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Review Article

**OVERVIEW OF ULCERATIVE COLITIS AND IMMUNE
FUNCTION AT HIGH ALTITUDE PLATEAU****Mohammed Gamah^{1,3}, Yu Zhang¹, Moshera Al-ansi³, Abdul Baset Abbas⁴,
Maged Almezgagi^{1,4}, Muhammad Shoaib¹, Yi-ling Zhou¹, Qiao-rong Ji¹,
Zhou-yang Yuan¹, Wei Zhang^{1,2Δ}**¹Medical College of Qinghai University, Qinghai Xining 810001²The Key Laboratory of High-Altitude Medical Application of Qinghai Province, Qinghai Xining 810001³Medical Laboratory Department, Faculty of Medicine and Health Sciences, Hodeidah University, Al Hodaydah, Yemen.⁴Department of Medical Microbiology, Faculty of Sciences, IBB University, IBB City 70270, Yemen.**Article Received:** February 2020**Accepted:** March 2020**Published:** April 2020**Abstract:**

High altitude can be described in terms of elevations as low as 1500 meters to those as high as 8800 meters. For the particular purposes of tracking various immune parameters within humans, very few studies have been carried out so far at high altitude. For environmental conditions such as high-altitude military personnel and mountaineers may need to operate. There are various and varying stressors, for example, high altitudes, moisture and the supply of food and water, lengthy moderate to extreme physical activity, minimal or insufficient sleep, increased susceptibility to infection and injury, etc. The consequences of high exposure to high altitudes are discussed in this review.

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INTRODUCTION:

Inflammatory bowel disease can include two main types: Crohn's disease and Ulcerative colitis. These are damaged disorders that have a chronic inflammatory response to commensal intestinal flora¹. Ulcerative colitis is an inflammatory bowel disease correlated with dramatic weight loss, stomach pain, bloody diarrhea, and inflammatory cell infiltration²⁻⁴. Although IBD has not been correctly identified for pathogenesis, there is an apparent genetic susceptibility, and environmental factors have been established⁵. The hypoxia seems to be a principal cause of inflammation, and living organisms are creating instruments of acclimatization to ensure homeostasis^{6,7}. Scientific studies show high concentrations of inflammatory markers such as interleukin-6, C-reactive protein, and interleukin-8 and lower levels of an anti-inflammatory cytokine such as interleukin-10 in high altitude participants, indicating that hypoxia is an essential part of inflammation activity^{8,9}. The immune system consists of a complex network of cells and soluble mediators that communicate in a highly regulated procedure to create a suitable immune response.¹⁰ The nature of a variety of immunological functions and their control and amplification mechanisms, in particular, make it difficult to understand how diverse extreme environmental conditions such as high altitude, hypoxia, wind, cold and microgravity mediate some parts of immune changes.¹¹ For the study of complex biochemical processes, the use of high-altitude stress as a model of biological science has been of interest. Prolonged stay at high elevation will affect the human immune system physiologically. High-altitude environmental factors such as UV exposure, cold and hypobaric hypoxia can influence the immune system and make it more vulnerable to cancer, various infectious diseases, and autoimmune disorders¹². Specific environmental conditions by some pathways modulate the activities of the immunocompetent cells. The net result can be either immunostimulant or immunosuppression, depending on individual stress and other factors. The general concern is that stressful environmental conditions will interfere with immune homeostasis by modulating immunoregulatory activities. This can cause immunodeficiency or autoimmunity. A mechanistic analysis of the impact of environments at high altitude on human lymphocyte immunomodulation was performed less regularly than was the case for rodents¹³⁻¹⁵. To anyone, young or old, fit or unfit, it is important to have a general understanding of how environmental factors can affect overall health and daily task results. This analysis deals with recent immunological studies that examine how the body adapts to these

environmental stimuli or stressors for short-term (acute) and long-term (chronic) exposure.

