocols [6–9]. Severe asthma accounts for the majority of the morbidity, mortality, and healthcare expenditures associated with asthma [7–9]. In the Severe Asthma Research Program (SARP), we investigated the distinct pathophysiological features of asthma in general, and severe asthma in particular [6, 7, 9–13]. In the SARP, we used the asthma and severe asthma definitions in the American Thoracic Society/European Respiratory Society consensus guidelines [9].

Asthma prevalence increases with age in women relative to men [3, 12]. A particular focus of our SARP investigation has been to understand the relationship between asthma severity and sex hormones. Before puberty, the majority of patients with asthma are boys, while the majority of late adolescents and adults with asthma are women [12–14]. We measured circulating sex steroid levels and sex hormone-binding globulin (SHBG) in SARP subjects; specific hormones measured were estradiol, testosterone, progesterone, and dehydroepiandrosterone sulfate (DHEAS) [15]. Note that DHEAS is endogenously sulfated DHEA, and accounts for the majority of circulating DHEA. DHEA is synthesized from cholesterol via the enzymes cholesterol side-chain cleavage enzyme (CYP11A1; P450scc) and 17α-hydroxylase/17,20-lyase (CYP17A1), with pregnenolone and 17α-hydroxypregnenolone as intermediates [16]. It functions as a metabolic intermediate in the biosynthesis of the androgen and estrogen sex steroids both in the gonads and in various other tissues. Metabolites of DHEA include DHEA-S, 7α-hydroxy-DHEA, 7β-hydroxy-DHEA, 7-keto-DHEA, 7α-hydroxyepiandrosterone, and 7β-hydroxyepiandrosterone, as well as androstenediol and androstenedione [17].

We found that post-albuterol FEV1 was strongly associated with low DHEA levels [15] and that DHEAS levels were twice as high in non-severe as in severe asthma. We also found that women with severe asthma had low levels of DHEAS compared with women with non-severe asthma (58.1 vs 131.5 µg/dL, p < 0.001). Strikingly, no women in our initial (SARP 1 and 2) cohort with DHEAS < 200 µg/dL had a forced expiratory volume at 1 s (FEV1, the standard marker for asthmatic airflow obstruction) < 60% predicted. To our knowledge, no other marker in humans is associated with such complete protection from low lung function. These data led us to hypothesize that DHEA supplementation in asthma subjects with low DHEA levels could improve lung function.

Of note, asthmatic men with low total testosterone levels had lower lung function than asthmatic men with normal testosterone levels—consistent with studies in non-asthmatic populations [18, 19]—and total testosterone values in men with severe asthma were lower than those in men with non-severe...
asthma. These data also suggest a protective effect of androgens on lung function. Further, DHEAS levels were strongly associated with lung function in male children [15]. For the majority of women and younger boys, adrenal-derived DHEAS is the predominant androgen: the effect of testosterone is smaller. Taken together, these data suggest that androgens might improve lung function in asthma patients with low androgen levels. We have focused on DHEAS in women because DHEA supplementation is relatively safe and simple—it is an over-the-counter nutritional supplement used for inflammatory conditions [20–29]—while testosterone administration involves injection of a controlled substance. Note also that glucocorticoid therapy can suppress endogenous DHEA production [30, 31]. Glucocorticoids are, as a class, steroid hormone derivatives that are beneficial preventively and therapeutically in both chronic and acute asthmatic airway inflammation [8, 9]. Patients with severe asthma tend to be glucocorticoid-refractory, even when treated with high doses [9, 10, 32]. It can be appropriately argued that low lung function associated with low DHEAS levels in our SARP data and related studies [30, 31] may reflect higher corticosteroid dosing used for these refractory patients with low lung function: that is, that low DHEAS might not be causally related to low lung function.

To begin to address whether low lung function is a cause or effect, we performed a pilot study, supplementing low DHEAS women with DHEA to determine whether increasing DHEAS levels by supplementation increased post-albuterol FEV₁.

DHEA has benefited patients with COPD [28, 33] and pulmonary hypertension [28, 34] in small trials, as well as animal models [35, 36]. Therefore, we hypothesize that DHEA treatment may also improve asthma outcomes.

METHODS

Subjects and Approval

We recruited premenopausal, nonsmoking, otherwise healthy women 18–50 years of age with non-severe asthma and a baseline FEV₁ > 60% predicted. They were recruited by public advertisement and from pulmonary clinics in Cleveland. All subjects who made inquiry regarding the study were screened and, if they met the criteria, were enrolled, with one exception: one woman declined to participate for family reasons. Inclusion and exclusion criteria were identical to those in the SARP for non-severe asthma, as we have published [37], except as noted in Table 1. Because of the slow turnaround in DHEAS levels, we treated all eligible women, but our target was women with low baseline DHEAS levels. Once we had the initial DHEAS levels, we stratified by level, above and below 200 ug/dL. The study met ethics compliance and received institutional review board approval on 1 November 2016, UHCMC IRB number: 09-16-30. It was not entered into ClinicalTrials.gov because the protocol was approved and initiated in 2016, before the National Institutes of Health (NIH) clinical trials policy was posted or went into effect (18 January 2017), and it was not an NIH-funded clinical trial.

