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Original Article

Association between low serum testosterone level and severe asthma among elderly women

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BMI, body mass index; COPD, chronic obstructive pulmonary disease; DHEA, dehydroepiandrosterone sulfate; FEV_1, forced expiratory volume in 1 s; FEV1/FVC ratio, the forced expiratory volume in 1 s divided by the forced vital capacity ratio; OCS, oral corticosteroids

ABSTRACT

Background: Elderly asthma has distinct pathophysiologic and phenotypic characteristics compared with asthma in younger patients. However, a potential relationship between sex hormones and the severity of asthma remains unknown in the elderly population. The aim of the present study was to elucidate the relationship between the level of circulating free testosterone and severity of asthma among Japanese with elderly asthma.
Methods: The level of free testosterone was measured using sera from elderly patients with asthma aged ≥60 years (n = 192), and its association with the severity of asthma was examined after stratification by sex.
Results: Based on previous literature and our preliminary analysis showing that current oral corticosteroid (OCS) use might be a risk factor for a lower free testosterone level regardless of severity of asthma, analyzed patients were limited to those who were not currently using OCS (n = 164). Regarding elderly men who were not currently using OCS (n = 62), there was no significant association between free testosterone level and severity of asthma. However, in female counterparts (n = 102), a low free testosterone level was significantly associated with severe asthma even after adjustment for age (p for trend, 0.03).
Conclusions: The present study showed a significant association between the serum free testosterone level and severity of asthma among elderly women who were not currently using OCS. Although the causal relationship is unclear, this finding may provide a clue to understand the sex difference in the mechanisms of severe asthma in elderly populations.

Introduction

The proportion of elderly people with asthma is increasing worldwide. Elderly asthma has distinct pathophysiologic and phenotypic characteristics compared with asthma in younger patients, but the mechanisms involved in this difference remain unknown.[1–3] In particular, the relationship between circulating levels of sex hormones and the severity of asthma in the elderly is infrequently investigated.

Recent epidemiological studies highlighted the effects of testosterone on asthma prevalence.[4] Analyses of a nationally representative sample of people in the US showed an association between higher serum testosterone levels and a lower prevalence of asthma.[4,5] Another large-scale epidemiological study of British adults aged 40–69 years in the UK Biobank showed elevated serum free testosterone levels were associated with a lower prevalence of asthma in women and men, as well as lower odds of hospitalization for women.[6] It is well documented that testosterone levels in humans decreases with age due to an age-related decline in gonadal and adrenal functions.[7] Although age-related low testosterone levels might contribute to disease presentation in elderly asthma, there has been no proof on this scenario. This study examined the relationship between sex hormone levels and

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severity of asthma among elderly people, especially focusing on the association with free testosterone.

Methods

Study design

We performed a cross-sectional study of consecutive elderly patients with asthma aged ≥60 years old who visited Sagamihara National Hospital, one of the largest tertiary hospitals for allergic diseases located in central Japan. Patients were asked to answer various questionnaires and underwent lung function and blood tests. Some of the findings from this study population were reported previously.[8] The study protocol was approved by the Ethics Committee of Sagamihara National Hospital (No. 2019-015). All patients provided written informed consent.

Patients

Consecutive elderly patients with asthma aged ≥60 years old who visited the Allergology Department of Sagamihara National Hospital between February 25, 2020 and November 16, 2020 were screened for enrollment in this study. When they made their regular visits to the outpatient clinic, they were invited to participate in the study. Asthma was diagnosed according to the American Thoracic Society criteria by pulmonologists and allergists, and patients having a history of outpatient visits for more than one year for asthma were eligible for this study. Exclusion criteria included i) having respiratory diseases other than asthma/chronic obstructive pulmonary disease (COPD) (i.e., interstitial lung disease, bronchiectasis, cystic fibrosis), ii) complications of diseases other than asthma that require continuous steroid therapy (i.e., rheumatoid arthritis, inflammatory bowel disease, nephrotic syndrome, and other collagen diseases including eosinophilic granulomatosis with polyangiitis), iii) those considered inappropriate to participate in the study by the principal investigator or sub-investigator, or iv) those who did not give consent for a blood test. Thus, patients with asthma and COPD overlap and were included in this study.

Although there were 260 patients who met the inclusion/exclusion criteria during this study period, 56 refused to participate in the study. After removing one patient with missing data for history of oral corticosteroid (OCS) usage and 11 cases in which serum samples for the current study were not available, 192 patients were finally analyzed in this study (Fig. 1).

Measurement of sex hormone levels

Serum samples were collected from patients between 9:00 AM and 11:00 AM and stored at −80 °C until measurement. Level of free testosterone was directly measured by radioimmunoassay (Immunotech, USA). Levels of dehydroepiandrosterone sulfate (DHEAs) were measured using an Electro ChemiLuminescence ImmunoAssay (ECLIA) (Beckman−Coulter, USA). Levels of estradiol were measured by ECLIA (Roche Diagnostics, Switzerland). The detection limits of the assay for free testosterone, DHEA, and estradiol were 0.2 pg/mL, 0.5 μg/dL, and 5.0 pg/mL, respectively. For levels below the lower limit of detection, 0.1 pg/mL, 0.25 μg/dL, and 2.5 pg/mL were assigned to free testosterone, DHEA, and estradiol, respectively when statistical analysis was performed.