1.1 What Is Ulcerative Colitis?

Ulcerative colitis is an inflammatory bowel disease, which is characterized by the development of ulcers in the colon. Scientific classified the gastrointestinal injury according to variation of the infected area. For example, the depth of the inflammation in the intestinal wall and the characteristic of their pathophysiology. Usually, the end of the colon is associated with the rectum¹⁶. Ulcerative proctitis is restricted to the rectum, and primarily affects the mucosal and submucosal layers in the gut wall. It can also happen in the whole region of the colon, even though UC impacts only some parts of the colon in some cases¹⁷. The inflammation might spread into the upper parts of the colon to different degrees. The whole colon infected is denominated generalized colitis. Symptoms of the disease grow over time rather than suddenly include intermittent rectal bleeding, crampy abdominal pain, and diarrhea³. Many patients have long remissions, including without medication. After a long history of symptoms, ulcerative colitis can cure suddenly. The most reliable diagnostic test is direct visualization by endoscopy and bowel lining biopsy. Ulcerative colitis treatment requires medications and surgery; food flexibility can be beneficial often¹⁸.

1.2 Prevalence of ulcerative colitis

In recent decades, IBDs were increasing not only in the Western but also in Asia with the growth of industrialization¹⁹. In 2015 an estimated 1.3% or 3 million people in the United States adults were diagnosed with IBD. It was a significant increase since 1999. Ulcerative colitis (UC) affects about 1 million people in the United States. The annual incidence of Ulcerative colitis (UC) cases is between 10.4 and 12 per 100,000 citizens, and the prevalence rate is between 35 and 100 per 100,000. Five times more severe than Crohn's disease are ulcerative colitis. The condition is more severe in women than for men^{20,21}.

The statistics of recent years indicate that ulcerative colitis is a more common digestive tract disease in China and becomes a new hot spot in the study of gastrointestinal disorders²². The latest IBD, UC, and CD incidences have risen to 1.80 (IBD), 1.33 (UC), and 0.46/1 million (CD), while they differ across territories and ethnic minorities. For example, 51 racial minorities live in the South-West of China in Yunnan Province and 33.41% of the total population of minority groups. The epidemiological data from this region showed that the most significant incidence rate of total IBD in the Han people

(9,463/100,000) was observed among 18 different racial minority populations, followed by the Hui (Muslim) minority population (8,563/100,000), the Man minority population (7,092/100,000) and the Bai minority population (5,271/100,000). The most considerable incidence rate of UC was also found in Han (8,918/100,000), followed by Hui (7,720/100,000), Man (7,092/100,000), and Bai (5,083/100,000) populations. The highest prevalence of CD was reported in the minority ethnic community of Tibet (1,376/100,000), followed by the racial group of Hui (0,842/100,000) and Han: (0,545/100,000). While the total number of IBD cases is not as small as previously thought and the prevalence of IBD disease in China is probably underestimated, China still has an enormous population, however²³.

1.4 Etiology of ulcerative colitis

Although there is no evidence of the specific pathogenesis of IBD, many factors contribute to the development of UC. The most critical hypotheses include infection food allergy, genetic and environmental, and microbial and other antigens immune response^{24,25}. In addition, the importance of genetic predispositions and their impact on interactions with microbial and environmental factors have been emphasized by genetic research and mouse models, leading to pro-colitogenic disturbances of host-commensal relationship^{26,27}. Enhanced pro-inflammatory reaction, including monocyte, macrophages, and cytokines activation is thought that the immune system responds abnormally to healthy gut flora, especially bacteria near colon mucosal.

1.4 Disorder of the immune system

Literature shows that the activation of immunocytes increases cytokines secretion induces inflammation, and increases cell signal death. Which causes chronic intestinal fluctuations in epithelial tissue¹⁸. Evidence indicates that the UC is triggered by anomalous cell immune responses in individuals with susceptible genes induced by the inflammatory response to intestinal microorganisms²⁸. The abnormal immune response results in exaggerated activation of effector T cell subsets and deficiency of regulatory T cells (Treg), leading to persistent immune mess and uncontrolled intestinal inflammation²⁹. The inflammation response and relapses of disease activity are associated with the engagement of the innate and adaptive immune responses, including increased production of TNF- α and IFN- γ in the intestine^{30,31}. The higher concentrations of tumor necrosis factor-alpha (TNF- α) in the blood, stool, and mucosa induces apoptosis and a valuable target for control of the disease in patients with ulcerative colitis³². There are

indications of a significant pathogenic role in the condition being an unregulated immune response in the intestine³³.

