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Associations among high altitude, allergic rhinitis, and bronchial hyperreactivity

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Abstract

Allergic respiratory diseases are common public health problem. Although several treatment options, some of patients cannot manage to get satisfactory recovery. High altitude (HA) is shown as a natural additive and/or salvage therapy option for this patient group. We aimed to present the effect of HA on allergic rhinitis and bronchial hyperreactivity in company with literature.

Keywords: High altitude, allergic rhinitis, bronchial hyperreactivity.

Özet: **Yüksek rakımın alerjik rinit ve bronşiyal hiperreaktivite üzerindeki etkileri**

Alerjik solunum hastalıkları genel bir halk sağlığı sorunudur. Çeşitli tedavi seçeneklerine rağmen bazı hastalar tatmin edici bir iyileşme elde edemez. Yüksek rakım, bu hasta grubu için doğal bir ilave ve/veya kurtarma tedavisi seçeneği sunmaktadır. Bu çalışmamızda, yüksek rakımın alerjik rinit ve bronşiyal hiperreaktivite üzerindeki etkilerini literatür eşliğinde sunmayı amaçladık.

Anahtar sözcükler: Yüksek rakım, alerjik rinit, bronşiyal hiperreaktivite.

Allergic respiratory diseases, including allergic rhinitis and asthma, are common health challenges associated with social and economic problems worldwide.[1,2] Industrial development, exposure to pollutants, indoor mites and other allergens, and humidity problems are increasing the incidences of allergic airway disease, bronchial responsiveness, and airway inflammation.[3] Several treatment options have been developed. These include nasal steroids and antihistamines and inhaled steroids and β_2-agonists. Sometimes, however, these treatments are inadequate, and oral steroids are required to treat refractory disease. Side-effects may develop; thus, patients increasingly seek natural treatment options.

A therapeutic effect of high altitude (HA) has been shown in some studies.[4–7] HA reduces supposedly the incidence of allergic respiratory disease. The daily symptoms of asthma and the extent of bronchial obstruction are significantly less in children living in mountainous areas.[5] Reduced air pollution, humidity, pollen and house dust mite (HDM) concentrations facilitate airway recovery.[6,7] However, some studies found that HA did not benefit those with allergic respiratory disease.[8–10]

We sought associations among HA, allergic rhinitis, and bronchial hyperreactivity in which relevant literature was reviewed.

Discussion

HA differs physically from sea level. The air temperature, humidity, barometric pressure, and inspired oxygen pressure are significantly reduced at HA.[11–13] Several reports have explored the effects of HA on the human airway. The relationships between HA and allergic airway diseases, including allergic rhinitis, have received a great deal of attention. However, few definitive conclusions have emerged. Several parameters may change the effects of HA on the respiratory tract. We thus decided to investigate the topic by reference to three distinct features of HA

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(Table 1): (i) The altitude per se, (ii) the time spent at HA, and (iii) climatic features of HA regions.

Table 1. Three describing parameters of high altitude.

Degree of altitude
Up to 1500 meters Between 1500 and 2500 meters Between 2500 and 5300 meters Over 5300 meters
Staying period at HA
Climber trekking Between 3 days to 2 weeks Between 2 and 12 weeks Residents at HA
Climate features of HA region
Alps Andes Mount Everest, Tibet, and Nepal region

Degree of altitude

The concentrations of HDMs and other allergens decrease when the altitude increases. One questionnaire study found a negative correlation between asthma symptoms and altitude. Each increment of 100 m in altitude was associated with a 0.88% reduction in wheezing symptoms among 13–14-year-old children.[14]

HDM concentrations at sea level and at HA did not differ significantly in one study performed at altitudes from 400 to 2600 meters in the Alps.[8] More than half of all dust samples (53.3%) were collected at altitudes below 1500 m.[8] Another study performed at over 1500 m in the Alps found that positive HDM skin test results were significantly fewer in mountain schoolchildren, and the levels of HDM antigens in mattresses were much lower than those at sea level.[7]

One study evaluated the prevalence of allergic diseases (rhinoconjunctivitis and asthma) in 3196 children living 3658 m above sea level in Lhasa, Tibet. The prevalence of "wheezing at any time", "diagnosed asthma", and "current wheezing" was 1.4, 1.1, and 0.8% respectively. The prevalence of current exercise-induced asthma and current nocturnal cough was 7.1 and 4.6%, respectively. The prevalence of allergic rhinoconjunctivitis was 5.2%. The International Study of Asthma and Allergies in Childhood (ISAAC) considered that these prevalence of asthma and allergic rhinoconjunctivitis was the lowest of all studies published worldwide in the previous 12-month period.[4]

