3 High Altitude Related Diseases: Milder Effects, HACE, HAPE, and Effect on Various Organ Systems

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Abstract

Proteomics has emerged as an excellent biomarker discovery tool in recent years owing to the rapid emergence and growth of high throughput proteomics approaches and advancements in mass spectrometry methods especially in terms of mass analysers and resolution. Moreover, plasma and serum have always been a choice of diagnostic fluid since historical times and have always been a preferred diagnostic sample by clinicians. Although plasma is disproportionate in terms of composition as some proteins such as albumin and globulins are highly abundant, while others are found in traces. The emergence of methods to deplete the high abundance of proteins has led to a remarkable refinement in plasma or serum composition for its diagnostic abilities. Plasma proteins are always considered the gold standard for several metabolic changes induced by diseases or altered physiology. High altitude related physiological changes have also been evaluated recently over the proteomic scale and seemingly represent a potential source for exploring biomarkers for such physiological changes. This chapter describes the hypobaric hypoxia-induced changes in the plasma and serum proteome and potential biomarkers which have enormous commercial and clinical potential.

Keywords

High altitude · Diseases · AMS · HAPE · HACE

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N. K. Sharma, A. Arya (eds.), *High Altitude Sickness – Solutions from Genomics, Proteomics and Antioxidant Interventions*,
https://doi.org/10.1007/978-981-19-1008-1_3

3.1 Introduction

Mountains occupy nearly a quarter of the Earth's land area (Kapos et al. 2000) and remain a dwelling place to 140 million people across the globe. These statistics not only include remote, economically disadvantaged groups of communities such as Northern India, Tibet, and Nepal, but also several urban centres and adjacent areas to hills such as valleys, including some megacities such as Santigo, Chile, and Mexico (Meybeck et al. 2001). Apart from permanent residence, high altitudes are also visited by millions of individuals for recreational activities such as skiing, hiking, mountaineering and even peak climbing, performance budding training of athletes; religious pilgrimages and in some cases as military support to safeguard the national territories on the military front. Altitudes have always been foreseen as one of the most beautiful creations of nature, and always admired. But the darker side also exists, particularly, for the people ascending to an altitude beyond 2500 m at a steep rate from sea level.

In such conditions high altitude poses its own set of risks and challenges to the human physique and psyche, resulting in several sickness symptoms and worst-case scenarios, death. The major cause for these ill effects that have been revealed in many scientific studies is a reduction in the partial pressure of air (hypobaric hypoxia) causing altered cardiopulmonary responses associated with pathophysiology thereof. Although some of the high altitude regions are not accessible to common people yet, others are accessible and frequently visited by travel enthusiasts and inhabitants. High altitudes of the greater Himalayas in the north of India, especially in the Leh district are some of the frequently visited and well-inhabited high altitudes places. Not only due to local inhabitants but also due to strategic situations, these areas have some of the highest often visited places. Moreover, the Leh-Nubra highway is also connected by the highest motorable road with the highest mountain top existing at a staggering altitude of 17,982 feet (5481 m), commonly known as Khardung La Pass (Fig. 3.1). The Himalayas, particularly due to strategic reasons, have many such inhabited high altitude stations and roads in India, China, Nepal, Pakistan and Afghanistan.

Although researchers have not developed a consensus that a distinct altitude boundary persists between a high altitude and low altitude, yet, from the scientific evidence on clinical symptoms, generally, high altitude is considered above 1500 m above mean sea level (MSL). Several high altitude experts have stratified high altitude into three levels, first, high altitude at an altitude between 1500 m and 3500 m; second, very high altitude from 3500 to 5500 m; and third, extreme altitude beyond 5500 m of altitude (Bakonyi and Radak 2004). The highest altitude noted on the lithosphere is 8848 m (Mount Everest) and has been an attraction for mountaineers. Several other mountains in the Himalayas, Swiss Alps, and Andes have altitudes reaching 6096 m (20,000 ft), and numerous tourist attractions in the altitude range of 3000–5000 m. As one moves to a higher altitude the rate of air becomes sparse due to lower atmospheric pressure and thereby causing decreased partial pressure of oxygen. The rate of decrease in atmospheric pressure is exponential (Fig. 3.2) (Peacock 1998). Although the most impacting environmental effect of