It is presently accepted that a changed adjust between regulatory and inflammatory cytokines makes a difference sustain mucosal irritation in UC¹⁸. IL-12 induces Th1 cell and usually secrete large quantities of IFN- γ , TNF- α , and IL-12, relative to IL-4, IL-5, and IL-13, which are the cytokines secreted from the Th2. IL-13 is highly cytotoxic to epithelial cells, which further increases intestinal permeability³⁴. Crohn's disease is expected to be a Th1, while it is believed that Th2 responses regulate UC. The Mucosal T cells displayed elevated IFN- γ and IL-2 levels in CD patients compared to UC patients T cells. Moreover, recent data showed that the paradigms CD-Th1 and UC-Th2 are not so clear. Also, data indicate that the Th17 cell manufactures of IL-17 and IL-23 have an essential role in IBD pathogenesis with DCs derived from patients with CD developing a higher volume of IL-23 more than UC patients³⁵. Later considers have appeared that, besides its activity on Th17 cells, IL-23 can moreover act on cells of the innate immune system. Offbeat, innate-like T cell populations, which are primarily represented at mucosal destinations, have been found to reply to IL-23 incitement and secrete Th17-related cytokines. The Th17 cells are a T helper subset cells that are activated by IL-6 and TGF-B, are expanded to IL-23, with the abundant secretion of IL-17A, IL-17F, IL-21, and IL-22. ROR γ t is recognized as the principal element for the transcription of Th17³². The IL-17 cytokine comprises of IL-17A to F. IL-17A, and IL-17F are 50% similar in their amino acid structure. IL-17A and IL-17F have the main proinflammatory impact on the activation of multiple cell targets such as fibroblasts, epithelium, monocytes, neutrophils, macrophages, endothelium, and which produce TNF- α , IL-1 β , and IL-6. Among multiple immune-mediated disorders, including RA, asthma, IBD, and recurrent autoimmune encephalitis (EAE), IL-17 has been involved³⁶. Th17 is complicated according to the role of either "pathogenic" or non-pathogenic "in various laboratory models. It is believed that pathogenic Th17 cells are distinguished by their IL-17, IFN- γ production, and the expression of specific surface markers. The pathobiology of Th17 is also very challenging⁴⁸. In the DSS colitis model, the deficit in IL-17F ameliorated mucosal inflammation, but exacerbated it by IL-17A deficiency, thereby indicating the essential role for IL-17F in treatment. It was also shown that IL-17A directly inhibits Th1 cells and eliminates inflammatory growth, as it supports a protection function for IL-17A. Furthermore, monoclonal antibody therapy anti-IL-17A has been shown to intensify DSS-induced

colitis. IL-23 produced by macrophages and dendritic cells that help to replicate, live, or both³⁷.

1.5 DSS model

Generally, Dextran sodium sulfate induces experimental colitis; this model is intuitive and provides the highest consistency and reproducibility of most injuries in the distal colon. By beginning with study, the intestinal barrier function, and following fortifying neighborhood aggravation, DSS is regularly utilized to actuate the form of mouse colitis that mimics the clinical and histological highlights of IBDs that have characteristics of UC. The ordinary highlights of colitis show up on day three and are maximally on day 7³⁸. The expansion of 30-35 kDa dextran sulfate sodium (DSS) to drinking water from 3-10%. It results in weight loss, bloody diarrhea, mucosal ulceration, shortening of the colon, and neutrophilic infiltration. Many studies showed DSS contribution to the breakdown of the mucosal epithelial barrier and enabled microorganisms to penetrate the mucosa. The inflammatory reactions and overexpression of pro-inflammatory cytokine increased, and clinical symptoms of colitis appear.^{39,40}

