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Bronchoscopy and bronchoalveolar lavage findings in cross-country skiers with and without "ski asthma"

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Bronchoscopy and bronchoalveolar lavage findings in cross-country skiers with and without "ski asthma". M. Sue-Chu, L. Larsson, T. Moen, S.I. Rennard, L. Bjermer. ©ERS Journals Ltd 1999.

ABSTRACT: Bronchial hyperresponsiveness to methacholine with asthma-like symptoms ("ski asthma") is frequent in elite cross-country skiers.

To further the understanding of "ski asthma", 10 nonasthmatic, nonatopic controls and 30 adolescent elite skiers were investigated by bronchoscopy and bronchoalveolar lavage (BAL). Nine skiers were atopic without allergy symptoms.

Compared with controls, the macroscopic inflammatory index in the proximal airways in skiers was three-fold greater (median (interquartile range) 3.0 (2.0–5.0) *versus* 1.0 (0.8–2.3), p=0.008). In the BAL fluid, skiers had significantly greater total cell ($p<0.05$) and percentage lymphocyte ($p<0.01$) and mast cell counts ($p<0.05$). Neutrophil and eosinophil counts were not significantly different and eosinophil cationic protein was not detected. Tumour necrosis factor-α and myeloperoxidase were detected in 12 (40%) and six (20%) skiers, respectively. In skiers with ski asthma, the inflammatory index was greater than in nonasthmatic skiers. Lymphocyte subtypes and activation markers, and concentration of albumin, fibronectin and hyaluronan were not different from those in controls.

Cross-country skiers have a minor to moderate degree of macroscopic inflammation in the proximal airways at bronchoscopy and a bronchoalveolar lavage fluid profile which differs in several respects from healthy controls. Skiers with ski asthma tend to show even higher degrees of bronchial inflammation.

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Attacks of asthma can be provoked by physical exercise or exposure to cold air in up to 80% of asthmatic individuals [1, 2]. Such attacks, with symptoms such as wheezing, chest tightness, abnormal shortness of breath or cough, may be the only manisfestation of mild asthma. Bronchial responsiveness to chemical stimuli such as methacholine and to physical stimuli such as exercise and cold air is also usually increased in asthmatic individuals.

Similar respiratory symptoms during or shortly after training and competition are reported by highly trained athletes. The frequency of these asthma-like symptoms is greater in athletes participating in winter sports, such as cross-country skiing, than in athletes participating in summer sports [3, 4]. Bronchial responsiveness to methacholine is also increased in highly trained athletes [5]. In elite cross-country skiers, the prevalence of bronchial hyperresponsiveness is greater than in nonathletic control subjects, and bronchial responsiveness to methacholine increases in the course of the training season and appears to be related to the intensity of the training [6]. Furthermore, the common use of antiasthmatic drugs among these athletes is a reflection of the high prevalence of self-reported asthma and asthma-associated symptoms [7]. Since up to 80% of elite skiers have persistent asthma-like symptoms with bronchial hyperresponsiveness, LARSSON *et al.* [4] suggested that the combination of strenuous training at low temperatures and repeated inhalation of cold air may be a pathogenic factor for asthma. However, it is possible that asthma-like symptoms with bronchial hyperresponsiveness in these athletes ("ski asthma") may be a normal physiological response to extreme stimuli [8].

In asthma, airway symptoms and bronchial hyperresponsiveness are secondary to inflammation in the airways. Knowledge of the asthmatic inflammatory process has been greatly enhanced by assays of inflammatory cells and their mediators and of markers of the remodelling process in the bronchoalveolar lavage (BAL) fluid [9]. To further the understanding of ski asthma, bronchoscopy was performed to assess the degree of macroscopic inflammation in the proximal airways and to obtain BAL for analysis of the distribution of inflammatory cells and lymphocyte subtypes, and of markers of inflammatory cell activation and fibroblastic activity.

