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Original Article

Phenotypic analysis of asthma in Japanese athletes

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EIB, exercise-induced bronchoconstriction; FEV_1, forced expiratory volume in 1 s; FeNO, fraction of exhaled nitric oxide; FVC, forced vital capacity; GETE, Global Evaluation of Treatment Effectiveness; ICS, inhaled corticosteroid; IgE, immunoglobulin E; LABA, long-acting β-adrenergic receptor agonist; LTRA, leukotriene receptor antagonist; PC_{20}, provocative concentration causing a 20% drop in FEV_1; RAST, radioallergosorbent test

ABSTRACT

Background: Asthma in athlete populations such as Olympic athletes has various pathogeneses. However, few reports are available on the features of asthma in the athlete population in clinical practice. In this study, we focused on classifying asthma in Japanese athlete population.
Methods: We performed a cluster analysis of data from pulmonary function tests and clinical biomarkers before administering inhaled corticosteroids (ICS) therapy in athlete population of individuals diagnosed with asthma (n = 104; male, 76.9%; median age, 16.0 years), based on respiratory symptoms and positive data on methacholine provocation tests. We also compared backgrounds, sports types, and treatments between clusters.
Results: Three clusters were identified. Cluster 1 (32%) comprised athletes with a less atopic phenotype and normal pulmonary function. Cluster 2 (44%) comprised athletes with a less atopic phenotype and lower percent predicted forced expiratory volume in 1 s (%FEV_1) values, despite less symptomatic state. Cluster 3 (24%) comprised athletes with a strong atopic phenotype such as high eosinophil count in the blood and total serum immunoglobulin E level. After treatment with ICS or ICS plus long-acting β-adrenergic receptor agonist for 6–12 months, %FEV_1 values were significantly improved in Cluster 2 athletes, whereas Cluster 3 athletes had a significant decrease in the fraction of exhaled nitric oxide compared to pretreatment values.
Conclusions: These data suggest three clusters exist in Japanese athlete population with asthma. Between the clusters, the characteristics differed with regard to symptoms, atopic features, and lower %FEV_1 values. The pathogeneses between clusters may vary depending on the inflammation type and airway hyperresponsiveness.

Introduction

Exercise is a well-established factor that is associated with asthma exacerbation.[1] Approximately 70%–80% of asthma patients experience exercise-induced bronchoconstriction (EIB).[2] A higher prevalence of asthma has been reported in athletes than in the general population.[3,4] Athletes participating in sports such as cross-country skiing, skating, swimming, cycling, and marathon running have an increased risk of developing airway hyperresponsiveness (AHR). These sports are characterized by cold air exposure or a high amount of ventilation.[5,6]

Inhaled corticosteroids (ICS) are recommended for managing asthma in the athlete population and in the general population.[7] We previously reported that monotherapy with ciclesonide (CIC), a new ICS administered once daily as a prodrug, is more effective for symptom control and reducing the fraction of exhaled nitric oxide (FeNO) compared with montelukast, a leukotriene modifier administered once daily.[8] Another study[9] of cross-country skiers showed that ICSs have a minimal effect in ameliorating respiratory symptoms and AHR to methacholine. Based on these reports, the pathogeneses of athlete asthma are likely diverse. We previously

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reported differences between ICS-responders and ICS−non-responders in an athlete population.[10] Another study reported that the features of asthma in an athlete population were characterized by two distinct phenotypes: (1) atopic asthma and (2) sports asthma.[11] However, detailed investigations of a less atopic phenotype that is less responsive to ICS and presumably induced by hard training has been insufficiently described.

Cluster analysis has recently been used for the classification of populations with asthma, especially in difficult-to-treat asthma.[12–14] This technique is helpful for classifying phenotypes and for determining treatment or warning of exacerbation. To date, cluster analyses of asthma were conducted on individuals with severe asthma,[12,13] adult asthma,[14,15] and pediatric asthma,[16,17] whereas a cluster analysis of asthma in an athlete population has not been reported. Moreover, most studies associated with asthma analyzed the data after the induction of therapy because the aim of the analysis was to elucidate the classification of difficult-to-treat asthma[13] or asthma with rapidly declining forced expiratory volume in 1 s (FEV_1).[15]

In this study, we classified asthma in an athlete population by using the data from pretreatment with a controller such as an ICS. We separated asthma patients in an athlete population into three clusters based on data from lung function and biomarkers before the induction of therapy.