1.6 Role of high-altitude hypoxia on immune function

High altitude environments exist in the three largest high-altitude regions (Qinghai-Tibetan Plateau, Andean Altiplano, and Semien Plateau of Ethiopia). This environment is defined by dry air, severe cold, ionizing radiation, high wind, and primarily hypobaric hypoxia. Although high altitude environment is a secondary region on Earth⁴¹. Many high-altitude people have existed in this unique environment for hundreds of generations, and typically have specific physiological mechanisms than communities at low altitudes. Therefore, acclimatization to altitude has been a significant subspecialty in high-altitude medicine⁴². Each year, more than 100 million individuals from plains areas come to highland either for the job, enjoyment, sport, worship or for strategic goals. Furthermore, the numbers are increasing day by day⁴³. The High-altitude areas can be divided into high altitude (1,500–3,500m), very high altitudes (3,500–5,500m) and extreme altitudes (> 5,500m). Sudden rises to high altitudes without acclimatization will lead to hypoxia. The decrease of O₂ supply leads to significant changes in the respiratory, cardiovascular, and hematology systems, particularly for improving transport and the use of O₂, and these are the focus of traditional high-altitude medicine⁴⁴. Some reports recently showed that the development and regeneration of bones at high altitudes are different from low altitudes.

Nonetheless, the current view is the adverse effects on bone marrow, bone structural properties, biomechanical activity. Bone compensation is clear in the hypobaric hypoxia setting, with reduced body weight^{45,46}. When traveling to these elevated areas, many healthy people may suffer from high-altitude diseases. The significance of environmental components of the pathogenesis of this illness is progressively recognized⁶. Hypoxia is a crucial trigger in many different diseases. Global hypoxia, for example, is the critical factor in high altitude illness. However, many illnesses, including acute myocardial infarction, stroke, but also several shock forms, are also at the center of tissue hypoxia. Hypoxia often plays a significant role in exercise environments and altitude training of athletes in addition to its function in diseases. Biological agents play an essential role in these diseases and conditions^{47,48}. As such, hypoxia appears to be a vital driver of inflammation, and the living things establish acclimation instruments to guarantee homeostasis. However, in the event malfunction, it leads to the expansion of pathological processes⁴⁹. However, living at high altitudes may lead to hypoxia. The effects of hypobaric hypoxia at high altitudes plateau depending on the length of time spend through at high altitudes and the height reached⁵⁰. The specialized blood supply and internal composition of the intestine enhance its sensitivity to hypoxia, rendering the intestine vulnerable to hypoxic stress effects. It has been shown that different degrees of human gastrointestinal tract damage exist in hypoxic conditions at high altitudes^{13,14,51}.

The immune system is a combination of cells, tissues, and organs which act together to defend the invading harmful stressors to produce an immune response in the body. Many studies had carried to monitor the effect of hypobaric hypoxia in immunity. High altitude has been known to induce alterations in different immune cells like T-cells, B-cells, NK cells. Moreover, a study conducted on healthy females exposed to an elevation of 5050 m for 21 days revealed that acute as well as chronic exposure causes alterations in T cells as well as NK cells when these parameters were analyzed by flow cytometry in peripheral blood lymphocytes. However, B cells' population was not changed much¹⁵. In hypoxia, the acquired immune response may be regulated by induction of phenotypic shift from Th1 to Th2 cells by HIF-1 α , as interferon-gamma production is reduced (INF- γ) and interleukin secretion 10 (IL-10) is increased⁵². Also, the excessive functioning of the TH1 cells secreting IFN- γ generally related to intestinal inflammation, particularly in IBD^{53,54}. In hypoxia, it also reported that HIF-1 α prompts TH17 differentiation in inducing ROR γ t transcription and

