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Review

Lower Incidence of COVID-19 at High Altitude: Facts and Confounders

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Abstract

Pun, Matiram, Rachel Turner, Giacomo Strapazzon, Hermann Brugger, and Erik R. Swenson. Lower incidence of COVID-19 at high altitude: Facts and confounders. *High Alt Med Biol*. 21:217–222, 2020.—The rapid transmission, increased morbidity, and mortality of coronavirus disease 2019 (COVID-19) has exhausted many health care systems and the global economy. Large variations in COVID-19 prevalence and incidence have been reported across and within many countries worldwide; however, this remains poorly understood. The variability and susceptibility across the world have been mainly attributed to differing socioeconomic status, burden of chronic diseases, access to health care, strength of health care systems, and early or late adoption of control measures. Environmental factors such as pollution, ambient temperature, humidity, and seasonal weather patterns at different latitudes may influence how severe the pandemic is and the incidence of infection in any part of the world. In addition, recent epidemiological data have been used to propose that altitude of residence may not only influence those environmental features considered key to lesser viral transmission, but also susceptibility to more severe forms of COVID-19 through hypoxic-hypobaria driven genomic or non-genomic adaptations specific to high-altitude populations. In this review, we critically examine these factors and attempt to determine based upon available scientific and epidemiological data whether living in high-altitude regions might be protective against COVID-19 as recent publications have claimed.

Keywords: COVID-19; high altitude; hypoxia; public health; SARS-CoV-2; UV rays

Introduction

Over 140 million people live at high altitude (>2500 m) across several continents (Cohen and Small, 1998; Penaloza and Arias-Stella, 2007), and many of these mountainous regions are increasingly accessible with modern means of transportation (West, 2008; Reisman et al., 2017). Cases of coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have been reported from high-altitude regions of Europe, Asia, South America, North America, and Africa (Arias-Reyes et al., 2020; Huamaní et al., 2020; Xi et al., 2020; Zeng et al., 2020). Interestingly and provocatively, an epidemiological analysis by Arias-Reyes et al. (2020) pointed out a lower reported incidence of COVID-19 and proposed a possible weaker transmission rate of severe SARS-CoV-2 among high-altitude populations. Similarly, Xi et al. (2020) reported negligible sustained local COVID-19 transmission on the Qinghai-Tibetan plateau, China. There are numerous possible reasons for this apparent protection of living in mountainous regions such as physiological adaptation to hypoxia, ethnic and genetic population differences, environmental factors pertaining to viral transmission, social structure and norms, and success and extent of lockdown measures. However, the fact that some lowland countries have also had very little COVID-19, particularly the island nations of the Pacific, suggests a much more complex epidemiology.

In this review, we critically examine currently available scientific and epidemiological data pertaining to COVID-19 transmission in the attempt to determine whether living at high altitude and associated adaptations to hypobaric hypoxia might be protective as recent publications have claimed (Arias-Reyes et al., 2020; Xi et al., 2020). First, the role of

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hypoxia and genomic adaptations to prolonged high-altitude residence is explored and then followed by a discussion of the numerous other environmental aspects of mountainous regions and the societal characteristics of countries with high-altitude populations. We will highlight what is known about the role of the angiotensin-converting enzyme 2 (ACE-2) and its differences in tissue expression and genetic variants in COVID-19 pathogenesis and identify areas where robust scientific data are lacking and complex interactions should be surmised with caution. We conclude by summarizing those areas where further biological and epidemiological research is needed to better understand whether living at high altitude offers any benefits against SARS-CoV-2 infection and severity.