Definition of severe asthma

The definition of severe asthma was determined according to the American Thoracic Society/European Respiratory Society definition using information collected from a structured questionnaire and medical chart review.[9]

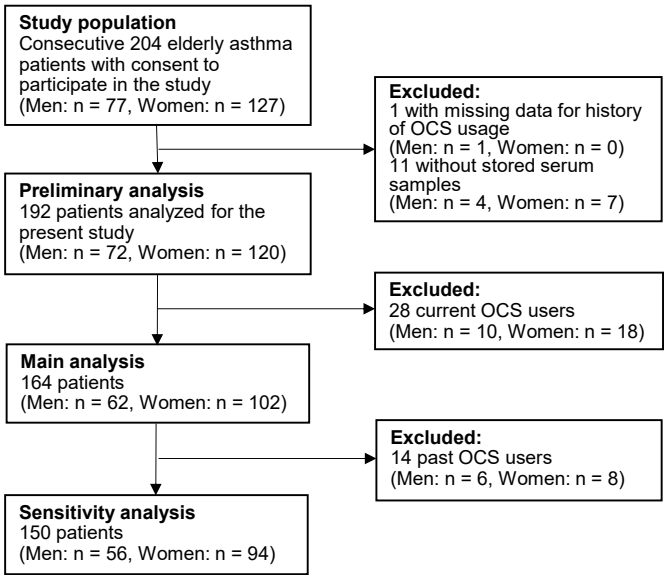

Fig. 1. Flowchart of the population analyzed in this study. OCS, oral corticosteroids.

Clinical characteristics

Information of clinical characteristics was assessed from a self-reported structured questionnaire as well as information obtained from a medical chart review and face-to-face interviews with patients by their attending physicians or trained nurses.[8]

Information on age, hospitalization for asthma, history of mechanical ventilation of asthma, smoking history, body mass index, asthma control test, comorbidities (chronic sinusitis, nasal polyposis, aspirin-exacerbated respiratory disease, COPD, diabetes mellitus, and osteoporosis), and medications for asthma (inhaled corticosteroids, theophylline, anti-allergic drugs, and biologics) were collected.

Measurement of variables

OCS exposure was measured using a structured questionnaire fulfilled by an attending physician or a trained nurse at enrollment, referring to the information obtained from the face-to-face interview with the patient as well as the medical chart review. Based on the collected information, OCS exposure was categorized into past OCS user or non-user, or current OCS user or non-user, respectively.

Lung function was measured using an electronic spirometer (Auto Spiro AS-303; Minato Medical Science, Osaka, Japan). The evaluation items were forced vital capacity (FVC) (ml), forced expiratory volume in 1 s (FEV_1) (ml), and the forced expiratory volume in 1 s divided by the forced vital capacity ratio (FEV_1/FVC ratio) (%). The prediction equation proposed by the Japanese Respiratory Society was used for the calculation. FVC (% predicted) (%) and FEV_1 (% predicted) (%) were calculated using the prediction equation.

We obtained a blood sample and performed lung function tests on the same day as patient registration. We assessed blood counts (leukocytes, neutrophils, eosinophils, lymphocytes), total immunoglobulin E, and brain natriuretic peptide.

Statistical analysis

The difference between groups was examined by the Mann–Whitney *U*-test or Kruskal–Wallis test for continuous variables and Fisher's exact test or Chi-squared test for categorical variables. Serum levels of free testosterone, DHEAs, and estradiol were log-transformed and presented as continuous variables, respectively. All analyses in this study were conducted separately for men and women. The subject groups were analyzed by dividing sex hormone levels into three categories as tertiles (lower-middle-higher) according to serum levels of free testosterone, DHEAs, or estradiol, respectively. Multivariate analysis was performed using a binomial logistic regression model with asthma severity as the objective variable and free testosterone, DHEAs, and estradiol tertiles as explanatory variables adjusted for age. P for trend was analyzed using a linear regression model with asthma severity as the objective variable, and free testosterone or DHEAs tertiles as explanatory variables adjusted for age. A P-value <0.05 was considered statistically significant. Statistical analysis was performed using IBM SPSS Statistics ver. 23.

Results

Study population (N = 192)

The mean age of patients was 74.6 years (standard deviation [SD] ±7.3) and 15 % of patients were currently using OCS (data not shown). The median prednisolone equivalent dose of OCS among current OCS users was 3.0 (interquartile range, 2.5 to 4.5) mg/day. None of the patients had received systemic glucocorticoid therapy for acute asthma exacerbation nor had suffered from acute infections within 2 weeks prior to study enrollment. Additionally, none of the patients were currently receiving hormonal therapy for