Methods

Athletes

Between January 2010 and December 2013, we screened regional athletes, primarily high school students, at Niigata Institute for Health and Sports Medicine (Niigata City, Japan). Athletes with respiratory symptoms and positive findings on the methacholine provocation test were diagnosed as having asthma. Some athletes with relatively low FEV_1/forced vital capacity (FEV_1/FVC) levels (i.e., FEV_1/FVC <80%) and AHR to methacholine were diagnosed with asthma, despite having few symptoms. One hundred fifty-four athletes were diagnosed with asthma. Eighteen athletes had already undergone maintenance therapy such as with an ICS or an ICS plus a long-acting β-adrenergic receptor agonist (LABA) combination (e.g., budesonide/formoterol or fluticasone/salmeterol). For 24 athletes, we did not have important pretreatment data such as FeNO values, the provocative methacholine concentration causing a 20% drop in FEV_1 (PC_{20}), immunoglobulin E (IgE) levels, or pulmonary function indices. We also excluded three athletes with complications (e.g., anemia and irritable bowel syndrome) and five athletes who underwent ICS or ICS/LABA combination therapy within 6 months. A total of 104 athletes (80 men) who were nonsmokers and had continued ICS therapy or ICS/LABA combination therapy for at least 6 months were enrolled in this retrospective analysis.

Athletes in this study were individuals who were competitive at the regional to national level and trained approximately 20 h/week. Sports types were categorized as endurance/nonendurance sports, winter/summer sports, and indoor/outdoor sports based on the work of Alaranta *et al.*[18] (Table 1). This study was performed in accordance with the Ethical Principles for Medical Research Involving Human Athletes, the Declaration of Helsinki, and with the approval of the Ethics Committee of Niigata Institute for Health and Sports Medicine (Niigata City, Japan).

Clinical assessment

Before treatment, all athletes underwent a physical examination; pulmonary function testing; methacholine provocation tests; measurements of the FeNO level, peripheral blood eosinophil count, and total IgE level; and a radioallergosorbent test (RAST) for mites, ragweed, and cedar pollen. Pulmonary function testing was performed using a spirometer (SpiroSift SP-470; Fukuda Densi, Tokyo, Japan) in accordance with the American Thoracic Society guidelines.[19] The FeNO level was measured using a nitric oxide (NO) analyzer (Kimoto Denshi, Osaka, Japan) with an online method. The method of measuring FeNO conformed to a previous mutual consensus statement from the American Thoracic Society/European Respiratory Society.[20] The methacholine challenge involved 2 min of tidal breathing of methacholine, and the PC_{20} was determined.[21] A PC_{20} < 8 mg/mL was defined as a positive response in this study. The athletes also underwent the Asthma Control Test (ACT) in the clinic. The details of the procedures are provided in the Supplementary Methods.

Table 1
Sports classifications of the athletes.

Sport classification	Sport (percentage of athletes)
Endurance	Cross-country skiing (27.9), canoeing (2.9), badminton (2.9), track and field (1.9; >800 m runners), tennis (1.9)
Winter	Cross-country skiing, alpine skiing (11.5), figure skating (2.9), snowboarding (1.0)
Indoor	Judo (8.7), badminton, figure skating, basketball (1.9), fencing (1.9), volleyball (1.0), karate (1.0), kendo (1.0)
Other	Baseball (12.5), soccer (7.7), track and field (5.8), archery (1.0), ultimate frisbee (1.0)