Fig. 3.1 A view of the highest motorable road in the world at Khardung La Pass, (**a**) Motorable road across the valley. (**b** and **c**) A view of hill-top at Khardung La pass, (**d**) Signboard for tourists indicating the hill-top altitude of 17,982 feet or 5481 m. (Photo—Author)

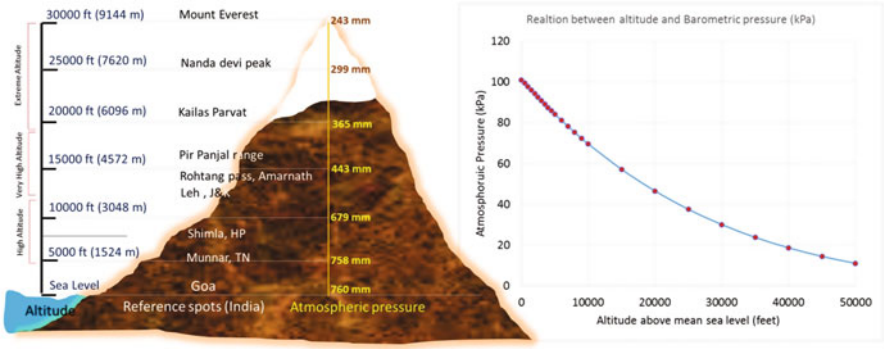

Fig. 3.2 High altitude and changes in relative atmospheric pressure, Altitude above 5000 ft is considered high altitude, 11,500 ft–18,000 ft. as very high altitude and 18,000- beyond is considered as extreme altitude (some reference tourist locations are mentioned from Indian terrain). The barometric pressure drops exponentially with increase in altitude (right panel)

high altitudes is hypoxia, yet the low temperatures and dry environment in some arid areas cannot be ignored while considering the overall impact on human physiology.

At low atmospheric pressure, partial pressure (pO_2) of oxygen also decreases, which adversely affects human physiology (Rick 1995) leading to high altitude illness. The rate of ascent determines the severity of illness. The first clinical symptoms usually appear within 2 days of reaching the high altitude. Among the most commonly reported symptoms are fatigue, nausea and vomiting, headache, breathlessness, inability to sleep, and occasional swelling of the face and limbs (Hultgren 1996). Rapid ascent to high altitude is often known to be associated with

some additional physiological changes such as breathlessness, drowsiness, loss of appetite, loss of sleep, lassitude, and irritability to further ascend to higher altitude. These aforementioned symptoms are commonly referred to as acute mountain sickness (AMS in short) or high altitude sickness. To develop AMS at an altitude above 5000 m, a period of a few hours is required. Nevertheless, exposure at altitudes as low as 2500 m (8000 ft) have also been sensitive enough for few people and led to the development of AMS. The development of AMS at these altitudes may be significantly increased after a long-haul flight. It is generally suggested that a person on arrival at a high altitude should take proper rest for at least 24 h and should avoid any physical activity and may extend the period of rest if mild symptoms appear (Wilson et al. 2009). While the milder effects remain limited to the aforementioned acute symptoms which are relieved with rest and prolonged stay, the chronic and more severe forms of altitude sickness might impact vital organs such as the lungs and brain to a great extent while other vital organs such as the heart, liver, and kidney as a secondary manifestation of the effect on brain and heart. The most severe form of mountain sickness that affects the lung is known as high altitude pulmonary oedema or HAPE in short, while the most severe and occasionally lethal effect of altitude sickness on the brain is known to be high altitude cerebral oedema or HACE in short. During the International Hypoxia Symposium in 1991, a consensus was developed over the proposal of Peter Hackett and Oswald Oelz (Hartig and Hackett 1992) to define and quantify the various altitude illnesses. This later turned into a draft in 1992 and evaluation criteria for high altitude sickness commonly known as Lake Louise criteria. The scoring system includes severity on a scale of zero to three for the five common symptoms related to high altitude, i.e. headache, gastrointestinal upset, and fatigue/weakness, dizziness/light T headedness, and sleep disturbance. A total score ≥ 3, in the presence of a headache, was decided to be considered as a diagnostic feature for AMS. An updated version of the consensus redrafted in the year 2018 is provided in Table 3.1.