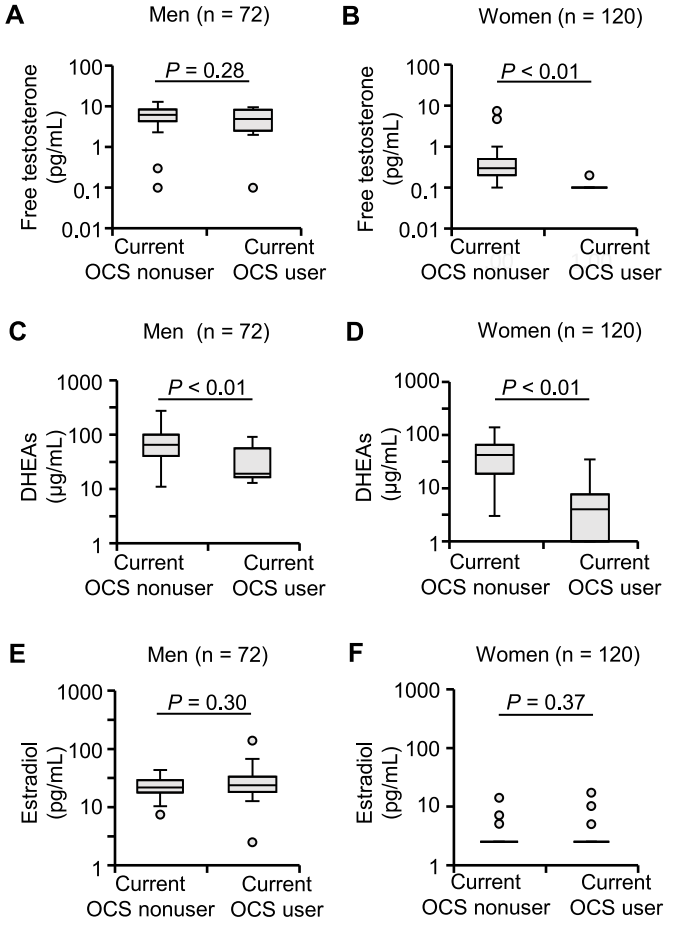

Fig. 2. Association between current oral corticosteroid (OCS) usage and levels of sex steroid hormones by sex (n = 192). DHEA, dehydroepiandrosterone sulfate.

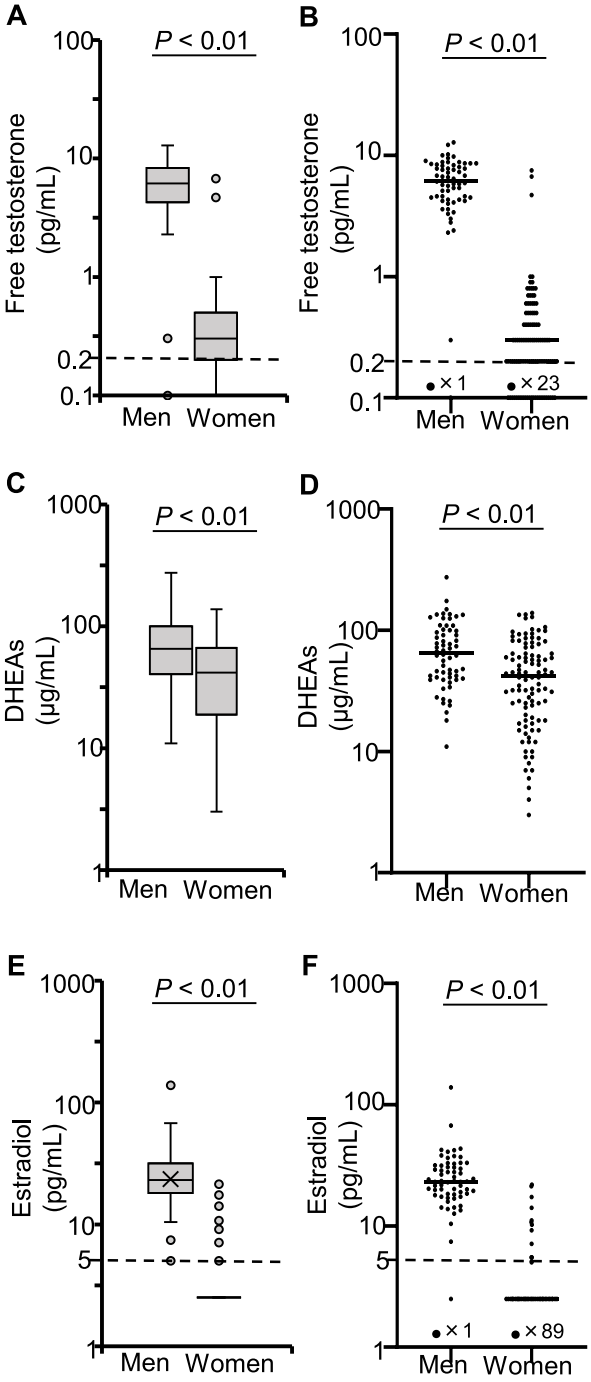

Fig. 3. The Distribution of the levels of free testosterone (**A**, **B**), DHEAs (**C**, **D**), and estradiol (**E**, **F**) by box plots and dot plots. Among elderly patients with asthma not using regular oral corticosteroids (n = 164). Horizontal bar in dot plots (**B**, **D**, and **F**) indicates the median. The number of patients with levels below the detection limit is indicated below the dotted detection limit line.

breast or prostate cancer. Higher age was significantly correlated with lower levels of free testosterone and DHEAs in men (Spearman's rank correlation coefficient for free testosterone = −0.38, $p < 0.01$; for DHEA = −0.36, $p < 0.01$), but not women (Spearman's rank correlation coefficient for free testosterone = −0.06, $p = 0.49$; for DHEA = −0.11, $p = 0.22$). Age was not correlated with estradiol levels for either sex (data not shown).