Material and methods

Subjects

Thirty (23 male) elite cross-country skiers, aged 16–20 (mean 17.3) yrs, and 10 (seven male) healthy nonathletic control subjects, aged 21–31 (mean 24.4) yrs, participated in the study. Written informed consent was obtained from each subject, as well as from the parents of those subjects

under 18 yrs of age, and the study was approved by the Regional Ethics Committee in Trondheim.

Data about respiratory symptoms, respiratory allergy and use of antiasthmatic medication within the last 12 months were collected with a self-completed questionnaire [7]. Each skier was asked to estimate the time spent in training during the previous year and the number of years of competition. Asthma-like symptoms were defined as the presence within the last year of wheeze, and abnormal breathlessness or chest tightness either on exertion, at rest or on exposure to irritants. Lung function was assessed by spirometry using a Microlab 3300 Mk2 spirometer (Micro Medical, Gillingham, Kent, UK). The better of two measurements with <5% variation was recorded as a percentage of predicted normal values (European Coal and Steel Community/Zapletal reference values). Bronchial responsiveness to methacholine was assessed by a controlled tidal volume breathing jet nebulizer technique as described previously [10]. Hyperresponsiveness was defined as a provocative dose of methacholine causing a 20% fall in forced expiratory volume in one second (PD_{20}) $\leq$1,800 μg ($\leq$9.1 μmol). Serum from all subjects was screened by a Phadiotop CAP™ test (Pharmacia Diagnostics, Lund, Sweden) for the presence of immunoglobulin (Ig)E to a panel of eight aeroallergens (house dust mite, cat, dog, horse, timothy grass and birch pollens, mugwort and cladosporium). There were nine subjects, all skiers, with a positive Phadiotop test.

All subjects were lifetime nonsmokers and had no history of respiratory allergy or use of antiasthmatic medication. Control subjects denied asthma-like symptoms and were not hyperresponsive on methacholine challenge. Of the skiers, 11 (37%) were nonhyperresponsive and 19 (63%) were hyperresponsive to methacholine. Nonhyperresponsive skiers did not have a history of any asthma-like symptoms and were classified as nonasthmatic. Three of these skiers were atopic with a positive Phadiotop test. Of the hyperresponsive skiers, 12 reported asthma-like symptoms and were classified as "ski asthma" (table 1). Two of these skiers had a positive Phadiotop test.

Bronchoscopy, macroscopic inflammatory index and bronchoalveolar lavage

Transoral fibreoptic bronchoscopy (Olympus BF-XT 20 or BF-IT 30 bronchoscope, Tokyo, Japan) was performed under local anaesthesia with xylocaine hydrochloride and premedication. The latter consisted of inhalation of nebulized salbutamol (2.5 mL, 1 mg·mL^{-1}) and ipratropium bromide (1 mL, 0.25 mg·mL^{-1}) 15 min prior to bronchoscopy and intravenous administration of glycopyrronium (0.3–0.5 mg), midazolam (1–2 mg) and alfentanil (0.25 mg) immediately prior to bronchoscopy. Supplementary oxygen (2 L·min^{-1}) was administered *via* a nasal cannula and oxygenation status was monitored by pulse oximetry during the procedure.

A macroscopic inflammatory index, based on friability, vascularity and oedema of the bronchial mucosa, and the amount of secretions in the proximal airways, was recorded in all control subjects, 11 nonasthmatic skiers and 13 hyperresponsive skiers, of whom eight had ski asthma. Friability was the susceptibility of the mucosa to bleed on contact with the bronchoscope. Each parameter was assessed on a five-point scale (0–4) by an experienced bronchoscopist (L. Bjermer) who was blinded to the status of the respiratory symptoms and bronchial responsiveness of the skiers. A maximum score of 16 indicated the presence of severe macroscopic inflammatory changes.

BAL of the medical segment of the middle lobe was performed with 2 × 60 mL aliquots of prewarmed (37°C) phosphate-buffered saline. The BAL fluid was recovered into siliconized plastic containers, stored in an icebath (4°C) and filtered through a nylon filter with a pore diameter of 100 mm (Sintab Product AB, Malmö, Sweden). Aliquots of pooled fluid were processed within 2 h of recovery for the assessment of cellular and noncellular components.