3.2 Epidemiology of High Altitude Sickness

If one considers the epidemiology of high altitude sickness, scanty and sparse evidence and data is available. There is a lack of suitable global data accessible to clinicians despite enormous reporting and efforts made by local authorities and clinical teams. The incidences of high altitude sickness are known to increase with ascending altitude. While high altitude sickness is reportedly seldom at an altitude below 2500 m, the percentage of travellers facing difficulties in acclimatization above 3000 m is approximately 75%. Moreover, travellers with a clinical history of high altitude sickness are more susceptible than those who have surpassed similar trips in the past (Prince et al. 2021) The susceptibility of high altitude sickness is exaggerated by pre-existing ailments such as asthma, anaemia, hepatic or renal dysfunctions. Although it is difficult to keep the global record of high altitude sickness, yet the emerging networking and informatics tools have allowed the collection to be integrated. One such integration of data on high altitude illness

Table 3.1 2018 Lake Louise Acute Mountain Sickness Score (After Roach et al. 2018)

Headache	Dizziness/light-headedness
[a]None at all	[a]No dizziness/light-headedness
[b]A mild headache	[b]Mild dizziness/light-headedness
[c]Moderate headache	[c]Moderate dizziness/light-headedness
[d]Severe headache, incapacitating	[d]Severe dizziness/light-headedness, incapacitating
Gastrointestinal symptoms	AMS clinical functional score
[a]Good appetite	[a]Not at all
[b]Poor appetite or nausea	[b]Symptoms present, but no change in activity
[c]Moderate nausea or vomiting	[c]Symptoms forced me to stop the ascent or to go down
[d]Severe nausea and vomiting, incapacitating	[d]Had to be evacuated to a lower altitude
Fatigue and/or weakness	
[a]Not tired or weak	
[b]Mild fatigue/weakness	
[c]Moderate fatigue/weakness	
[d]Severe fatigue/weakness, incapacitating	

[a]Score of zero or no effect
[b]Score 1
[c]Score 2
[d]Score 3. (Based on original Lake Louis Criteria)

was performed by Hackett and coworkers in 2004 that reported global sampling of high altitude sickness. It is known that a correlation exists between altitude and the number of AMS cases.

For example, in one study by Maggiorini et al., reports of AMS incidences have been described, where they have indicated about 9% at an altitude of 2850 m in the swiss alps, while 13% at 3050 m, and above 3650 m it was nearly 36% (Maggiorini et al. 1990). Besides AMS, HAPE, a much severe version of high altitude sickness, typically occurs at altitudes over 3000 m, but it has been recorded at a lower altitude threshold of 1400 m.

In a study, containing a brief epidemiological profile of HAPE, ND Menon, has been described the prevalence of HAPE with clinical evidence, estimating it in a range from 0.2% at an altitude of 4550 m to approximately 15% in sojourns ascending to an altitude of 3500 m or above especially via flight (Menon 1965). Compared to HAPE, HACE is less life-threatening in terms of epidemiology as evidently, it is much less common than HAPE and ACE. The incidences of HACE are known to be less than 1–2% and observed only above the altitude of 4000 m. HACE is often, but not always, preceded by the development of HAPE. Some efforts towards epidemiological data collections have been made by organizations such as altitude.org as a part of the apex project led by Dr. J. Kenneth Baillie (https://www.altitude.org/), where they have started collecting the global HAPE data and also host valuable information related to altitude sickness. The statistics of deaths occurring at high altitude is also sparsely available and no integrated global data is yet available.