OCS use as a potential risk factor for reduced serum free testosterone level: preliminary analysis

Previous studies reported reduced levels of serum testosterone in men with COPD/asthma treated with regular OCS compared to those without,[10–13] suggesting serum testosterone levels were decreased due to the hormonal side effects of glucocorticoid therapy. Indeed, a preliminary analysis of our present data revealed a lower level of free testosterone in women currently using regular OCS (Fig. 2B). In accordance with the definition of severe asthma,[9] all OCS current users were classified as having severe asthma. Thus, severe asthma patients currently taking OCS had lower serum testosterone levels, regardless of whether there is a true relationship between testosterone levels and severity of asthma. Therefore, subsequent analyses were limited to patients not currently taking regular OCS (n = 164, Fig. 1). The mean age of this analyzed population was 74.5 years (±7.3), and 62 % (n = 102) were women. As shown in Figure 3, there were significant differences in the distribution of hormone levels between men and women. In this population, the frequency of intermittent administration of systemic corticosteroids for acute asthma exacerbation during one year prior to the study enrollment was not associated with serum free testosterone/DHEAs levels for either sex (data not shown). Table 1 shows comparisons between severe and non-severe asthma by sex. The demographic parameters were similar between severe and non-severe asthma cases. Also in this

Table 1
Demographics, lung function, levels of sex hormones, and other laboratory markers among elderly patients with severe and non-severe asthma who are not using regular oral corticosteroids (n = 164).

	Men (n = 62)			Women (n = 102)		
	Non-severe (n = 26)	Severe (n = 36)	P-value	Non-severe (n = 34)	Severe (n = 68)	P-value
Age (years)	76.5 ± 6.8	75.1 ± 7.8	0.47	73.7 ± 6.0	73.9 ± 7.8	0.88
History of administration, no. (%)	6 (23)	23 (64)	<0.01	9 (26)	35 (51)	0.02
Smoking status (pack-years)	25.9 [0–41]	22.8 [1.5–45]	0.86	0 [0-0]	0 [0–0.8]	0.13
BMI (kg/m^2)	24.2 ± 3.4	23.7 ± 5.4	0.15	24.1 ± 4.2	23.1 ± 3.8	0.36
ACT <20, no. (%)	2 (8)	8 (22)	0.13	1 (3)	15 (22)	0.01
At least 2 AEs in the last 12 months, no. (%)	1 (4)	7 (19)	0.07	1 (3)	14 (21)	0.02
At least 1 AE treated in hospital or requiring MV in the last 12 months, no. (%)	0 (0)	1 (3)	0.39	1 (3)	2 (3)	1.00
Comorbidity						
Chronic sinusitis	10 (38)	12 (33)	0.68	12 (35)	30 (44)	0.40
Nasal polyposis	5 (19)	5 (14)	0.58	4 (12)	15 (22)	0.21
N-ERD	0 (0)	1 (3)	0.40	3 (9)	6 (9)	1.00
Asthma-COPD overlap	16 (62)	24 (67)	0.68	1 (3)	6 (9)	0.27
Diabetes mellitus	5 (19)	4 (11)	0.37	5 (15)	11 (16)	0.85
Osteoporosis	0 (0)	2 (6)	0.23	4 (12)	15 (22)	0.21
Lung function						
FEV_1 (% predicted) (%)	0.78 ± 0.20	0.63 ± 0.21	<0.01	0.86 ± 0.20	0.83 ± 0.20	0.60
FVC (% predicted) (%)	0.91 ± 0.20	0.85 ± 0.16	0.06	0.96 ± 0.13	0.95 ± 0.17	0.94
FEV_1/FVC ratio (%)	63.7 ± 13.3	54.0 ± 12.2	<0.01	69.0 ± 9.1	66.6 ± 12.4	0.47
Laboratory data						
Eosinophils (/μL)	270 [130–640]	220 [150–440]	0.65	200 [130–330]	270 [110–610]	0.22
Serum IgE (IU/mL)	178 [92.4–474.5]	315 [113–1193]	0.20	163.5 [51.4–385.6]	174 [68–383]	0.63
BNP (pg/mL)	12.2 [5.8–28.9]	18.8 [8.4–34.1]	0.25	26.0 [13.7–41.6]	21.2 [11.4–35.3]	0.34
Free testosterone (pg/mL)	5.3 [4.0–7.1]	7.6 [4.6–8.6]	0.03	0.3 [0.2–0.7]	0.2 [0.1–0.4]	0.03
Free testosterone, tertile			0.13			0.03
Lower, no. (%)	11 (42)	10 (28)		12 (35)	36 (53)	
Middle, no. (%)	10 (38)	13 (36)		8 (24)	18 (26)	
Higher, no. (%)	5 (19)	13 (36)		14 (41)	14 (21)	
Free testosterone under LOD†, no. (%)	1 (4)	0 (0)		4 (12)	19 (28)	
DHEAs (μg/dL)	62.0 [41.8–89.3]	72.5 [39.0–109.8]	0.62	57.0 [42.5–88.5]	32.0 [17.3–59.8]	<0.01
DHEAs, tertile			0.94			0.02
Lower, no. (%)	9 (35)	12 (33)		7 (21)	28 (41)	
Middle, no. (%)	11 (42)	10 (28)		11 (32)	22 (32)	
Higher, no. (%)	6 (23)	14 (39)		16 (47)	18 (26)	
DHEAs under LOD†, no. (%)	0 (0)	0 (0)		0 (0)	0 (0)	
Estradiol (pg/mL)	21.7 [17.8–29.1]	23.2 [18.2–33.2]	0.30	2.50 [2.50–2.50]	2.50 [2.50–2.50]	0.37
Estradiol, tertile			0.42			0.19
Lower, no. (%)	9 (35)	12 (33)		N/A	N/A	
Middle, no. (%)	11 (42)	10 (28)		N/A	N/A	
Higher, no. (%)	6 (23)	14 (39)		N/A	N/A	
Estradiol under LOD†, no. (%)	0 (0)	1 (3)		28 (82)	61 (90)	
GINA treatment step 1–3/4/5, no. (%)	26 (100)/0 (0)/0 (0)	0 (0)/13 (36)/23 (64)	<0.01	34 (100)/0 (0)/0 (0)	0 (0)/38 (56)/30 (44)	<0.01
Biologic therapy	0 (0)	6 (17)	0.03	0 (0)	8 (12)	0.04