The procedure was performed in the late autumn in the skiers and in the late autumn and in winter in controls. The skiers were in daily training in preparation for the competitive season and did not train on the day of bronchoscopy. Bronchoscopy and BAL were well tolerated by all subjects.

Bronchoalveolar lavage fluid analysis

Cellular components

Total cell counts were performed with an automated cell counter (Technicon H1; Technicon Instruments, Tarrytown, NY, USA).

Differential cell counts were made on cytospin preparations. These were prepared by centrifugation of 400 μL aliquots of BAL fluid at 500 × *g* for 5 min at 4°C. After air-drying, the slides were stained with May-Grünewald-Giemsa for differential cell counting of macrophages, lymphocytes, neutrophils and eosinophils in 300 cells, excluding epithelial cells. Slides were stained with acid toluidine blue and counterstained with Mayer's haematoxylin for mast cell quantification [11]. Differential cell counts were expressed as a percentage of the total cell count.

Lymphocyte subtyping by flow cytometry

Subtyping and the activation status of T-lymphocytes in the BAL fluid were determined by flow cytometry, as the inflammatory process in asthma may be a T-lymphocyte-driven process. Thirteen aliquots of 1.5–2 mL pooled BAL fluid from each subject were placed into 5-mL plastic tubes and centrifuged at 2,500 × *g* for 5 min at 4°C. The supernatant was decanted and stored at -70°C for later analysis and the tubes with cell pellets were placed in an icebath. Ten microlitres of the following combinations of mouse monoclonal antibodies, conjugated with fluorescein isothiocyanate and phycoerythrin, CD3/CD4, CD3/CD8, CD4/CD8,CD45RA/CD4,CD45RO/CD4,CD16+56(NK)/CD3, CD4/DR, CD8/DR, CD4/CD25,CD3/DR (Becton Dickinson Immunocytometry Systems, CA, USA; DAKO A/S, Denmark, Ortho Diagnostic System, New Jersey, USA) were used to stain for surface markers of mature T-cells (CD3), T-helper cells (CD4), T-suppressor cells (CD8), primary T-helper cells (CD4+CD45RA), memory T-helper cells (CD4+CD4RO), natural killer cells (CD16+56) and lymphocyte activation markers of human leukocyte antigen (HLA)-DR (DR) and interleukin IL–2 receptor (CD25).

Table 1. – Characteristics of control and skier groups

	Controls	Skiers	Skier subgroups				
			NBHR (nonasthmatic)	BHR	Ski asthma	Nonatopic	Atopic
n (male)	10 (7)	30 (23)	11 (10)	19 (13)	12 (9)	21 (16)	9 (7)
Training h in the last year	NA	435 (200–650)	428 (200–650)	440 (250–630)	469 (300–630)	435 (200–630)	437 (250–650)
Competitive skiing yrs	NA	7.1 (2–11)	7.2 (3–11)	7.1 (2–11)	7.3 (4–11)	7.0 (3–11)	7.4 (2–10)
FEV1 % pred	97.3±3.1	98.0±2.4	105.0±3.0	94.0±3.0*	94.2±4.5	99.1±3.0	95.4±3.8
FVC % pred	97.8±2.3	97.1±2.5	103.0±9.7	93.7±3.3	95.2±4.5	98.2±3.0	94.5±4.6
FEV1/FVC % pred	101.9±1.7	102.8±1.5	102.1±5.3	103.3±2.2	101.9±2.1	102.9±1.6	102.7±3.3

Data are presented as mean (range) or mean±SEM. Skier subgroups: NBHR (nonasthmatic), nonbronchial hyperresponsive with no asthma-like symptoms; BHR, bronchial hyperresponsive to methacholine with or with asthma-like symptoms; ski asthma, BHR with asthma-like symptoms; nonatopic and atopic. FEV1: forced expiratory volume in one second; FVC: forced vital capacity. *: $p<0.05$ (BHR *versus* NBHR skiers), by analysis of variance.