Pathophysiological Considerations

Hypoxia

The unique exposure for high altitude residents is that of chronic hypobaric hypoxia, which evokes many immediate and sustained compensations to increase tissue oxygen delivery and enhance oxygen utilization by both nongenomic and genomic mechanisms. Thus it can be argued that high-altitude residents may be somewhat tolerant to the consequences of more hypoxemia and systemic tissue hypoxia developing as a result of COVID-19 infection and subsequent lung injury. However, because high-altitude residents already have lower baseline arterial oxygenation than sea level residents, it could make their disease-related hypoxemia worse for any given degree of developing lung dysfunction despite any preexisting adaptations to hypoxia. Although impossible to test in humans, cell and tissue culture techniques or animal models mimicking clinically relevant COVID-19 could be used to test this hypothesis.

One aspect of high-altitude hypoxia with particular relevance to COVID-19 is possible hypoxia-mediated differences in tissue expression of ACE-2 that could afford protection against the virus in people living in mountainous areas. SARS-CoV-2 entry into human cells is through binding of its exterior spike protein to ACE-2 and subsequent internalization to access cell machinery for its replication (Lu et al., 2020; Zhou et al., 2020). ACE-2 is widely present in many human organs (Baig et al., 2020) with particularly high expression in the upper and lower respiratory tract epithelia, vascular endothelium, myocardium, renal tubules, gastrointestinal tract epithelium, testes, and central nervous system. This expression helps to explain the particular morbidity of COVID-19 including acute respiratory distress syndrome, coagulopathy and thromboembolism, myocarditis, acute kidney injury, diarrhea, anosmia, encephalitis, and orchitis (Cardona Maya et al., 2020; Menni et al., 2020; Wadman et al., 2020).

The pathophysiological rationale to quantitatively link the expression level of ACE-2 to differences in viral susceptibility, symptomology, and outcomes in those infected with SARS-CoV-2 at high altitude was suggested by Arias-Reyes et al. (2020). These authors proposed that SARS-CoV-2 may be less virulent at high altitude owing to hypoxia-induced downregulation of ACE-2 expression providing fewer receptors for the virus, but data supporting this contention are not consistent or convincing. Zhang et al. (2009) reported a blunted expression of ACE-2 in cell lines exposed to severe hypoxia (2% oxygen) over 12 days. A similar observation was made by Dang et al. (2020) when rats were exposed to the hypoxia equivalent of $\sim$4500 m altitude over 45 days.

However, other studies in different models have reported that hypoxia upregulates ACE-2. Oarhe et al. (2015) found that hypoxia (1%) in fetal lung fibroblasts increased ACE-2 expression by twofold (Oarhe et al., 2015). Hampl et al. (2015) showed that rats exposed to 10% oxygen for 2 weeks had a doubling of lung tissue ACE-2 content (Hampl et al., 2015). Joshi et al. (2019) demonstrated that human hematopoietic stem cells respond to 1% oxygen with an increase in mRNA and ACE-2 protein (Joshi et al., 2019). Most importantly, it needs to be emphasized that there are currently no human or animal data characterizing ACE-2 expression during hypoxic conditions along the epithelium of the upper and lower respiratory tracts, where the virus first infects humans through inhalation. Furthermore, any such experimental observations on hypoxia exposure may not be relevant to genetically adapted high-altitude populations such as Tibetans, Sherpas, Andeans, Ethiopian highlanders, or those not of these ethnic groups, who were born and raised at high altitude. Thus far, there are no published data that genetically or highly adapted high-altitude residents have downregulated ACE-2 expression. With multiple variants of the ACE-2 gene found by single nucleotide polymorphism analysis present across the world (Cao et al., 2020), high-altitude populations might conceivably have protective variants. Such information may become available with completion of the COVID-19 Host Genetics Initiative (Ganna, 2020) now underway.