BMI, body mass index; ACT, Asthma Control Test; AE, acute exacerbation; MV, mechanical ventilation; N-ERD, NSAIDs-exacerbated respiratory disease; COPD, chronic obstructive pulmonary disease; FEV_1 (% predicted), predicted forced expiratory volume in 1 s; FVC (% predicted), predicted forced vital capacity; FEV_1/FVC ratio, the forced expiratory volume in 1 s divided by the forced vital capacity; BNP, brain natriuretic hormone; LOD, limit of detection; DHEAs, dehydroepiandrosterone sulfate; N/A, not applicable; GINA, Global Initiative for Asthma.
We summarized the results using the mean ± SD and median [interquartile range] for continuous variables and frequency (%) for categorical variables.
† free testosterone <0.2 pg/mL, DHEAs <0.5 μg/dL, estradiol <5.0 pg/mL.

population, higher age was significantly correlated with lower levels of free testosterone and DHEAs in men (Spearman's rank correlation coefficient for free testosterone = −0.39, p < 0.01; for DHEA = −0.43, p < 0.01), but not women (Spearman's rank correlation coefficient for free testosterone = −0.09, p = 0.36; for DHEA = −0.18, p = 0.08).

Testosterone and severity of asthma in patients not currently taking regular OCS: main analysis (n = 164)

As shown in Table 1, levels of free testosterone in women were significantly lower in those with severe asthma. Figure 4B shows the results of multivariate logistic regression analysis demonstrating the association between lower tertiles of serum free testosterone, and severe asthma among women remained significant even after adjustment for age (p for trend, 0.03). Although univariate comparisons of levels of serum free testosterone in men showed significantly higher level in severe asthma (Table 1), there was no statistically significant association between tertiles of free testosterone level and severe asthma after adjustment for age (Fig. 4A). An association between lower levels of DHEAs and severe asthma was observed only in women (p for trend, 0.02, Fig. 4D). Levels of estradiol were similar between severe and non-severe asthma in men. In women, estradiol was not detected in 87 % of cases, and the prevalence of detection was not different between those with severe and non-severe asthma.

There was no statistically significant association between the levels of any of studied sex hormones and spirometry measures (FEV_1 (% predicted), FEV_1/FVC ratio, and forced expiratory flow at 50 % of forced vital capacity), serum total IgE level, nor blood eosinophil counts for either sex. A significant positive correlation was observed between the level of free testosterone and hand grip strength among women (Spearman's Rank correlation coefficient = 0.24, p = 0.02), whereas levels of other sex hormones were not correlated with hand grip strength. The correlation between the level of free testosterone and hand grip strength among women was statistically significant even after adjustment for age, body mass index (BMI), and serum creatinine level (standard partial regression coefficients for multiple regression analysis = 0.181, P = 0.04).

Testosterone and asthma severity in lifetime non-OCS users: sensitivity analysis (n = 150)

In the sensitivity analysis, we restricted the study population to lifetime non-OCS users to exclude the potential influence of past regular use of OCS on the association between sex hormone levels and asthma severity (Fig. 1). Even after this limitation, the statistical association of lower serum levels of free testosterone and DHEAs with asthma severity was marginally significant in women (Fig. 5).

A significant positive correlation was also observed between the level of free testosterone and hand grip strength among women (Spearman's rank correlation coefficient = 0.24, p = 0.02), whereas levels of other sex hormones were not correlated with hand grip

