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High altitude journeys and flights are associated with an increased risk of flares in inflammatory bowel disease patients

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Abstract

Background and aims: Hypoxia can induce inflammation in the gastrointestinal tract. However, the impact of hypoxia on the course of inflammatory bowel disease (IBD) is poorly understood. We aimed to evaluate whether flights and/or journeys to regions lying at an altitude of >2000 m above the sea level are associated with flare-ups within 4 weeks of the trip.
Methods: IBD patients with at least one flare-up during a 12-month observation period were compared to a group of patients in remission. Both groups completed a questionnaire.
Results: A total of 103 IBD patients were included (43 with Crohn's disease (CD): mean age 39.3 ± 14.6 years; 60 with ulcerative colitis (UC): mean age 40.4 ± 15.1 years). Fifty-two patients with flare-ups were matched to 51 patients in remission. IBD patients experiencing flare-ups had more frequently undertaken flights and/or journeys to regions >2000 m above sea level within four weeks of the flare-up when compared to patients in remission (21/52 [40.4%] vs. 8/51 [15.7%], p = 0.005).
Conclusions: Journeys to high altitude regions and/or flights are a risk factor for IBD flare-ups occurring within 4 weeks of travel.

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1. Introduction

Inflammatory bowel disease (IBD) is a chronic, often debilitating intestinal disorder.[1–3] The etiology of IBD has not yet been fully elucidated; however, results of multiple studies point to a role of dysregulated innate and adaptive immune responses to intestinal bacteria.[4] Over the last few years, several studies have demonstrated that hypoxia can induce inflammation. Plasma levels of several inflammatory markers, such as interleukin-6, interleukin-1 receptor antagonist, and C-reactive protein, were found to be increased in healthy volunteers spending 68 h at an elevation of 3400 m above the sea level.[5] In murine models, exposure to normobaric hypoxia leads to tissue accumulation of polymorphonuclear neutrophils, increased serum levels of pro-inflammatory cytokines, and vascular leakage.[6–10] Hypoxia is a hallmark of many disease states and is known as a potent inflammatory stimulus. For example, ischemia in organ grafts increases the risk of inflammation in the graft with consecutive graft failure or rejection.[11] While hypoxia may lead to inflammation, inflammation can also lead to hypoxia in the tissue via different mechanisms, such as edema, vasoconstriction or production of reactive oxygen species triggering local oxygen depletion.[12] A steep oxygen concentration gradient, a consequence of the close proximity of the richly perfused oxygen bed to the anoxic bowel lumen, contributes to the unique oxygenation profile of the gut. Several studies have examined the role of hypoxia in mucosal tissue damage in IBD and shown that surgical specimens taken from patients with active CD and UC were found to contain elevated levels of hypoxia-inducible factors (HIF)-1α and HIF-2α.[13,14] These two factors trigger the expression of genes that are responsible for the maintenance of intestinal epithelial barrier function.[13,14] Furthermore, NF-κB also appears to play a role in response to stress, such as hypoxia, as activation of NF-κB in intestinal epithelial cells in response to gut ischemia–reperfusion in mice leads to increase in the production of proinflammatory cytokine tumor necrosis factor (TNF) and simultaneous attenuation of intestinal epithelial apoptosis.[15]

The fraction of oxygen in the air is 21%, and barometric pressure at sea level is approximately 760 mm Hg. During airplane flights, the oxygen partial pressure in the cabin decreases, which leads to a reduction in the percentage of oxygen-saturated hemoglobin in the blood.[16] International laws demand that the cabin pressure must not be lower than the one measured at 8000 ft (2438 m; barometric pressure is 564 mm Hg).[17] A study evaluating the cabin pressure during 240 flights revealed that the cabin pressure ranged between the one detected at 5000 ft (1524 m; barometric pressure is 632 mm Hg) to that measured at 8000 ft with a mean value corresponding to a pressure measured at 6214 ft (1894 m; barometric pressure is 604 mm Hg).[18] Breathing at 8000 ft or at 5000 ft is equivalent to breathing a hypoxic mixture with an oxygen fraction of 15.1% or 17.1% at sea level, respectively. Healthy subjects exposed to a hypoxic mixture of gases with 15.1% or 17.1% oxygen had a mean arterial oxygen pressure of 53 or 64 mm Hg (normal values 65–100 mm Hg) and mean arterial oxygen saturation of 85% or 91%, respectively.[19] While such decreases of arterial oxygen saturation are tolerated well by healthy subjects, this hypobaric hypoxia during aircraft travel may cause difficulties for patients with pulmonary disease.[16] Clinical data evaluating a potential impact of hypobaric hypoxia on disease activity in IBD is currently lacking. Therefore, we evaluated whether reduced oxygen partial pressure during aircraft travel and/or journeys to regions lying at an altitude of >2000 m above the sea level is associated with changes in clinical disease activity in four weeks following the trip.

2. Materials and methods

2.1. Patients

In this study, a questionnaire-based survey was conducted. IBD patients from in- and outpatient clinics of three Swiss tertiary hospitals (Triemli Zurich, University Hospital Zurich, and Centre Hospitalier Universitaire Vaudois) were recruited. The study was conducted as a project of the Swiss Inflammatory Bowel Disease Cohort Study and was approved by the Ethics Committees (SNSF 33CSC0_134274).[20] Prior to inclusion into the study, written informed consent was obtained from all patients.

2.2. Methods

For the purposes of the survey, IBD patients with at least one flare-up episode in the observation period from September 1st, 2010 to August 31st, 2011 were compared to IBD patients, who were in clinical remission during the same observation period. Data were obtained by the means of a structured questionnaire and review of medical charts. The questionnaire contained items addressing the following topics: demographics, medical history, medication history and the history of aircraft travel and/or high-altitude journeys (>2000 m above sea level), the duration of the trip(s) (in hours), date and flight destination, as well as details on travel habits within 4 weeks of the flare. CD patients were categorized into the groups with different disease location based on Montréal classification, where L1 corresponds to disease in the terminal ileum, L2 corresponds to disease in the colon, L3 corresponds to ileocolonic disease, and L4 corresponds to isolated disease in the upper gastrointestinal tract.[21] UC patients were categorized into the groups with different disease locations according the Montréal classification, where E1 corresponds to rectal disease, E2 corresponds to left-sided colitis, and E3 corresponds to an extensive colitis.

Inclusion criteria for enrollment of CD and UC patients with flare-up episode(s) into this study were as follows: age 18–80 years, at least one flare-up episode in the observation period between September 1st, 2010 and August 31st, 2011. It was mandatory that the occurrence of a flare-up episode as reported by the patient was verified by a physician in the course of a clinical examination. Furthermore, in order to attribute a flare-up episode to IBD, an infectious etiology had to be excluded. For this reason, microbiological workup of fecal samples for known infectious agents, such as *Salmonella*, *Shigella*, *Campylobacter* spp., test for presence of *Clostridium difficile* toxin in feces, examination of 3 different fecal samples for parasites, and evaluation of biopsies for cytomegalovirus