Protocol

At 8:00 a.m., after withholding medication for 12 h, women underwent a urine pregnancy test as well as a history and physical exam. Those who were not pregnant and were not experiencing asthma exacerbation proceeded with the study. Baseline spirometry, maximum bronchodilator testing, and phlebotomy were performed at the initial visit and 2 weeks later, after the completion of DHEA treatment, according to SARP protocols [7, 37]. Three milliliters of blood were drawn and sent to measure baseline DHEAS and other sex steroid levels (all assays required a total of 400 mL serum in the SARP). All serum was bar-coded in Dr. Marozkina’s lab and stored at −80 °C until assayed.

Subjects received 100 mg DHEA orally every 12 h for 2 weeks, and they also continued their routine asthma management. Patients were given 28 pills by the research pharmacist. Those with non-allergic comorbidities were excluded [7, 8]. The primary outcome variable was post-
albuterol \( \text{FEV}_1 \); the secondary outcome variables were circulating DHEAS levels and pre-albuterol spirometry values.

**DHEA Preparation**

DHEA 100 mg capsules were obtained from General Nutrition Corporation (GNC; Pittsburgh, PA 15222) and distributed by the research pharmacy.

**Statistical Analysis**

The primary outcome variable was change in post-bronchodilator \( \text{FEV}_1 \). We used the paired Student \( t \) test, Bonferroni test, and one-way analysis of variance (ANOVA) on ranks to analyze the data.

**RESULTS**

In this pilot study, 16 premenopausal women, 18–50 years of age, with non-severe asthma were studied. Three women were excluded from study: one who could not perform reproducible spirometry, one who had COPD, and one non-compliant (no changes in pre-post DHEAS levels). Those with low DHEAS (< 200 ug/dL) and baseline \( \text{FEV}_1 \) < 80% predicted (baseline obstruction) who met the inclusion criteria (Table 1) had been identified in the screening visit. These exclusions included smoking and any major comorbidity.

Serum DHEAS increased after DHEA treatment from 71 ± 23 to 725 ± 295 \( \mu \text{g/dL} \) (\( n = 10; p = 0.0001 \)) in the low-DHEAS group (baseline DHEAS < 200 \( \mu \text{g/dL} \)). However, in the high-DHEAS group (baseline DHEAS ≥ 200 \( \mu \text{g/dL} \)), the increase in serum DHEAS after DHEA treatment did not reach statistical significance, increasing from 214 ± 18 to 458 ± 170 \( \mu \text{g/dL} \) (\( n = 3; p = \text{NS} \)).

We compared the change in post-albuterol \( \text{FEV}_1 \) (primary outcome) and change in DHEAS in women whose starting DHEAS was < 200 \( \mu \text{g/dL} \). Post-albuterol \( \text{FEV}_1 \) increased by 51 mL, from 3.026 ± 0.5 to 3.077 ± 0.49 L (\( n = 10; p = 0.034 \)) by paired \( t \) test, significant after Bonferroni test, in women with low DHEAS (Table 2). However, in the high-DHEAS group (baseline DHEAS ≥ 200 \( \mu \text{g/dL} \)), corrective post-albuterol \( \text{FEV}_1 \) did not change significantly (\( n = 3; p = \text{NS} \)).

We analyzed other respiratory parameters obtained by spirometry, such as pre- and post-albuterol changes in forced vital capacity (FVC), \( \text{FEV}/\text{FVC} \% \), \( \text{FEV} 75/25 \) following DHEA treatment by one-way ANOVA on ranks, and paired

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**Table 1** Inclusion and exclusion criteria

| Inclusion                                      | Exclusion                                                   |
|------------------------------------------------|-------------------------------------------------------------|
| Female, 18–50 years old                       | Pregnant                                                    |
| Asthma, stable and managed by an asthma specialist [9] | Using hormonal contraception, pregnant                     |
| Using hormonal contraception, pregnant        | Exclusion criteria for SARP [37], including both major comorbidities and smoking |
| Endocrinopathy such as diabetes or PCOS (polycystic ovarian syndrome) | Using androgens for any reason                              |
| Postmenopausal                                 | Active asthma exacerbation                                  |
| FEV\(_1\) < 60%                                |                                                             |

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Student t test. In all these parameters, changes did not reach statistical significance.