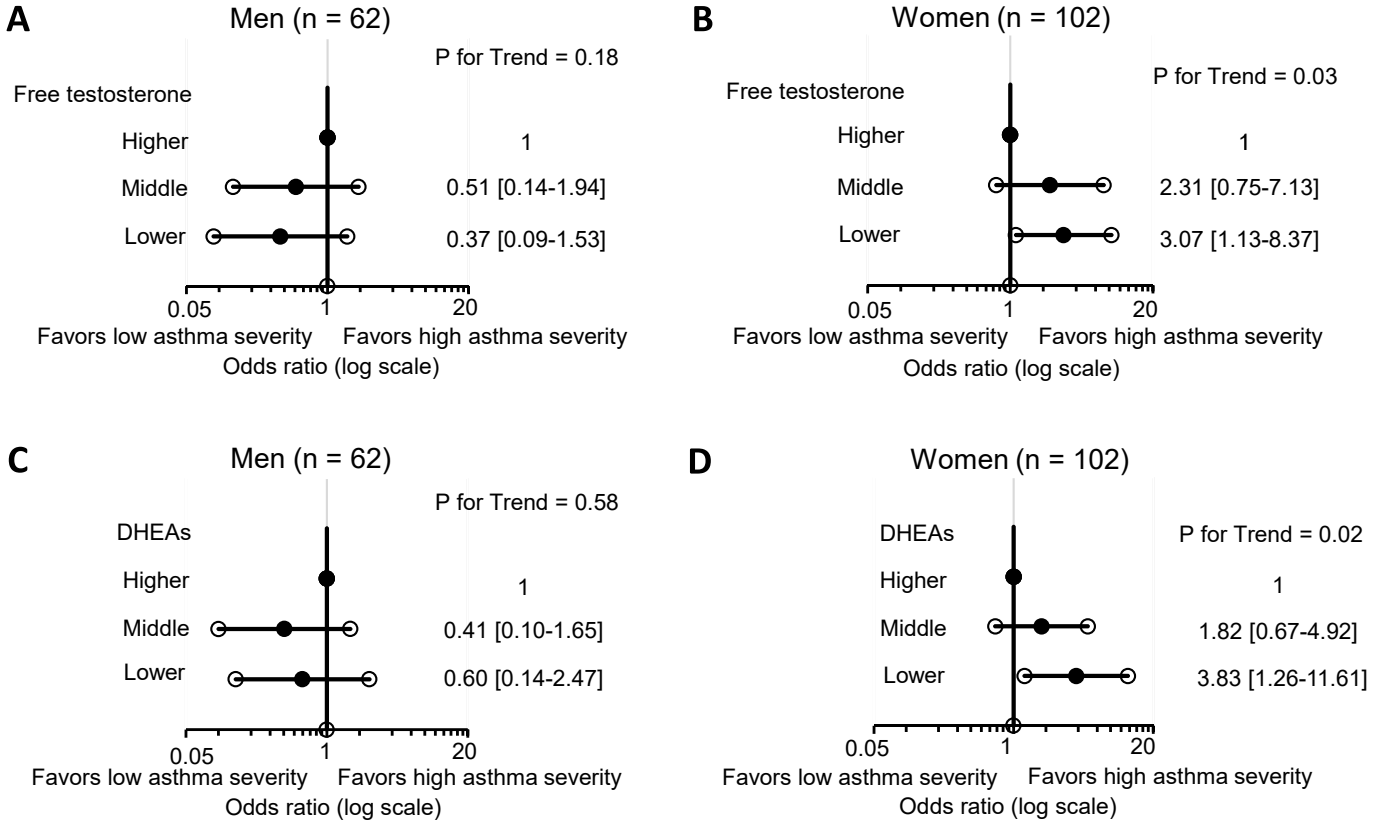

Fig. 4. Association of lower levels of free testosterone and DHEAs with severe asthma by sex among elderly patients with asthma not using regular oral corticosteroids. Odds ratios for the association between tertiles of hormone levels after adjustment for age are shown. Free testosterone and DHEAs are not mutually adjusted. DHEA, dehydroepiandrosterone sulfate.