Thus, when altitude increases, allergen concentrations and the incidence of allergic airway disease fall. Reductions in air pollution and pollen and HDM concentrations may reduce airway inflammation.[4]

Period Spent at HA

A short time at HA may create a sense of nasal obstruction. Inspiration of cold air causes congestion of the nasal erectile tissues and increases nasal secretions. Consequently, the number of breaths/min increases and the maximal possible work performance decreases. Nose and throat sores may develop at HA, compromising the ability of mountaineers to climb higher.[15,16] One study on climbers trekking at 5300 m on Mount Everest, Nepal, identified an increase in nasal blockage and reduced nasal mucociliary transport.[15]

Mildly asthmatic patients were studied while trekking at approximately 5000 m over 3 days. No subject had an asthma attack or acute mountain sickness either while trekking or during the stay at HA. The basal FEV_1 value did not differ significantly from the value at sea level; the reduction in the challenge-induced FEV_1 decrease at sea level was significantly greater than those at 5000 m ($p<0.001$).[11]

A stay at HA for 2 weeks to 3 months is recommended before therapeutic effects are apparent. In a prospective cohort study, 137 adults with severe refractory asthma (92 with allergic asthma) lived at 1600 m in Davos, Switzerland for 12 weeks. The 6-min walk test, the sinonasal outcome test, and the asthma quality-of-life test were performed; the total IgE level, the postbronchodilator FEV1, medication requirements, the exhaled nitric oxide fraction (FeNO), and the serum eosinophil level were assessed at the beginning of the study and 12 weeks later.[17] After 12 weeks, the asthma symptoms were controlled and all of the quality-of-life, sinonasal symptoms, the FEV1, and the 6-min walk test score improved. The total IgE level and the requirement for oral corticosteroids also decreased. Fourteen (48%) of 29 patients sensitized to HDM and 15 (36%) of 41 not sensitized no longer required oral steroids. The oral steroid requirements of the remaining patients were reduced. Serum eosinophil and the exhaled nitric oxide levels decreased in HDM-sensitized patients but not in non-sensitized patients. No other parameter differed between HDM-sensitized and non-sensitized patients.[17]

In another study, patients in whom asthma persisted despite the use of inhaled steroids underwent 10 weeks of HA therapy. The quality-of-life, lung function, adenosineand histamine- aggravated bronchial hyperresponsiveness and the urinary eosinophil, leukotriene E4, and 9a11b prostaglandin F2 (U-9a11b PGF2) levels improved significantly after HA therapy (all p values <0.05).[6]

Natives become adapted to HA and inherit relevant, physiological phenotypic features. Additionally, those who live and/or work at HA for years become adapted. Life at HA is not without difficulties. The inspired oxygen and barometric pressures are reduced, as well as the temperature and humidity. But HA exerts a therapeutic effect in those with allergic airway diseases; the air is fresh, with low levels of pollen and HDMs.[4–7]

The prevalence of pediatric allergic rhinoconjunctivitis and asthma were evaluated (in conformity with the ISAAC Phase III guidelines) at an altitude of 3658 m in Lhasa, Tibet. The frequencies of allergic respiratory symptoms were evaluated in natives (3190 students) who were asked if they "experienced an asthma attack", "were wheezing", and "had asthma"; the prevalence of these conditions was 1.4%, 0.8%, and 1.1%, respectively. Current exercise-induced asthma and current nocturnal cough were evident in 7.1% and 4.6% of patients, respectively. Rhinoconjunctivitis was slightly more common than other diseases. The incidence of nose problems in the past, current nose problems, and itchy/runny eyes was 9.3%, 5.2%, and 1.5% respectively. Rhinoconjunctivitis was diagnosed in 1.3% of patients.[4] The prevalence of wheezing at rest, wheezing during exercise, nocturnal wheezing, nocturnal cough, and severe wheezing was 0.3%, 1.2%, 0.03% (only one student), 1.4%, and 0.3%, respectively.[4]

The lowest prevalence of "current wheezing" worldwide was evident in children living in urban Lhasa. In a questionnaire study, the prevalence was 0.8%. The prevalence of "current exercise-induced asthma" and dry cough at nights was 7.1% and 4.6%, respectively. The prevalence of current allergic rhinoconjunctivitis was 5.2%, and did not change throughout the year.[4]