Any direct association of altitude and possible differences in ACE-2 expression may oversimplify a very complex interaction. First, it is well established that ACE-2 is a key element of the renin–angiotensin system (RAS) promoting vasodilation and maintenance of normal capillary integrity and affording cytoprotective anti-inflammatory, antioxidative, and antithrombotic actions in the lungs and other organs (Kuba et al., 2005). ACE-2 acts by catalyzing the formation of angiotensin 1–7, which opposes the opposite actions of angiotensin II (Xie et al., 2006; Lakatta, 2018), particularly in severe acute lung disease such as that present in patients with COVID-19. Second, it remains unclear whether any modest differences in ACE-2 expression, which depend on circumstances such as age (Bunyavanich et al., 2020), host genetics (Ghafouri-Fard et al., 2020), smoking status (Berlin et al., 2020; Zhang et al., 2020), air pollution (Aztatzi-Aguilar et al., 2015; Frontera et al., 2020), and drugs affecting the RAS (Gao et al., 2020; Vaduganathan et al., 2020), translate into differing degrees of susceptibility to SARS-CoV-2 infection. Indeed, regardless of the inference that individuals with reduced ACE-2 expression may be less susceptible to severe infection, there appears to be a paradoxical relationship between virally mediated membranous ACE-2 downregulation and a predisposition to suffer more severe forms of COVID-19 lung injury, perhaps related to decreased angiotensin 1–7 production (Zambelli et al., 2015; Cheng et al., 2020; Peiró and Moncada, 2020).

Thus, the potential positive or negative impact of ACE-2 upregulation or downregulation in COVID-19 pathogenesis and differing expression levels among populations should be critically examined, as currently there is no definitive clinical evidence in humans. The best evidence against any pertinent disease modifying effect of differences in ACE-2 expression relates to the widespread use of angiotensin receptor blockers and ACE inhibitors. Therapeutic use of these drugs, while

having been reported in some studies, but not all, to increase ACE-2 expression has led to fear regarding their continued usage during the pandemic (Bavishi et al., 2020; Patel and Verma, 2020). The concern is unjustified because their administration does not appear to cause any increased risk for COVID-19 in patients on these medications for their intended use in heart disease, hypertension, diabetes, and chronic kidney disease (Amat-Santos et al., 2020; Khera et al., 2020).

Other environmental factors

The high-altitude environment has higher ultraviolet (UV) radiation and is generally drier and colder. Atmospheric measurements suggest that the general distribution of UV energy below the ozone layer is 3%–5% of total sunlight energy in the <400 nm wavelength range. Of this UV radiation ~95% is UV-A (wavelength: 315–400 nm), 5% is UV-B (280–315 nm), and 0% is in the germicidal UV-C (200–280 nm). Because a UV wavelength of 254 nm is most cidal for SARS-CoV-2 and other viruses (Sangripanti and Lytle, 2020), it would be predicted that sunlight should not cause significant UV inactivation of SARS-CoV-2. Arguably, there might be some impact of the lesser killing efficiency of higher UV-B wavelengths in sunlight, particularly if the amount of UV-B at higher altitudes is greater than at sea level. Another benefit of greater UV radiation at high altitude will be possibly higher vitamin D levels, which afford protection against several other viral and bacterial infections by T cell enhancement (Grant et al., 2020). Thus, UV radiation might, theoretically, contribute to slowing the spread of the virus as some groups have suggested (Cadnum et al., 2020; Hamzavi et al., 2020; Keil et al., 2020), but this needs to be examined carefully. However, any action of UV radiation will only be relevant to the outdoor environment and most viral transmission occurs indoors, where people congregate in closer quarters and spend many hours of the day.

The lower water content and humidity present at high altitudes may hasten viral desiccation and inactivation as a possible benefit. Conversely, the generally colder temperatures at high altitude, which decline by ~0.6°C/100 m, may increase COVID-19 risk. The incidence of COVID-19 reportedly declined with increasing temperature in the United States (Sehra et al., 2020) and China (Shi et al., 2020). The reported peak incidence of SARS-CoV-2 in a range of 5°C–15°C with humidity range of 3–10 g/m^3 further highlights the niche of higher viral infection rates (Huang et al., 2020). However, a consensus is yet to be reached on this topic, because a further analysis incorporating meteorological data from different Chinese cities found that both temperature and UV radiation were not significantly associated with viral transmission (Yao et al., 2020).