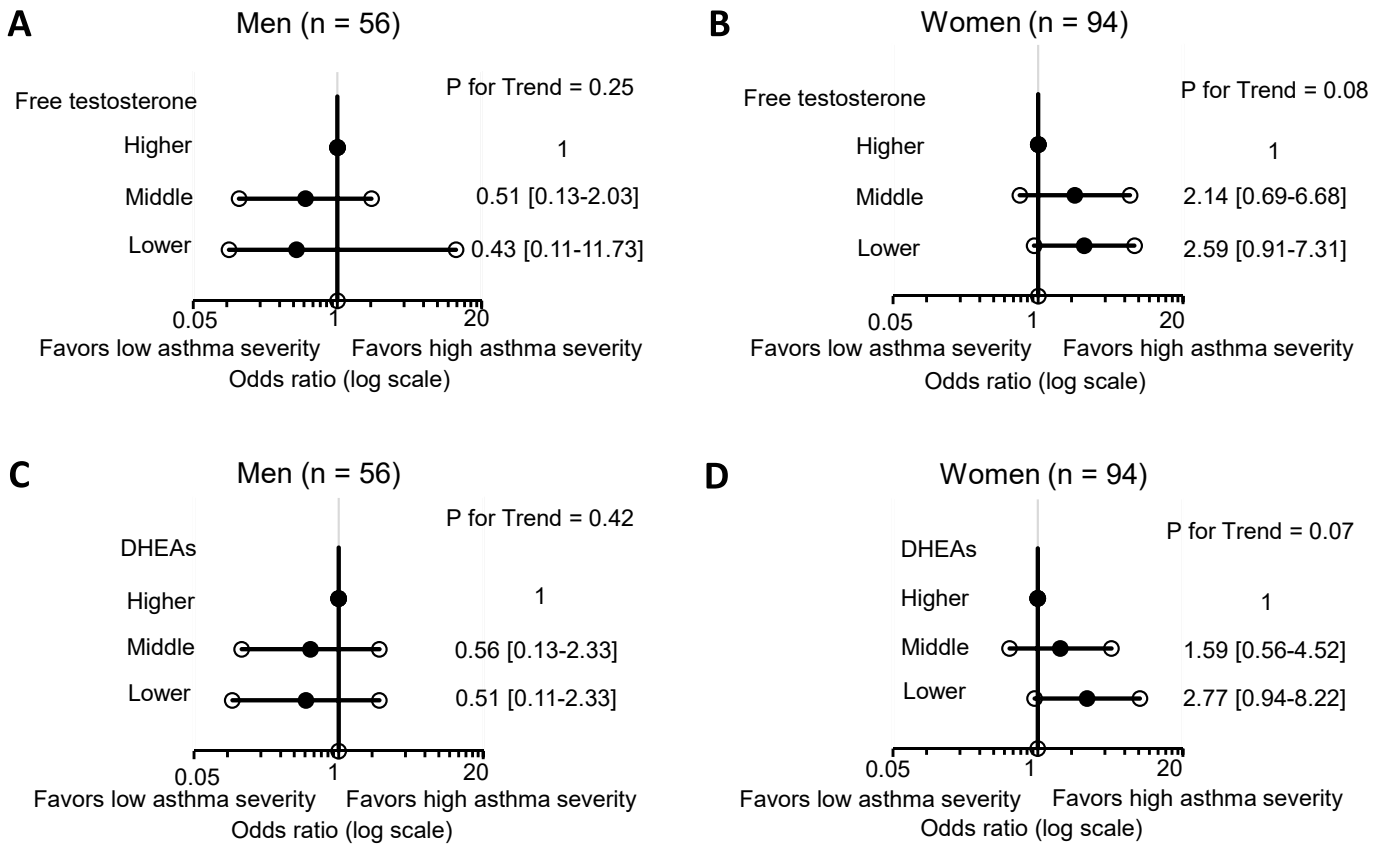

Fig. 5. Association of lower levels of free testosterone and DHEAs with severe asthma by sex among elderly patients with asthma who had not used regular oral corticosteroids over their lifetime. Odds ratios for the association between tertiles of hormone levels after adjustment for age are shown. Free testosterone and DHEAs are not mutually adjusted. DHEA, dehydroepiandrosterone sulfate.

strength. The correlation between the level of free testosterone and hand grip strength among women showed marginal statistical significance after adjustment for age, BMI, and serum creatinine level (standard partial regression coefficients for multiple regression analysis = 0.164, p = 0.08).

Discussion

The major findings in the present study are as follows. First, current regular use of OCS in elderly women with asthma was associated with a lower serum testosterone level. Second, this is the first study to show a significant association between lower serum levels of testosterone and severe asthma among elderly women not using OCS.

DHEAs are mainly produced by the adrenal cortex in men and women, and DHEA levels are reduced in OCS users because of the treatment-related, negative feedback suppression of adrenal function. Inhaled corticosteroids have also been linked with decreased levels of serum DHEA in patients with asthma.[15] Regarding testosterone, its association with OCS use is controversial. In some studies, low serum testosterone levels were reported in men who used OCS,[10–13] whereas, in other studies, there was no association between glucocorticoid therapy and levels of serum testosterone.[14] In our study, no statistically significant association was noted in men. The gonads (testes) are the main source of testosterone production in men. Potential mechanisms for reduced serum testosterone levels among men using OCS include the negative feedback suppression of gonadotropin releasing hormone, resulting in decreased luteinizing hormone secretion.[11]

However, regarding elderly women in our study, significantly lower serum free testosterone levels were observed in current OCS users. This is consistent with a recent study of severe adult asthma in Europe that found lower urinary testosterone levels in women with severe asthma taking corticosteroids.[15] The reason for the sex difference in the association between OCS use and free testosterone level may be linked to sex differences in organs producing testosterone. Gonads (ovaries) are a critical source of testosterone in women. Furthermore, the adrenal cortex also greatly contributes to the production of testosterone in women.[16] Thus, the suppression of adrenal function associated with glucocorticoid therapy is likely to decrease serum testosterone levels in women rather than in men.[16]

Recent studies suggested the protective roles of androgens in asthma. Using a mouse model, Cephus and colleagues showed that testosterone negatively regulated group 2 innate lymphoid cell-mediated allergic airway inflammation.[17] In a clinical study of women with moderate-to-severe asthma, nebulized DHEAs improved asthma symptoms.[18] Another study showed that the oral intake of DHEA increased the FEV_1 compared with placebo in premenopausal women with mild-to-moderate asthma with low baseline DHEA.[19] However, the result of our study suggests that OCS used to treat severe asthma can cause decreased levels of serum testosterone due to the suppression of adrenal function in women. Taken together, we speculated that OCS treatment used to control severe asthma in elderly women might decrease their serum testosterone levels, which in turn may cause more severe disease in the opposite direction. A hypothetical illustration of a vicious cycle involving OCS, decreased serum testosterone levels, and severe