then cooperates with ROR γ t to control TH17 genes downstream. Furthermore, HIF-1 α restrain differentiation of Treg by an active mechanism aimed at the degradation of Foxp3 protein and Treg converted to TH1 like secreting IFN- γ and worsen of colitis^{55,56}. The authors have shown that the inflamed intestines of IBD patients are increased in the number of IL-17 producing cells compared to healthy controls⁵⁷. In monolayers of intestinal epithelial cells, the transepithelial reduction has been recorded with Interleukin-4⁵⁸. Although Th2 cell immune reactions are typically linked to intestinal homeostasis and tissue repair, increased Th2 cytokines in the epithelium of patients with ulcerative colitis have been detected^{59,60}. Cytokines are proteins that are formed and produced by various cells, such as leukocytes, muscle cells, and neurons. These proteins can work pleiotropically or synergistically with other substances and modulate other cytokines production. Cytokines are crucial modulators of the immune response, which can be affected by exposure to high altitude. Cytokines play a central role in the immuno-response during increasing the stimulation of receptor-specific and unspecific effector pathways and tissue repair. The outcomes of a reaction can be considered by activating a protective mechanism or triggering an immune system. Cytokines may be pathogenic by the over-production of inflammatory cells if they are secreted in abundance. Therefore, several cytokine levels occur to ensure that cytokine production is limited in time and space in most circumstances. Further, it was reported that the level of IFN- γ was decreased in 13 female individuals at 5050 m altitude, which affects the body defense against differing conditions. It was observed that the negative correlation between nor-epinephrine and IFN- γ of high altitude expose females¹⁰. Cytokines work in metabolism regulation by influencing hormone secretion, controlling immune responses to TH1/TH2, and stimulating inflammatory immune responses¹¹. Additionally, the results recommend that there is impairment of homeostatic regulation of Th1/Th2 immune stability. This increases the chances of infections as well as long-term immunological alterations¹⁵. Also, expressions of HIF-1 α and iNOS significantly increase with expanding hypobaric hypoxia exposure and may play a crucial role in the intestinal mucosa damage¹². Luo et al. have been developed an intestinal barrier injury model by displaying rats to simulated hypobaric hypoxia of 4000 m for three days. It was observed that after three days of exposure, intestinal mucosa was thinner, and epithelial cells were irregular and fewer. Occludin and tight junction protein were also down-regulated in the hypoxia group, thus confirming mucosal barrier injury occurs with hypobaric hypoxia exposure¹⁰.

Enhanced pro-inflammatory reaction, including monocyte, macrophages, and cytokines activation is thought that the immune system responds abnormally to healthy gut flora, especially bacteria near colon mucosal. Therefore, changes in the intestinal microbiota composition may be involved in high-altitude-induced immunological challenges. These causes induce a cascade of inflammatory mediators and provoke the release of multiple cytokines, thereby evoking the occurrence and development of ulcerative colitis. Indeed, a recent study examining hypoxia-inducible factors HIF-1 α and HIF-2 α expression in biopsies from UC patients in remission and with the active disease found a positive relationship between HIF-1 α expression and disease severity^{61,62}. Multiple studies have also demonstrated elevated C-reactive protein, interleukin-6, and interleukin-8 levels as markers of inflammation and reduced interleukin-10 levels as an anti-inflammatory cytokine in healthy volunteers in high altitude^{8,9}. Moreover, hypoxia is also competent in affecting cellular immunity, and low oxygen pressure increases the concentration of natural killer cells. Furthermore, hypoxia leads to a significant relative lymphopenia and neutrophilia. hypoxia influences cellular functions in parallel to affecting the levels of immune cells in the blood. Hypobaric hypoxia at 3000 m significantly reduces the production of plasmacytoid dendritic cells in humans⁶³. The intestinal immune system must defense against infections by activating defensive responses to pathogens also maintain immunity to self-antigens, diet, and commensal microflora⁶⁴. Dendritic mucosal cells (DCs) are essential to this balance. Immature DCs are in peripheral tissue, activated by antigens that reify and transfer through the draining lymph nodes in the intestine. There are several subsets of DCs in the bowel⁶⁵. DCs can induce proinflammatory T helper cells type 1 Th1 or type 17 Th17 or humoral Th2 immune response, according to their cell-surface receptor expression and cytokine profile. Induction of regulatory T cells is a primary feature of intestinal DCs⁶⁶. Almost every continuously inflamed tissue is characterized by a low supply of oxygen due to vascular malfunction and increased oxygen use by infiltrated leukocytes, mostly neutrophils^{67,68}. In respect to inflammatory bowel disease, hypoxia is potentially very significant as the lumen of the intestines are almost anoxic. Anoxia can spread to formerly normoxic tissue, which now must adjust to this condition through inflammatory impairment of the intestinal barrier. In the small intestine of experimental animals that spending nine days at a simulated altitude of 4000 meters above sea level showed increased mRNA levels of interleukin-6, tumor necrosis factor-alpha, and protein expression of nuclear factor-kappa B⁶⁹. Once the epithelial