Assessment

The athletes were treated with an ICS alone or an ICS/LABA combination for at least 6 months, based on a physician's judgment. Briefly, athletes who had a relatively lower (i.e., <85%) percent predicted FEV_1 (%FEV_1) or some symptoms unrelated to exercise underwent ICS/LABA treatment rather than ICS treatment alone. The response to treatment was assessed using the physician's Global Evaluation of Treatment Effectiveness (GETE), as previously described.[10,22,23] An overall clinical evaluation of asthma control from 3 to 6 months was judged from all available information, which included patient interviews, physical examinations, pulmonary function tests, and FeNO levels. Asthma treatment was stepped down if the GETE rating for 6 months was “excellent” (i.e., complete control of asthma) or “good” (i.e., marked improvement of asthma), whereas therapy was stepped up if the GETE rating for 6 months was “poor” (i.e., no appreciable change in asthma symptoms) or there was a worsening of asthma at any time. The definition of step-down and step-up are described in the Global Initiative for Asthma guidelines.[24] The data from pulmonary function testing and the FeNO after treatment were also compared to the baseline data.

Statistical analysis

A hierarchical cluster analysis using Ward's method was conducted to generate a dendrogram to estimate the number of clusters. Previous research[12] has consistently revealed important variables for cluster establishment such as age at onset, eosinophilic inflammation, airflow variability, and IgE levels. One-half of the athletes in this study had a history of pediatric asthma, although all athletes had reached at least clinical remission during their elementary school years and were therapy-naïve patients. Therefore, we determined that their age at onset was when they were newly diagnosed. Furthermore, age and sex were indispensable variables; however, the age composition in this study was limited and male athletes were overrepresented. Therefore, these factors may drive the hierarchical clustering results. We applied the

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Table 2
Clinical characteristics.

Sex (M/F) (n)	80/24
Age (y) median (IQR)	16.0 (15–17)
Sports	
Winter (%)	43.3
Endurance (%)	37.5
Indoor (%)	22.1
Symptoms unrelated to exercise	14.4
Symptoms related to exercise	86.5
Asthma in childhood (%)	51
Allergic rhinitis (%)	61.5
Serum total IgE (IU/L) median (IQR)	223.0 (47.4–598.5)
Positive rate of mite-specific IgE (%)	64.4
Positive rate of cedar pollen-specific IgE (%)	55.8
Blood eosinophil (/μL) median (IQR)	177.5 (107.5–333.8)
FeNO (ppb) median (IQR)	38.2 (24.4–81.5)
PC_{20} (mg/mL) median (IQR)	1.7 (0.7–3.5)
% FEV_1 (%) mean (SD)	94.0 (13.1)
FEV_1/FVC (%) mean (SD)	86.2 (6.8)
% MMF (%) mean (SD)	98.5 (27.4)

IgE, immunoglobulin E; FeNO, fraction of exhaled nitric oxide; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; MMF, maximum mid-expiratory flow rate; PC_{20}, provocative concentration causing a 20% drop in FEV_1. Data are expressed as the median (interquartile range [IQR]) or mean (standard deviation [SD]).

data from FeNO, pre-bronchodilator %FEV_1, PC_{20}, and IgE levels. The values of %FEV_1 were distributed normally; therefore, we applied logarithmic data for FeNO, PC_{20}, and IgE because these data became normally distributed after the log transformation. Finally, four variables were selected for cluster analysis: 1) FeNO (log-transformed), 2) %FEV_1, 3) PC_{20} (log-transformed), and 4) IgE (log-transformed).

To compare the differences between the clusters, a one-way analysis of variance and the chi-square test were used for continuous and categorical variables, respectively. The in-group (i.e., pre- and post-treatment) comparisons were performed by using Wilcoxon's signed-rank test. Most statistical analyses were performed with JMP software, version 11 (SAS Institute, Tokyo, Japan). Decision tree analysis was performed using CAnalysis ver. 4.0 software. For all statistical analyses, $p < 0.05$ was considered significant.