LeukoGATE^{TM}(CD45/CD14) and negative control simulTEST^{TM} (IgG_1 and IgG_2) stains were also prepared (Becton Dickinson Immunocytometry Systems). After 20 min of incubation in the dark, 2 mL phosphate-buffered saline at 4°C was added to each tube, followed by centrifugation at 2,500 × *g* for 5 min at 4°C. The supernatant was discarded and 500 µL 1% formalin at 4°C was added to each cell pellet. The tubes were stored at 4°C in the dark until analysis with the FACSCAN flow cytometer (Becton-Dickinson Immunocytometry Systems).

Soluble components

Concentrations of markers of inflammation, inflammatory cell activation and fibroblastic activity were measured in the unconcentrated supernatant BAL fluid. Albumin and tumour necrosis factor (TNF)-α were measured by immunoturbidimetry (Unimate 3 ALB; F Hoffmann-La Roche, Basel, Switzerland) and indirect enzyme-linked immunosorbent assay (ELISA), respectively. The detection limit for TNF-α was 0.5 $ng \cdot L^{-1}$. A radioimmunoassay (RIA) was used to measure the concentrations of myeloperoxidase (Pharmacia MPO RIA; Kabi Pharmacia Diagnostics, Uppsala, Sweden; detection limit of 8 $\mu g \cdot L^{-1}$) and eosinophil cationic protein (Pharmacia ECP RIA; detection limit of 2 $\mu g \cdot L^{-1}$). The concentrations of hyaluronan and fibronectin were determined by a radiometric assay (Pharmacia HA test; detection limit of 5 $\mu g \cdot L^{-1}$) [12] and ELISA (detection limit of 10 $\mu g \cdot L^{-1}$) [13], respectively.

Statistical analysis

Data on age, training and years of competitive skiing are presented as mean (range) values and data on lung function as mean±SEM values. Other continuous data were not normally distributed and are presented as median values with interquartile ranges (IQR).

Group data for skiers and controls were analysed by the independent sample t-test or Mann–Whitney U-test, as appropriate. Skiers were divided into subgroups by responsiveness to methacholine, ski-asthma status and atopic status, and compared with controls using either analysis of variance (ANOVA) with Neuman–Keuls multiple comparison test or Kruskal–Wallis H-test with Dunn′s correction for multiple comparisons, as appropriate.

Differences in the detection of inflammatory markers were assessed by Chi-squared test with Fisher′s two-tailed exact test as appropriate. Correlations were assessed by calculation of Spearman correlation coefficients. A p-value of <0.05 was considered to be statistically significant.

Results

The characteristics of controls and skiers are shown in table 1. Training hours and competitive skiing experience were not significantly different in the different skier subgroups. Lung functions parameters were normal and were not significantly different between skiers and controls. Forced expiratory volume in one second (FEV1) (% predicted)

Table 2. – Macroscopic inflammatory index in controls and skiers

Macroscopic appearance	Controls	Skier subgroup				
		NBHR (nonasthmatic)	BHR	Ski asthma	Nonatopic	Atopic
n	10	11	13	8	17	7
Total index	1.3 (0.5–2.3)	2.3 (1.0–3.1)	5.0 (3.0–6.0)***,‡	5.3 (3.7–6.3)***,#	2.9 (2.1–4.5)*	4.0 (1.5–5.8)**
Friability	0.1 (0–0.6)	0.5 (0.1–1.0)	1.0 (0.3–1.9)**	1.3 (0.6–2.0)***,†	0.7 (0.1–1.4)	1.0 (0.3–2.8)**
Vascularity	0.8 (0.3–1.0)	1.0 (0.4–1.6)	1.4 (0.5–2.4)	2.0 (0.7–2.8)	1.2 (0.5–2.0)	1.2 (0.4–1.9)
Oedema	0.3 (0–0.8)	0.1 (0–0.6)	0.8 (0.2–1.6)‡	0.9 (0.3–1.5)#	0.5 (0–1.1)	0.3 (0–0.9)
Secretions	0.2 (0–0.8)	0.6 (0.1–1.3)	0.8 (0.2–1.6)	0.8 (0.2–1.6)	0.8 (0.2–1.5)	0.5 (0–1.2)

Data are expressed as median (interquartile range). Skier subgroups as defined in table 1. ***: $p<0.001$; **: $p<0.01$; *: $p<0.05$, *versus* control. #: $p<0.001$; †: $p<0.05$, *versus* nonasthmatic skiers. ‡: $p<0.001$, *versus* NBHR skiers, by Kruskal–Wallis test with Dunn′s correction.