Air pollution may be a factor in greater susceptibility to the virus (Brandt et al., 2020; Fattorini and Regoli, 2020) and in general many mountainous areas have less pollution related to industry and automobiles. However, this may be countered by biomass burning for heating and cooking, which can make the indoor environmental conditions problematic along with outdoor air quality in valley regions prone to meteorological inversions (Thakur et al., 2020). Personal pollution exposure in the form of tobacco smoking may be a risk factor for greater COVID-19 rates (Alqahtani et al., 2020; Engin et al., 2020), but this has not been found in all studies (Rossato et al., 2020). Smoking increases airway epithelium expression of ACE-2 (Leung et al., 2020; Zhang et al., 2020) and this may be further driven independently by airway nicotine exposure (Russo et al., 2020).

Social Structure and Population Dynamics

In high-altitude communities, especially above 3000 m, population density is lower compared with lowland areas (Cohen and Small, 1998). Villages and towns at higher altitudes are often remote, difficult to access, and take many days to reach, especially under the restrictive travel conditions of a global pandemic. Low population density and remoteness may have played a major role in keeping COVID-19 at bay in these regions, where social (physical) distancing is more an extension of everyday life than an unusual hardship. Equally, the active lifestyle required to sustain a livelihood at high altitude means the population is typically younger, fitter, and without a high prevalence of preexisting medical conditions known to contribute to greater morbidity and mortality with SARS-CoV-2 infection. However, the harsh lifestyle and austere environment of some high-altitude regions, along with limited access to health care, resources spent on health care, capacity for viral testing and contact tracing will complicate any public health intervention required if complacency allows the virus to infiltrate these communities. Some of these issues may not pertain as greatly to larger cities at high altitude (e.g., Mexico City, La Paz, or Lhasa) or in high-altitude mining operations, such as in the Andes.

Transportation and Lockdown Measures

It is possible that early lockdown measures, media coverage, and preventive guidelines may have favorably worked in slowing the spread of the virus among high-altitude residents, because the virus appeared later in mountainous regions. Low population density, low traffic, or travel avoidance (from low-altitude population centers to high-altitude communities), and remoteness may have worked in tandem to further protect high-altitude residents. It is also likely to take many days in some mountainous regions of developing countries to reach destinations, which may have provided sufficient isolation time in some cases. However, cases of COVID-19 identified in the Qinghai-Tibet high-altitude plateau were related to contact with persons who had travelled from the Wuhan province (Xi et al., 2020). Aggressive implementation of preventive measures that target social isolation have helped to nullify sustained local transmission in Qinghai-Tibet high-altitude region. Therefore, it might be easier to prevent community transmission at high altitude with travel restriction alone.

Conclusions: Challenges of SARS-CoV-2 Infection at High Altitude

The reported lower incidence of COVID-19 among high-altitude residents is quite intriguing, but epidemiological observations presented so far from high-altitude regions are preliminary. The data regarding virus transmission should be carefully interpreted and any current observations regarding high altitude-related differences in incidence, prevalence, and morbidity/mortality of COVID-19 must be considered speculative and hypothesis-generating because of the multitude of other environmental, political, temporal, and health care system factors at play. There is currently little supporting evidence for any protective benefit of genetic or nongenomic

adaptation to high-altitude hypoxia, including the concept that hypoxia-mediated alterations in ACE-2 expression or ACE-2 variants in particular population groups might have relevance to the pathogenesis or severity of disease.

Given the myriad of other contributing factors to viral infection rates and transmission enumerated previously, deciphering whether high-altitude hypoxia is important either as a risk factor or potential form of protection will remain difficult to establish without further high-quality epidemiological studies. We should avoid reaching the conclusion that any community has an innate protection from COVID-19 in the absence of robust evidence. Therefore, standard preventive measures currently implemented by health agencies worldwide must also be practiced by high-altitude travelers and residents, until adequate controls are in place, and ultimately effective treatments and vaccines become available.

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