Another study enrolled 2026 children aged 12–14 years living at 3900 m on the north face of Mount Everest, Tibet. Asthma and rhinitis symptoms were evaluated. Only a few children complained of asthma symptoms such as wheezing. Only 2.8% of children complained of ever-wheezing and 1.4% of severe wheezing. The frequencies of these symptoms over the previous 12 months were 1.1% and 0.5%, respectively. However, upper airway respiratory infections and rhinitis were common. Over 30% of the children had sneezing, runny noses, and nasal obstructions. Continual rhinitis symptoms were evident in 8.7% of children.[18] However, it was unclear whether the rhinitis symptoms were caused by cold air or allergens or not. The prevalence of "wheezing even at rest" and "severe wheezing" was 2.8% and 1.4% respectively. Adoption of a Western lifestyle increases the risk of asthma, in line with the observed low prevalence of the condition in rural regions.[18] The hygienic Western lifestyle also increases the risk of other allergic diseases. However, the harsh climate at HA causes sneezing, and runny and blocked nose symptoms.[18] Despite the low oxygen saturation, harsh climate, and their poor general health, asthma and related allergic diseases were reported only in a few children. This suggests that the immune system acts in a non-allergic manner under non-hygienic conditions.[18,19] Asthma is more prevalent in those living at higher temperatures,[14] and the prevalence decreases with altitude.[14,18,20]

Climatic Features of HA Regions

Studies at HA are usually performed in the Alps, the Andes, and the Mount Everest-Nepal-Tibet regions. The concentrations of HDMs, fungal spores, and pollen are low in the Alps.[20] Air pollution is less than those at many European sea-level locations.[20] Air density and respiratory resistance are lower at HA, rendering expiration easy. Lung resistance decreases and the lungs can enlarge completely. All of these effects render breathing easier.[17]

The Alps enjoy abundant sunshine, allowing photosynthesis of vitamin D and effective regulation of the immune system. Thus, the severity of chronic allergic respiratory disease is potentially decreased.[17] A study performed in Davos (1560 m) on 16 children with allergic asthma showed that airway inflammation decreased at altitude. The FEV_1 provoked by AMP improved significantly and the peak flow variability was reduced after 1 month at HA. The levels of total serum eosinophils and eosinophil cationic protein (ECP) decreased but the levels of serum IgE did not.[21]

Eighteen patients with severe asthma who were resistant to inhaled steroids were examined in another study. Ten patients stayed in the Swiss Alps (at an altitude of 1560 m) for 10 weeks and 8 patients remained home at sea level. The quality-of-life, lung function, adenosine- and histamine-challenged bronchial hyperreactivities, induced sputum levels, and urine chemistry were evaluated before and after the stay at HA; the control group was also evaluated. The required drug doses did not change over the course of the study. All of the quality-of-life, lung function, adenosine- and histamine- challenged bronchial hyper-reactivity, and induced sputum, urinary eosinophil protein-X, urinary leukotriene E4, and urinary 9a11b prostaglandin F2 levels differed in the study group before and after the stay at HA (all p values <0.05). The quality-of-life and the adenosine- and histamine-challenged bronchial hyperreactivities were higher in patients who stayed at HA than controls (all p values <0.05). Thus, 10 weeks in the Swiss Alps (1560 m) improved bronchial hyperreactivity even in severely asthmatic patients resistant to inhaled steroids.[6]

On the contrary, in the HA environments of some South American countries, especially in the Andes of Colombia[22] Peru,[23] and Venezuela,[24] the prevalence of mites is high. Differences in the species and concentrations of mites among various places may be attributable to climatic features, especially humidity. These regions are in the equatorial tropics. Moderate temperature, high humidity, and heavy rainfall are the principal climatic characters. These characteristics, which induce the growth of mites, are not encountered in the Rockies of North America or the Alps of Europe.[10]

In Andean cities at 2500-2800 m, high concentrations of various HDM species were detected, unlike what was found in other HA studies. Dermatophagoides pteronyssinus and D. farina were much more prevalent than other species in patients with allergic respiratory disease, and sensitized such patients to disease.[9,25,26] One study was performed in Quito (at over 2800 m in the Andes). A total of 361 patients with allergic respiratory disease were screened in terms of mite sensitization; 182 were sensitized to *Dermatophagoides*. Asthma, rhinitis, and the combination were present in 45.6%, 97.8%, and 43.4% of sensitized patients, respectively.[25] The humidity and HDM levels are high all year in the Andes. The highest allergen concentration is seen in April, the lowest in August and September. Asthma and rhinitis symptoms were highest in the months of greatest allergen concentrations.[9]