Table 3. – Comparison of bronchoalveolar lavage fluid differential cell counts between skiers and controls

	Controls	Skiers
Cells $\times 10^7 \cdot L^{-1}$	28.0 (23.0–32.0)	33.0 (29.0–41.3)*
Macrophages %	92.0 (91.3–93.7)	89.4 (83.6–91.7)**
Lymphocytes %	5.7 (3.0–6.0)	8.5 (5.2–14.0)**
Mast cells %	0.02 (0–0.03)	0.04 (0.02–0.11)*
Neutrophils %	2.2 (2.0–2.5)	2.3 (1.3–3.4)
Eosinophils %	0.2 (0–0.3)	0.0 (0.0–0.3)

Data are expressed as median (interquartile range). *: p<0.05; **: p<0.01, Mann–Whitney U-test.

was significantly lower in hyperresponsive than in nonhyperresponsive skiers (p<0.05).

The median (IQR) PD_{20} methacholine value in hyperresponsive skiers was 6.3 (5.6–8.4) µmol and was not significantly different between atopic and nonatopic skiers (5.95 (3.94–6.56) *versus* 7.0 (6.0–9.1) µmol, p=0.09).

Macroscopic inflammatory index

The macroscopic inflammatory index in the proximal airways was greater in skiers than in control subjects (median (IQR) 3.1 (2.0–5.0) *versus* 1.3 (0.5–2.3), p=0.008). The index was significantly greater in both hyperresponsive and "ski asthma" skiers than in controls and skiers without bronchial hyperresponsiveness or ski asthma (table 2).

Compared with controls, mucosal friability was the only parameter in the inflammatory index which was greater in the skiers (median (IQR) 0.8 (0.2–1.5) *versus* 0.1 (0–0.6), p=0.01) and was greater in skiers with hyperresponsiveness (p<0.01), ski asthma (p<0.001) or atopy (p< 0.01). Mucosal oedema was also greater in skiers with hyperresponsiveness or ski asthma than in nonhyperresponsive or nonasthmatic skiers (both p<0.001).

Cellular elements in bronchoalveolar lavage fluid

A minimum of 40 mL BAL fluid was recovered from each subject. Compared with controls, total cell count and percentage counts of lymphocytes and mast cells were significantly greater and percentage macrophage count was significantly lower in skiers. Percentage counts of eosinophils and neutrophils were not significantly different in the two groups (table 3).

On subgroup analysis, nonhyperresponsive skiers had significantly greater total cell counts than hyperresponsive and ski asthma skiers and a greater mast cell count than controls (fig. 1). Hyperresponsive and "ski asthma" skiers