Results

One-hundred-four athletes who were diagnosed as having asthma were analyzed in this study. The sports classifications of the athletes and baseline data of all athletes are shown in Tables 1 and 2, respectively. The distribution by sports type was 43.3% for winter sports, 37.5% for endurance sports, and 22.1% for indoor sports. The baseline data for each sports type were apparently not different (data not shown). Approximately 50% of the athletes had a history of pediatric asthma and 66% and 50% of athletes were positive for IgE specific to mites and cedar pollen, respectively. The prevalence of pediatric asthma was not different among the different sports types (data not shown).

The hierarchical cluster analysis revealed three distinct phenotypic groups. The demographic features of the groups are shown in Table 3. Age, sex, body mass index, allergic rhinitis comorbidity, and sports type were not significantly different between the groups. Cluster 1 consisted of 33 (32%) athletes with moderate levels of FeNO and IgE as follows (values are listed as the median [interquartile range (IQR)]): 32.2 (18.3–39.2) parts per billion (ppb) and 223.0 (39.3–555.0) IU/L, respectively. Cluster 2 consisted of 46 (44%) athletes and included a considerable number of female athletes. This cluster also had the lowest levels of FeNO, total IgE concentrations, and peripheral eosinophil counts as follows (listed by median [IQR]): 28.6 (22.0–48.6) ppb, 89.0 (36.3–193.5) IU/L, and 137.1 (86.0–214.2)/μL, respectively. This cluster of athletes also had lower %FEV_1 values with a mean (standard deviation [SD]) %FEV_1 of 85.0% (10.0%), despite having fewer symptoms. Cluster 3 consisted of 25 (24%) athletes. Most athletes in this cluster were male; had a history of pediatric asthma; and had atopic features, which included higher levels (listed as the median [IQR]) of FeNO (125.2 [93.7–137.6] ppb), total IgE (632.0 [423.0–727.0] IU/L), and blood eosinophil count (400.1 [298.0–483.5]/μL), and a greater airway response to methacholine (PC_{20}, 0.8 [0.3–1.3] mg/mL).

A decision tree analysis was performed by using subsets of these four variables to assess significant determinants for this classification. The %FEV_1 and FeNO values and serum total IgE levels at baseline were identified as the determinants for assignments to each cluster (Fig. 1).

Table 3
Demographic features of the groups by cluster analysis.

	Cluster 1	Cluster 2	Cluster 3	*p* value
Sample	33	46	25	
Sex (M/F) (n)	26/7	32/14	22/3	$p = 0.2023$
Age (y) median (IQR)	16.0 (15–17)	16.0 (15–17)	16.0 (15–17)	$p = 0.9164$
Body mass index (kg/m^2)	21.4 (19.8–23.0)	20.7 (19.3–23.4)	20.8 (19.9–22.8)	$p = 0.7050$
Winter sport (%)	45.5	41.3	44.0	$p = 0.7357$
Endurance sport (%)	36.4	34.8	44.0	$p = 0.9315$
Indoor sport (%)	20.7	26.1	16.0	$p = 0.6127$
Symptoms unrelated to exercise	21.2	4.3	24.0	$p = 0.0322^*$
Symptoms related to exercise	90.9	80.4	92.0	$p = 0.2655$
Asthma in childhood (%)	33.3	39.1	96.0	$p < 0.0001^*$
Allergic rhinitis (%)	63.6	60.9	60.0	$p = 0.9536$
Serum total IgE (IU/L) median (IQR)	223.0 (39.3–555.0)	89.0 (36.3–193.5)	632.0 (423.0–727.0)	$p < 0.0001^*$
Positive rate of mite specific IgE (%)	63.6	47.7	100.0	$p < 0.0001^*$
Positive rate of cedar pollen specific IgE (%)	57.6	45.5	80.0	$p = 0.0202^*$
Blood eosinophil (/μL) median (IQR)	158.6 (96.0–239.7)	137.1 (86.0–214.2)	400.1 (298.0–483.5)	$p < 0.0001^*$
FeNO (ppb) median (IQR)	32.2 (18.3–39.2)	28.6 (22.0–48.6)	125.2 (93.7–137.6)	$p < 0.0001^*$
FEV_1/FVC (%)	89.1 (5.4)	83.4 (6.4)	87.3 (7.4)	$p = 0.0007^*$
%FVC (%)	108.8 (9.9)	98.6 (13.0)	104.3 (9.6)	$p = 0.0005^*$
%FEV_1 (%)	105.7 (6.8)	85.0 (10.0)	94.7 (12.5)	$p < 0.0001^*$
%MMF (%)	117.3 (20.7)	84.3 (23.7)	99.4 (27.5)	$p < 0.0001^*$
PC20 (mg/ml)	2.9 (1.0–5.4)	2.2 (0.9–3.7)	0.8 (0.3–1.3)	$p < 0.0001^*$