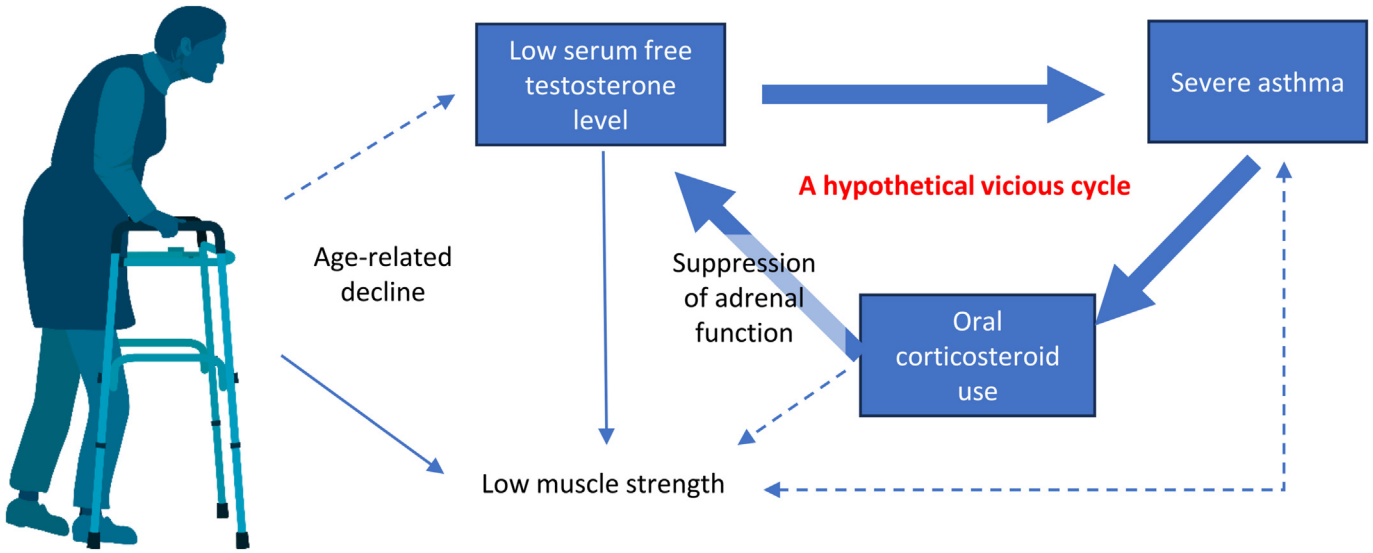

Fig. 6. A hypothetical vicious cycle between oral corticosteroid use, low serum testosterone levels, and severe asthma in elderly women estimated based on the findings of this study and those from previous studies. Associations indicated by solid lines were significant in this study, and those indicated by dashed lines were significant in previous studies.

asthma estimated by the findings of our study and those from previous studies is shown in Figure 6. Furthermore, lower testosterone levels among women in our study were associated with low hand grip strength, and low muscle strength was reported to be associated with poor clinical outcomes among those with moderate-to-severe asthma.[20] Thus, low testosterone levels may also be linked to asthma severity via muscle weakness (Fig. 6). Additionally, it is also possible that serum testosterone levels in women with severe asthma were reduced for reasons other than OCS use, e.g., through increased physical stress caused by chronic asthma symptoms and frequent exacaerbations,[21] which may also have caused severe disease.

Some studies have shown an association between increased estradiol levels and asthma severity among females. A study of adolescents with asthma aged 6–18 years enrolled in a severe asthma research program reported an association between higher estradiol levels with worse lung function and asthma control in females.[22] Another study of postmenopausal women with asthma showed higher levels of estradiol among those with severe disease than those with mild-to-moderate disease. However, these associations between estradiol and asthma severity have not been studied among older women, and our study is the first to evaluate this. However, most women in our study were postmenopausal, and 87 % of the women had estradiol levels below the detection limit. Furthermore, there was no association between estradiol levels and asthma severity. Instead, only low testosterone level was associated with asthma severity. There is a possibility that the association between serum testosterone levels and asthma severity, which was shown in our study, is pronounced in older women, because the effect of estradiol, one of the strongest contributors to asthma pathogenesis, on asthma severity had disappeared in this age group.

The major limitation of this study is related to its cross-sectional nature. A causal relationship between serum free testosterone and asthma severity is not clear in this study. Another limitation may be related to insufficient adjustment for confounding factors in the multivariate analysis due to sample size limitations.

In conclusion, the present study revealed a lower level of serum free testosterone in elderly women with severe asthma. Due to its cross-sectional nature, the causal relationship is unclear. However, this may open a novel avenue to better understand the pathogenesis of severe asthma in elderly women. Furthermore, the results of this study also suggest that OCS, which is used to control severe asthma, may contribute to decreased serum testosterone levels, which in turn may cause more severe disease in the opposite direction. To avoid the reduction of testosterone levels in women, other therapeutic agents may be preferred over systemic corticosteroids for the treatment of severe asthma. Future research should investigate the potential for treatment with testosterone replacement for severe asthma patients with low testosterone levels.

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Conflict of interest

KR received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Sanofi, and AstraZeneca. YF received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Thermo Fisher Diagnostics, Torii Pharmaceutical, Novartis Pharma, Kyorin Pharmaceutical, and Sanofi. YK received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Sanofi, GlaxoSmithKline, and AstraZeneca. KS received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Novartis Pharma, Kyorin Pharmaceutical, Sanofi, GlaxoSmithKline, and AstraZeneca. TI received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from AstraZeneca. JA received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Sanofi, AstraZeneca, GlaxoSmithKline, Chugai pharmaceutical, and Nippon Boehringer Ingelheim. MT received grants or contracts from any entity from GlaxoSmithKline (UK). MT received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from GlaxoSmithKline, Sanofi, and AstraZeneca. HM received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Sumitomo Pharma, Bayer Pharma Japan, and Daiichi Sankyo. The rest of the authors have no conflict of interest.

Authors' contributions

KR, YF, MT, and HM contributed to conceptualization and the design of the protocol; KR, YF, and EN were responsible for data analyses. YK, KS, TI, TN, JA, and KK contributed to interpretation of data; KR and YF drafted the manuscript; and MT and HM contributed to the critical revision of the manuscript. All authors approved the final version of the manuscript.

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