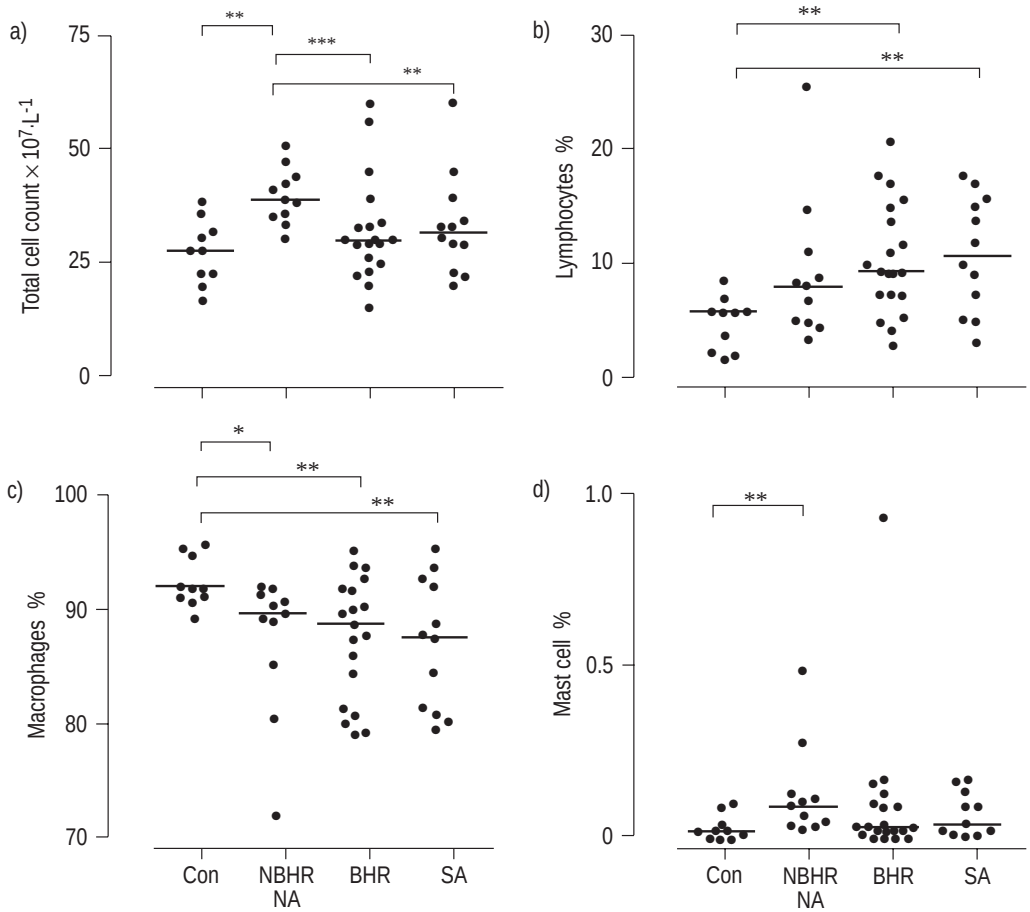

Fig. 1. – a) Total cell, b) lymphocyte, c) macrophage and d) mast cell counts in controls and skier subgroups on the basis of methacholine bronchial hyperresponsiveness (BHR) and asthma-like symptoms. Con: controls; NBHR NA: nonbronchial hyperresponsive, with no asthma-like symptoms; BHR: bronchial hyperresponsive to methacholine with or without asthma-like symptoms; SA: ski asthma, BHR with asthma-like symptoms. *: p<0.05; **: p<0.01; ***: p<0.001.

Table 4. – Lymphocyte phenotypes as determined by flow cytometry

Lymphocyte phenotype	Controls	Skiers
% CD3/CD4 (T-helper cells)	39 (31–47)	53 (39–63)*
% CD3/CD8 (T-suppressor cells)	47 (40–69)	35 (30–51)
CD4:CD8 ratio	0.7 (0.5–1.2)	1.5 (0.9–1.9)*
% CD45RO/CD4 (T-helper primary cells)	91 (80–97)	88 (78–95)
% CD45RA/CD4 (T-helper primary cells)	34 (19–65)	27 (15–33)
Memory:primary (T-helper cells)	2.5 (1.4–5.2)	3.0 (2.6–5.1)
% CD3/DR (activated T-cells)	21 (14–30)	21 (14–26)
% CD4/DR (activated T-helper cells)	21 (14–29)	20 (15–25)
% CD4/CD25 (IL-2 receptor-positive T-helper cells)	5 (4–7)	5 (4–7)
% CD8/DR (activated T-suppressor cells)	28 (18–49)	47 (33–61)*
% CD16+56/CD3 (total natural killer cells)	4 (2–7)	4 (3–6)
% CD3 positive natural killer cells	2 (1–2)	2 (1–3)
% CD3 negative natural killer cells	1 (1–5)	2 (1–3)

Data are median and interquartile range for 10 controls and 30 skiers. IL-2: interleukin-2. *: $p<0.05$ *versus* control, Mann–Whitney U-test.

had significantly greater lymphocyte and lower macrophage counts than controls.