IgE, immunoglobulin E; FeNO, fraction of exhaled nitric oxide; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; MMF, maximum mid expiratory flow rate; PC_{20}, provocative concentration causing a 20% drop in FEV_1. Data are expressed as the median (interquartile range [IQR]) or mean (standard deviation [SD]). The asterisks indicate a significant difference between clusters ($^*p < 0.05$).

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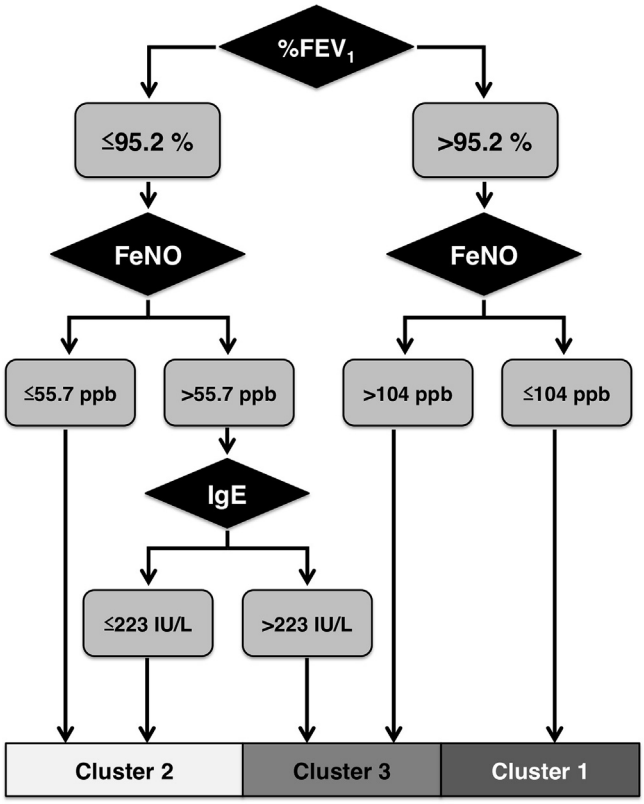

Fig. 1. Decision tree analysis. The athletes are classified into three clusters based on the %FEV_1, FeNO, and serum total IgE values at baseline. Among the 104 athletes, 100 have been correctly assigned to each cluster. FeNO, fraction of exhaled nitric oxide; %FEV1, percent predicted forced expiratory volume in 1 s; IgE, immunoglobulin E; ppb, parts per billion.

Therapeutic profiles in the clusters are shown in Table 4. All athletes were treated with an ICS alone or ICS/LABA combination depending on symptoms or the results of pulmonary function tests after receiving a diagnosis of asthma. Initial therapies of ICS usage and ICS/LABA combination usage were similar between the groups. We assessed the efficacy of treatment every 3–6 months for the GETE rating based on symptom control, pulmonary function test results, or FeNO values. A better rating of GETE (i.e., “excellent” or “good”) and a worse rating of GETE (i.e., “poor” or “worse”) were not significantly different between the groups. The additional rate of leukotriene receptor antagonist (LTRA) usage was not significantly different between the groups.