The primary reason for this non-follow-up of the patients and also, secondary reasons of deaths such as accidents or avalanche. Most of the travellers which travel to high altitude for personal tourism are unregistered to a database except those who are on special mountain expeditions, such as Mount Everest. Death statistics of the Everest summit from 1921 to 2006 provided in a study by Firth et al., showed that the mortality rate among mountaineers above base camp was 1.3%, which included both traumatic and non-traumatic deaths and even some deaths were reported as missing individuals. A number of altitude sickness symptoms such as profound fatigue, ataxia, and cognitive changes were also reported in non-traumatic deaths (Firth et al. 2008).

3.3 Mechanisms of High Altitude Sickness

Onset and progression of high altitude sickness may be categorized into three steps, (a) hypoxia stimulus, (b) sensing, and (c) molecular changes. Hypoxia is the primary stimulus since the initiation of the pathogenesis of acute mountain sickness, although symptoms become visible 6–7 h after the exposure, but worsen with increasing altitude (Savonitto et al. 1992) and relieved by normalizing the inspired PO_2 (Wu et al. 2007). These stimuli are sensed by cellular oxygen sensing systems and thereby evoking a compensatory response. Two major compensatory events are evoked, increased pressure (mechanical) and increased permeability (molecular). Increased permeability is regulated by potent vasodilators such as nitric oxide (NO) while pressure is increased due to hyperventilation response. These two changes adversely affect the cardiopulmonary and cerebral systems by increased capillary pressure resulting in accumulation of fluids in the brain and lung causing high altitude cerebral oedema (HACE) and high altitude pulmonary oedema (HAPE),respectively.

One of the acute changes during the high altitude related hypoxia at the physiological level is hypoxic pulmonary vasoconstriction or HPV, which can be considered as an adaptive physiological response. A few individuals with strong hypoxic pulmonary vasoconstriction (HPV) capacity rarely develop high altitude pulmonary oedema. Hypoxia is known to directly influence the vascular tone of the pulmonary vessels, as well as elevates the systemic resistance across vessels. This change is reportedly attributed to the peripheral chemoreceptors. Furthermore, the cross-talk between the ventilatory response of hypoxia chemoreceptor-mediated reflex on the cardiopulmonary physiology results in exacerbating the condition. Peripheral chemoreceptors activation leads to increased ventilation and hence alkalosis as well as sympathetic activation of the autonomic nervous systems thereby increasing heart rate, cardiac output, myocardial contraction velocity, and blood pressure. Alkalosis is not compensated by usual renal compensation mechanisms above the altitude of 3000–4000 m and thus leads to a rapid fall in serum potassium which can be more problematic for diuretic patients. Cold and exercise and further add the sympathetic activation and aggravate the symptoms. In fact, cold changes in renal function at high altitudes are also observed as a direct effect of hypoxia on the kidney