Compared with controls, the total cell count was not significantly different in atopic (30.0 (26.0–39.0) $\times 10^7$ cells·L^{-1}, p=0.1) and nonatopic skiers (33.0 (30.0–38.0), p=0.1). The lymphocyte count was significantly greater in atopic (8.7 (7.3–9.3)%, $p<0.05$) and nonatopic skiers (9.0 (5.0–14.7)%, $p<0.05$). The macrophage count was significantly lower in atopic (89.7 (87.7–90.0)%, $p<0.05$) and nonatopic skiers (89.0 (80.7–91.3)%, $p<0.01$). The mast cell count was not significantly different in the three groups (p=0.11).

Lymphocyte phenotypes

Because of the low numbers of lymphocytes, it was often difficult to isolate the lymphocyte fraction (lymphocyte gating). Therefore, the results were related to the number of T-cells (CD3) or expressed in relation to a specified lymphocyte subpopulation, *e.g.* CD3 or CD4 (T-helper cells).

Compared with controls, skiers had a greater percentage of T-helper lymphocytes (p=0.03), ratio of T-helper to T-suppressor cells (p=0.05) and expression of the HLA-DR epitope on T-suppressor lymphocytes (p=0.04). There were no significant differences between the two groups in the other lymphocyte subtypes (table 4).

On subgroup analysis, the median (IQR) percentage count of T-helper lymphocytes in atopic skiers was 56 (53–57), which was significantly greater than in nonatopic skiers (46 (33–56), $p<0.05$) and in controls (39 (35–56), $p<0.01$). Other lymphocyte subtypes were not significantly different from controls.

Noncellular elements of bronchoalveolar lavage fluid

The albumin concentration was not significantly different in skiers and controls. Of the inflammatory mediators, TNF-α was above the detection threshold (0.5 ng·L^{-1}) in 12 (40%) skiers and was not detected in control subjects (p=0.02). The median (IQR) concentration of TNF-α in these skiers was 0.83 (0.60–0.94) ng·L^{-1}. Myeloperoxidase (MPO) was detected in one (10%) control subject (10 μg·L^{-1}, detection limit 8 μg·L^{-1}) and in six (20%) skiers, with a median (IQR) concentration of 14.1 (10.4–23.5) μg·L^{-1}. Eosinophil cationic protein (ECP) was below the detection threshold of 2 μg·L^{-1} in all skiers and control subjects (table 5).

The fibronectin concentration was not significantly different in skiers and controls. The hyaluronan concentration was 30% lower in skiers than in controls (p=0.03). On subgroup analysis, the concentration of hyaluronan was not significantly different from that in controls.

Correlations

In the skiers, the inflammatory index did not correlate with training, competitive skiing experience, differential cell counts, lymphocyte cell phenotypes or the concentrations of albumin, hyaluronan and fibronectin in the BAL fluid.

Table 5. – Noncellular components in bronchoalveolar lavage fluid from controls and skiers

	Controls	Skiers	Skier subgroup				
			NBHR (nonasthmatic)	BHR	Ski asthma	Nonatopic	Atopic
Albumin g·L^{-1}	19 (11–33)	33 (19–42)	29 (23–36)	35 (17–43)	42 (18–46)	34 (23–42)	18 (14–20)
Hyaluronan μg·L^{-1}	27 (25–34)	19 (10–31)$^{+}$	20 (12–34)	19 (6–30)	19 (11–28)	20 (10–25)	16 (12–17)
Fibronectin ng·L^{-1}	0.13 (0.09–018)	0.14 (0.07–0.22)	0.14 (0.11–0.22)	0.14 (0.06–0.23)	0.19 (0.08–0.37)	0.16 (0.11–0.21)	0.11 (0.06–0.14)
Subjects with detectable n (%)†							
TNF-α	0	12 (40)$^{\#}$	5 (46)	7 (37)	5 (42)	9 (43)	3 (33)
MPO	1 (10)	6 (20)	4 (36)	2 (11)	2 (17)	6 (29)	0
ECP	0	0	0	0	0	0	0

Data are median and interquartile range for 10 control and 30 skiers with subgroups except where indicated. See table 1 for definition and composition of groups. $^{+}$: p=0.03; $^{\#}$: p=0.02, skiers *versus* control; †: detection limit for tumour necrosis factor (TNF)-α=0.5 ng·L^{-1}, eosinophil cationic protein (ECP)=2 μg·L^{-1} and myeloperoxidase (MPO)= 8 μg·L^{-1}.