The %FEV_1 values were significantly improved compared to the pretreatment data in Cluster 2 ($p < 0.0001$). With regard to FeNO values, Cluster 3 had a significant decrease in FeNO values compared to pretreatment values ($p = 0.0016$). In Cluster 1, the %FEV_1 and FeNO values did not change significantly (Fig. 2). In Cluster 2, %FEV_1 values in subjects treated with an ICS/LABA combination were greatly improved compared to those in subjects treated with an ICS alone (Fig. 3).

The ACT scores from the fourth visit were significantly improved in Clusters 1 and 3 compared to the scores from the second visit (Supplementary Fig. 1).

Table 4
Therapeutic profiles among the clusters.

	Cluster 1	Cluster 2	Cluster 3	*p* value
ICS usage (%)	100	100	100	$p = 1.0000$
ICS dose (FP equivalent: μg)	400	400	400	$p = 0.8334$
ICS/LABA (%)	48.5	60.9	48	$p = 0.4408$
LTRA usage (%)	15.2	13	24	$p = 0.4789$
GETE (excellent and good) (%)	58.3	40.9	57.1	$p = 0.2810$
GETE (poor and worse) (%)	16.7	20.5	4.8	$p = 0.2641$

ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; FP, fluticasone; LTRA, leukotriene receptor antagonist; GETE, Global Evaluation of Treatment Effectiveness.

Discussion

In this study, we conducted a cluster analysis based on the pretreatment data of Japanese athletes with asthma. The athletes were separated into three clusters. Among the clusters, the characteristics differed with regard to symptoms, atopic features, %FEV_1 values, and response to treatment. This study was retrospective in design and the sample size was limited. However, this study was the first to use a cluster analysis in a population of Japanese athletes.

For the variables in this cluster analysis, we applied FeNO, total IgE, %FEV_1, and PC_{20} data, which are representative of airway eosinophilic inflammation, atopic phenotype, airway obstruction, and airway response, respectively. These variables were discussed in a previous report,[25] which described an association between pulmonary function and airway inflammation. Age, sex, age at onset of the disease, and smoking history are important for the analysis of features in an asthma population, although we did not apply such parameters. The age composition in this study was concentrated at 15–18 years and male athletes were overrepresented. Therefore, these factors may have affected the results of the hierarchical clustering. All study participants were therapy-naïve patients and had never smoked; therefore, age at onset and smoking history were not applicable. However, one-half of patients had a history of pediatric asthma, and some of them may have had persistent minor symptoms or airway damage. In general, the features of pediatric asthma appeared to be the atopic type in which a person is sensitized to several environmental allergens and has some atopic comorbidities. Therefore, the percentage of asthma in childhood was accumulated in Cluster 3, which had high values for total IgE, FeNO, and eosinophil count in the blood.

The mechanisms of athlete asthma involve airway epithelial damage and mechanical stress caused by hyperpnea, which reflect the differences between athlete types.[26,27] Several reports have also described an increased prevalence of asthma among athletes participating in winter sports and endurance sports.[9,11,28] In this study, we did not apply the types of sports as variables and there was no specific clustering by type of sport. In practice, the type of sport is not restrictively distinguishable. For example, athletes engaged in indoor sports usually train outside. Therefore, we did not believe that applying this factor to this clustering was meaningful. However, cold and dry air exposure and long exercise durations, which are applicable to winter sports and endurance sports, respectively, seem to be associated with the pathogenesis of asthma in athletes. Cross-country skiing actually ranked highest for asthma among our athletes (Table 1).

In this study, Cluster 2 athletes had the lowest values for total IgE level, FeNO level, and blood eosinophil count, and lower positive rates for mite- and cedar pollen-specific IgE in spite of lower %FEV_1 values on spirometry. In previous reports,[29,30] %FEV_1 was negatively correlated with markers of airway eosinophilic inflammation such as FeNO or sputum eosinophilia. Among athletes, some individuals had obstructive impairment without eosinophilic involvement, which is an atypical feature in conventional asthma.[10] A previous report described two distinct phenotypes of asthma in elite athletes by latent class analysis.[11] One phenotype is “atopic asthma” with allergic sensitization, higher levels of FeNO, and