barrier is dysfunctional, a large number of bacteria and endotoxins may translocate to other tissues or organs via the bloodstream and activate the production of cytokines like TNF- α , IL-6, IL-1 β . These lead to further recruitment of neutrophils and macrophages that are more susceptible to bacterial stimulation than the resident macrophages and epithelial cells, on which the bacterial recognition receptors such as TLR or CD14 are down-regulated.⁷⁰⁻⁷² Also, reactive oxygen species are produced that local cause depletion of oxygen⁷³. Furthermore, In the human intestinal tract, a steep oxygen gradient exists from the crypts to a villus in which O₂ in Crypt highest and the villus tips lowest, closest to the anoxic gut lumen⁷⁴. This “physiological” hypoxia is, to a great extent, expanded with intestinal irritation⁷³. The HIF-1 complex is a crucial transcription factor for cellular adaption to low oxygen tension⁷⁵. Several studies have addressed the function of HIF-1 α in intestinal epithelial cells. Karhausen et al. showed that decreased expression of HIF-1 α from epithelial caused severe gut inflammation, while the increase in HIF protein was protective for epithelial⁶². Xue et al. recently reported that HIF-1 α activation in gut epithelial cells had reduced the number of intestinal tumorigenesis. Reducing the inhibition of HIF-1 decrease the apoptosis of epithelial cells in the murine colitis emphasizes the importance of HIF-1 in the intestinal epithelial⁷⁶. Phenotypes found in models of colitis in which epithelial HIF is modulated support the value of epithelial HIF. Mice with a lack of HIF-1 α were more sensitive to experimental colitis (TNBS colitis) in the intestinal epithelium and demonstrated the protective role of HIF-1 α in the intestine⁶². In addition, the HIF-2 α pathway was recommended, which aggravated colitis with a VHL-deficient mouse. In recent times, the reduction of HIF-2 α in the intestinal epithelium has contributed to the defense against DSS colitis and improved susceptibility to colitis induction from HIF-2 α over-expression(not HIF-1 α)⁷⁷. Therefore, HIF-1 α is simply considered to act to protect in colitis, while HIF-2 α promotes pro-inflammatory mediators and epithelial proliferation⁷⁸. This is still not completely clear in IBD about the temporal interaction between these reactions and is necessary to develop therapeutic strategies based on HIF. However, enzymes that control HIF (PHDs) could also be used independently of the HIF effect as an epithelial barrier⁷⁹.

The impact of the supplementing Vitamin E on Sprague Dawley rats subjected to hypo- hypoxia at simulated elevations of 7000 m over 5 days was observed. Vitamin E is an antioxidant and can be used as a possible tool to investigate its mechanism of action in immunity as well as high altitude disease¹⁰. vitamin E significantly alleviated hypoxia-caused

damage to the main organs including intestine, increased the serum superoxide dismutase (SOD), diamine oxidase (DAO) levels, and decreased the serum levels of interleukin-2 (IL-2), interleukin-4 (IL-4), interferon-gamma (IFN- γ) and malondialdehyde (MDA), and decreased the serum erythropoietin (EPO) activity. The HIF and TLR4/NF- κ B signal pathway may represent significant therapeutic targets for the prevention or treatment of intestinal barrier dysfunction and consequent intestinal diseases under high altitude hypoxia environment⁵¹.

CONCLUSION:

High altitude-induced Intestinal mucosa disorders in mountaineers, natives, and soldiers employed above sea level have become the main cause of morbidity. In this overview, impacts and strategies relevant to this area have been seen. From the study, we can suggest that the high-altitude climate causes problems in the gut that need to be treated or prevented through new treatments or using probiotics/prebiotics.

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