There were no adverse effects of DHEA treatment reported in any of the patients participating in this trial.

**DISCUSSION**

In our two SARP study cohorts combined (SARP 1 and 2; and SARP 3), women with a DHEAS level > 200 µg/dL did not have severely compromised FEV1. Indeed, DHEAS was previously shown to be associated with protection against inflammation in general, and asthmatic airway inflammation in particular [15, 19–21, 28, 29, 38, 39]. However, the heterogeneity of determinants of androgen levels makes it difficult to ascertain both efficacy and mechanism. In this pilot study, our low-DHEAS adult asthmatic women with airflow obstruction received a 2-week course of DHEA, and the primary outcome variable was improvement in FEV1. We may also have a better understanding of the potential protective effects of androgens that could help explain the tendency of asthma prevalence to increase with age in women relative to men. Cortisol-like compounds have been effective agents for the management of many patients with asthma, but other hormones have not been systemically studied. Here, we have studied the use of a safe, easily available, and inexpensive androgen to treat asthma. This study thus has a high potential for return on investment, improving the health of many patients with severe asthma and reducing asthma healthcare costs.

### Potential Mechanisms by which Androgens May Benefit Patients with Asthma

The potential protective effects of DHEAS likely involve effects both on airway smooth muscle and on airway inflammation. Indeed, there is evidence to support cross-talk between DHEAS anti-inflammatory effects and airway smooth muscle relaxation [38, 40]. DHEAS inhibits human airway smooth muscle and fibroblast proliferation [39, 41], may benefit airway epithelial-to-mesenchymal transition [42], and is itself a bronchodilator [43]. It also benefits pulmonary vascular smooth muscle tone, and is used as treatment for human pulmonary arterial hypertension [28]. Note that testosterone also promotes airway smooth muscle relaxation [41].

DHEAS also has anti-inflammatory effects in murine (dust mite) asthma models, decreasing airway interleukin (IL) 4, IL5, and interferon gamma [44, 45], and reducing airway eosinophilia in an ovalbumin model [38]. Note that testosterone was also recently shown to be associated with decreasing type 2 innate lymphoid cell-mediated inflammation in a murine asthma model [46]. DHEAS is also associated with lower systemic IL6 levels, proposed to be involved in its neuroprotective effects in human stroke [29]. DHEA exerts anti-inflammatory effects observed in a variety of non-asthmatic human conditions [20–23, 47, 48], in many of which it is used as a nutritional supplement therapy.

This pilot study will be the basis for larger double-blind randomized controlled trials. It was shown previously [21] that nebulized DHEA improves asthma symptoms (reflected by Asthma Control Questionnaire) in moderate-to-

### Table 2 Spirometry value changes after DHEA treatment

| Spirometry | Low-DHEAS group |  |  |
|------------|-----------------|--|--
|            | No treatment    | + DHEA treatment |  |  |
| Baseline FEV1 change | 2.952 ± 0.468 | 2.986 ± 0.505 | 7 | 0.276 |
| Post-albuterol FEV1 change | 3.026 ± 0.507 | 3.077 ± 0.489 | 7 | 0.034 |
severe asthma in a randomized, double-blind, placebo-controlled study. This pilot will be used to power a larger study of oral DHEA supplementation in the future larger double-blind randomized controlled trial.

CONCLUSIONS

Corticosteroids related to cortisol are a mainstay of anti-inflammatory treatment for moderate and severe asthma. Their use has improved asthma outcomes. However, androgens also reduce airway inflammation and promote airway smooth muscle relaxation. Our preliminary data suggest that the over-the-counter steroid DHEA also improves lung function in asthma outcomes among women with DHEAS < 200 ug/dL. Low-dose over-the-counter androgen supplementation may benefit certain women with asthma, particularly those with low serum DHEAS levels, and is safe in given doses. Additional studies will be worthwhile.

ACKNOWLEDGMENTS

Funding. This study was funded by the Children’s Lung Foundation and (U10HL109250 [SARP]). The Rapid Service Fee was funded by the authors.

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Disclosures. Nadzeya Marozkina, Joe Zein, Mark D. DeBoer, Laurie Logan, Laura Veri, Kristie Ross, and Benjamin Gaston have nothing to disclose.

Compliance with Ethics Guidelines. The study met ethics compliance and received institutional review board approval on 1 November 2016, UHCMC IRB number: 09-16-30. It was not entered into ClinicalTrials.gov because the protocol was approved and initiated in 2016, before the NIH clinical trials policy was posted or went into effect (18 January 2017), and it was not an NIH-funded clinical trial. Informed consent to participate was given by all participants.

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