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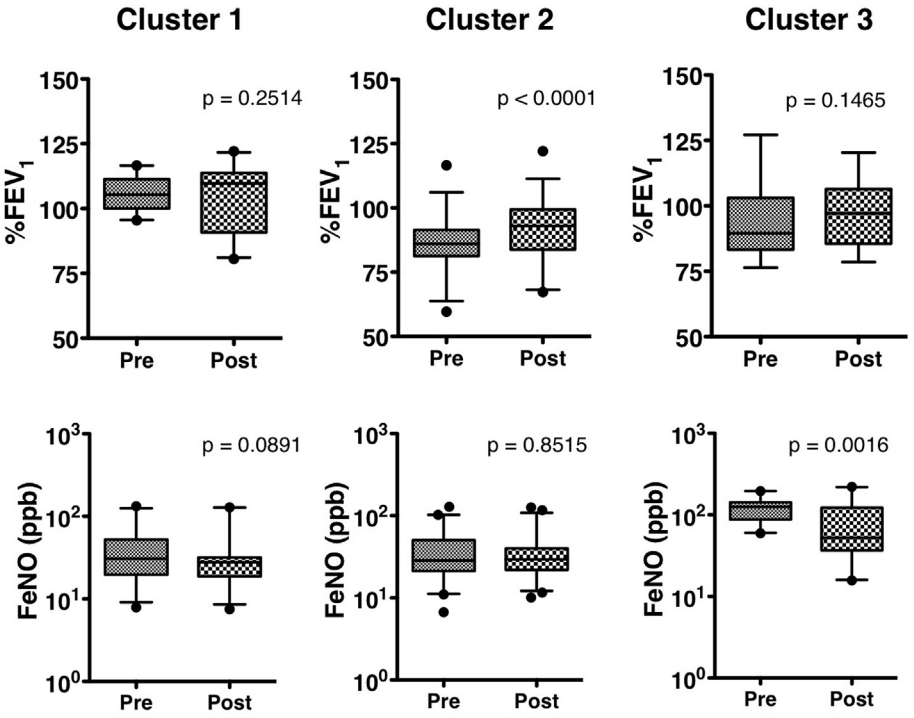

Fig. 2. The box-and-whisker plots show the medians and interquartile ranges and the minimum and maximal values for pretreatment (Pre) and posttreatment (Post) $\%FEV_1$ and FeNO in the clusters. FeNO, fraction of exhaled nitric oxide; %FEV1, percent predicted forced expiratory volume in 1 s.

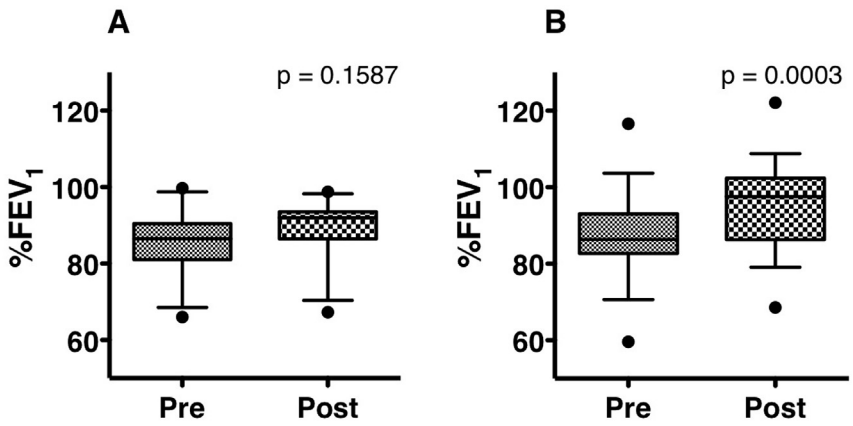

Fig. 3. The box-and-whisker plots show the medians and interquartile ranges and the minimum and maximal values for pretreatment (Pre) and posttreatment (Post) $\%FEV_1$ in the athletes treated with ICS monotherapy (**A**) and ICS/LABA combination (**B**) in Cluster 2. %FEV1, percent predicted forced expiratory volume in 1 s. ICS, inhaled corticosteroid; LABA, long-acting β-adrenergic receptor agonist.