Another study in HA areas of Ecuador investigated the prevalence of sensitization to HDMs, and the prevalence of allergic respiratory diseases. Mattress samples was collected from Quito (above 2800 m), Cuenca (above 2500 m), and Guayaquil (above 2500 m) in the Andes. Twenty-one mite species were detected. Of skin prick tests detecting antigens of *D. pteronyssinus*, *D. farinae*, *B. tropicalis*, *L. destructor*, *T. putrescentiae*, *A. ovatus*, *A. siro*, and *G. domesticus*, 60.9%, 56.8%, 17.0%, 19.3%, 10.6%, 15.8%, 8.8%, and 11.0% of them were positive, respectively. Thus, HDMs are present all year long in home products even above 2500 m in Ecuador. Patients from Quito who were sensitized to mites were evaluated, and it was found that 7.6% of them had asthma only, 67.1% of them had rhinoconjunctivitis only, and 25.3% of them had allergic asthma and rhinoconjunctivitis.[10]

The climate of the Mount Everest region (including Nepal and Tibet) is dry, windy, and frosty. Solar radiation is abundant. Ventilation is difficult.[18] The average temperature is approximately 8°C and the day-night temperature gap is 15.7°C. There are over 3000 hours of sunshine annually. The annual rainfall is 500 mm, of which 85% falls at night. Night falls reduce the temperature and remove dust formed during the day. All of these climatic features reduce mite and mold concentrations, decreasing exposure of the population to aeroallergens,[4] in turn explaining the low prevalence of asthma and allergic rhinoconjunctivitis.

Another study evaluated allergic respiratory diseases in 2026 children living at over 3900 m on the north face of Mount Everest, Tibet. Wheezing and other asthma symptoms were evident in a few of children. Wheezing and severe wheezing were detected in 2.8% and 1.4%, respectively. Upper airway and rhinitis symptoms were more common, independent of both gender and place of residence. Over 30% of children had sneezing, runny noses, and nasal obstructions, but it was uncertain whether the rhinitis was caused by allergy.[4]

Pathogenic hypotheses relevant to HA

HA mitigates allergic respiratory disease even when the allergen concentration is high; the mechanism remains poorly understood. The hypoxia-induced reduction in T-lymphocyte numbers may reduce local airway inflammation,[3] or the high levels of suprarenal hormones and/or atrial natriuretic peptide[4,11] may exert protective effects.

The activities of Th1 and Th2 cells are regulated principally by T-regulatory cells (Tregs). Th2 cells play roles in allergenic airway inflammation via secretion of IL-4, IL-5, and IL-13. Th1 cells stimulate the immune system by secreting interferon gamma (IFN-γ) when autoimmune and microbial challenges develop. Tregs create peripheral tolerance to allergens and autoantigens by secreting IL-10 and transforming growth factor-β1 (TGF-β1) (these are suppressive cytokines), and by stimulating synthesis of the key FOXP3 transcription factor.[3]

One study investigating the effects of HA on airway inflammation and the cell-mediated immune system showed that 3 weeks of HA therapy significantly reduced the exhaled nitric oxide (NO) level, a determinant of local airway inflammation, in patients with intrinsic moderate and severe asthma. Peripheral blood mononuclear cells (PBMCs) secreting IL-10 increased in numbers in 6 of 11 patients, but the numbers of PBMCs secreting TGF-β1 remained unchanged over 3 weeks at HA. Moreover, expression of CD80, a determinant of monocyte activation, decreased significantly. The number of CRTH-2-secreting T cells decreased but the number of regulatory T cells (Tregs) did not. The expression levels of FOXP3 and GATA-3 mRNAs within CD4+ T cells did not change, but the expression of mRNA encoding IL-13 expression was reduced. Secretion of IFN-γ mRNA by CD8+ T cells was reduced. Thus, HA reduced local airway inflammation. Moreover, monocytes exhibit tolerogenic phenotypes at HA. The CD80 expression level decreased from 5.02% to 3.32% at the end of 3 weeks of HA therapy ($p<0.01$).[3] Also, and importantly, the Treg/Th2 ratio increased, showing that HA was useful for endogenous control of allergen-triggered disease.[3]

After a stay above 3000 m, the plasma levels of the suprarenal hormones norepinephrine, epinephrine, and cortisol elevated. Cortisol secretion increased over the first 2 weeks at an altitude of 5000 m but later returned to the concentration associated with life at sea level.[11] Catecholamine secretion increased over the first few days at intermediate altitudes. The bronchial responsiveness of sensitized patients decreased at HA due to the increases in the concentrations of cortisol and catecholamines.[11]

Even a mild elevation in ANP level may lead to bronchial responsiveness to recover under hypoxic conditions.[11]

Conclusion

According to the literature, allergen concentration is different by degree of altitude and region's climate features so allergic rhinitis incidence and severity may be changeable. But in common wisdom, HA prevents bronchial hyperreactivity.

Conflict of Interest: No conflicts declared.

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