Discussion

In this study, skiers had mild-to-moderate inflammation in the proximal airways on macroscopic examination and a BAL fluid profile which was different from control subjects. The degree of macroscopic inflammation and the differences in the BAL fluid were more pronounced in hyperresponsive skiers with and without asthma-like symptoms than in nonhyperresponsive skiers.

The possibility of bias in the scoring of the macroscopic appearances is present, as the assessor was not blinded to the skiing status of the subjects and the inflammatory index was not recorded in six hyperresponsive skiers. However, this is considered to be unlikely, as the differences in the appearance of the airway wall in skiers and control subjects were very apparent, and the airways in those six skiers were clearly inflamed with oedema of the subcarinae, hyperaemia and increased secretions. Although semiquantitative and subjective, this method has been used to assess airway inflammation and has been suggested to be a useful additional indicator of disease activity in asthmatics [14].

Some findings in the BAL fluid in the skiers are of interest, such as the detection of TNF-α in more than every third skier with hyperresponsiveness and in almost every other skier without hyperresponsiveness. The presence of this cytokine in the BAL fluid in these skiers may suggest distal airway inflammation, as TNF-α has powerful pro-inflammatory effects and is considered to be a potential mediator in the pathogenesis of asthma and bronchial hyperresponsiveness [15]. Furthermore, the increased lymphocyte counts in skiers suggests increased traffic of these cells across the mucosa in the distal airway. In five skiers, the lymphocyte count was in excess of 14%, which is considered to be abnormal in healthy individuals [16]. The increase in T-helper lymphocyte count appears to be associated with the atopic status rather than with the bronchial responsiveness of the skier. However, the presence of activation surface markers was not different from that in controls. Finally, the presence of MPO in the BAL fluid in six skiers (two with "ski asthma" and four nonasthmatic skiers) suggests neutrophil activation, even though there was no neutrophilia.

The skiers with asthma-like symptoms and a mild degree of bronchial hyperresponsiveness to methacholine may be considered clinically to have mild asthma. However, there was no eosinophilia or evidence of eosinophil activation, while mast cell were paradoxically increased in nonsymptomatic skiers without bronchial hyperresponsiveness. These BAL fluid findings are at variance from those reported in studies of mild allergic and nonallergic asthma [17–20]. Furthermore, skiers with "ski asthma" did not have an increase in T-suppressor lymphocytes or increased activation of helper and suppressor lymphocytes, as has been reported in nonallergic asthma [21]. Finally, there was no apparent increase in fibroblastic activity, since levels of fibronectin, which is a chemoattractant for fibroblasts, and hyaluronan were not significantly different from controls.

While the BAL fluid profile suggests that ski asthma may be a different condition from that of common asthma, it should be remembered that intraluminal and airway indices of inflammation may be discordant. This is exemplified in asthmatics where T-lymphocyte numbers and activation markers are prominent in the airway wall and not in the airway lumen [22]. In order to exclude an inflammatory process with certainty, bronchial biopsy studies should be performed in these athletes. In a previous study, inflammation was not observed in bronchial biopsies of healthy sportsmen with bronchial hyperresponsiveness [23]. However, no mention was made of the level of fitness or the type of sport activity of those subjects. Elite cross-country skiing is an endurance sport which demands a very high level of fitness and exposes the airways of these athletes to severe thermal and osmotic stimuli.

In summary, young, elite cross-country skiers have a minor-to-moderate degree of macroscopic inflammation in the proximal airways at bronchoscopy. Their bronchoalveolar lavage fluid profile is different from that of healthy nonathletic controls, with an increased lymphocyte count and the presence of the pro-inflammatory cytokine tumour necrosis factor-α.

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