higher prevalences of other allergic diseases. The other phenotype is "sports asthma," which is defined by exercise-induced respiratory symptoms and AHR without allergic features. In this study, Cluster 3 corresponded to "atopic asthma" and Clusters 1 and 2 corresponded to "sports asthma" described in a previous report.[11] Our data indicated that "sports asthma" could be separated into two phenotypes; one of which (i.e., Cluster 1) is normal lung function before treatment and maintenance of lung function. The other phenotype (i.e., Cluster 2) has lower lung function, despite fewer symptoms before treatment, and ICS (with an LABA) effectively improves $\%FEV_1$; however, $\%FEV_1$ remains lower than in the other two clusters, even after therapy with an ICS or ICS/LABA combination (data not shown). Furthermore, cases of established airway remodeling with AHR, but not airway eosinophil infiltration, have been reported in cross-country skiing athletes.[9] These data indicated that airway obstruction in athletes with asthma was evoked without eosinophilic inflammation and led to airway remodeling that persisted after treatment with steroids and bronchodilators.

Another problem in Cluster 2 was that the athletes had fewer symptoms compared to the other two clusters. A previous report[31] reported less reliability when using self-reported symptoms to diagnose an individual with EIB. In some athletes, relatively low FEV_1/FVC values (i.e., FEV_1/FVC <80%) with AHR to methacholine were observed without obvious symptoms. We speculated that they have minor symptoms with exercise but did not recognize the symptoms before starting treatment. After treatment, they came to recognize symptoms with exercise

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because the symptoms and the performance of exercises were improved. From these data and this report, objective data such as pulmonary function tests with a bronchodilator, a provocation test, or biomarker levels are necessary to diagnose asthma in athletes.

In the guidelines for asthma management, ICS monotherapy and ICS/LABA are the mainstream therapies for the athlete population.[24,32] In this study, ICS monotherapy used to be the first choice from the standpoints of medication adherence and cost. However, there has been a change toward prescribing an ICS/LABA combination first after a report emerged that emphasized the relation between airway remodeling and episodic bronchial constriction.[33] Regarding ICS susceptibility, FeNO levels are predictors of the response to ICS.[34] Low levels of FeNO (i.e., <25 ppb) are required to reconsider the diagnosis or maintenance therapy strategy.[34] In asthmatic athletes, noneosinophilic airway inflammation, which is associated with resistance to ICS therapy, is important in developing the pathophysiological aspects of athlete asthma. Furthermore, ICS is less effective in this pathophysiology and a bronchodilator such as a β-agonist or anticholinergic agents are required to control the disease. From our data, the LABA must have contributed to improving the %FEV1 values in Cluster 2 (Fig. 3).

In summary, we conducted a cluster analysis based on pretreatment data from Japanese athletes with asthma. The athletes were separated into three clusters. Athletes in Cluster 1 had a less atopic phenotype and normal pulmonary function. Athletes in Cluster 2 had a less atopic phenotype and lower $\%FEV_1$ values, despite a less symptomatic state. Athletes in Cluster 3 had a strong atopic phenotype. After treatment with an ICS alone or ICS/LABA combination for 6–12 months, $\%FEV_1$ values were significantly improved in Cluster 2. However, Cluster 3 had a significant decrease in FeNO values compared to pretreatment values. These data suggested that the asthma phenotypes among athletes were heterogeneous, and the pathogeneses among subtypes may differ from the pathogeneses of typical chronic allergic airway inflammation.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.alit.2017.02.009

Conflict of interest

The authors have no conflict of interest to declare.

Authors' contributions

KT and TKo designed the study and wrote the manuscript. KT, HU, and MH contributed to data collection. KT, TKo, TS, TH, MA, ES, and TKi performed the statistical analysis and interpretation of the results. All authors have read and approved the final manuscript.

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