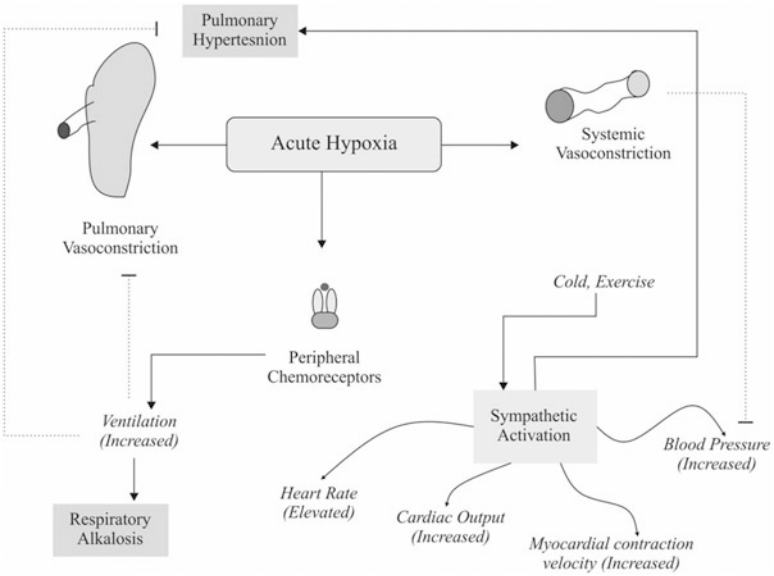

Fig. 3.3 Outline Mechanism of origin of high altitude sickness. Acute hypoxia at altitudes results in either direct impact on the tone of blood vessels by causing either pulmonary vasoconstriction or systemic vasodilation and secondly, sensory activity of peripheral chemoreceptors leads to increased ventilation or sympathetic activation of various cardiac functions. Renal functions are affected due to increased alkalosis and inability to perform compensation for respiratory alkalosis, while exaggerating the sympathetic activation and cardiac functions

especially as a renal compensation of hypoxia-induced alkalosis. As a part of this compensatory activity, urine output, sodium excretion, diuresis and natriuresis, elevated potassium and bicarbonate excretion. These changes are also activated by chemoreceptor based signalling as discussed above. These responses vary almost by about tenfold in the first 24 to 48 at high altitudes. Besides this, changes in renin, angiotensin, aldosterone, atrial natriuretic peptide, vasopressin, also impart their signalling effect, especially via nitric oxide messenger and further to hypoxia-inducible factor (Fig. 3.3).

3.4 Milder Effects of High Altitude (AMS)

Acute mountain sickness is initial milder symptoms initiated at the rapid ascent to a high altitude, which include headache, dizziness, tiredness, loss of appetite, and shortness of breath. AMS is not the same as high altitude cerebral oedema (HACE) and therefore must not be clinically confused as it is not known to be associated with prominent neurological perturbation. AMS is associated with much milder symptoms in contrast to much worse conditions as HAPE or HACE, which usually comes on between 24 and 72 h after a gain in altitudes. As the worsening of

symptoms can happen quickly after AMS, provoking factors such as running, exertion, high-physical activity, and smoking should be strictly avoided at extreme altitudes (Hackett et al. 1988; Willmann et al. 2014). Also, alcohol use and sleeping pills are additional factors that increase the chances of developing Acute mountain sickness and worsen it to HAPE or HACE. Besides AMS, a related issue is called sub-acute mountain sickness (or SMAS), which is a distinct syndrome symptomized by congestive cardiac failure and observed in lowlanders while they have prolonged stay at extremely high altitudes. We have discussed this in more detail in later sections on cardiopulmonary aspects of high altitude sickness.

3.5 High Altitude Pulmonary Oedema (HAPE)

HAPE was first reported and elaborated by Ravenhill in 1913 (West 1996). High Altitude Pulmonary Oedema or HAPE develops usually within 2 to 4 days after reaching high altitude (>2500 m). It is characterized by dyspnea at rest, decreased tolerance to exercise and tightness of the chest. HAPE is also linked with tachycardia (slow heart rate), tachypnea, and dry cough often with lung crackles. Some other signs associated with HAPE are wheezing possibly due to accumulation of lung fluid, and cyanosis (Hartig and Hackett 1992). Fever and haemoptysis have occasional occurrences. The clinical correlation does not need to be homogenous in chest radiography as it can vary across individuals, most commonly appearing as patchy alveolar infiltrates, the spread of which increases with severity (Marticorena and Hultgren 1979; Vock et al. 1991). Although the exact mechanism of HAPE is not well understood, some suggested mechanisms include an exaggerated hypoxic pulmonary vasoconstriction with an abnormal increase in the pulmonary artery (Hultgren 1996; Penaloza and Sime 1969; Allemann et al. 2000). This further leads to the irregular distribution of vasoconstriction with regional over perfusion (Zhao et al. 2001) and increased capillary pressure (Maggiorini et al. 2001) finally causing trans-microvascular fluid leakage (Schoene et al. 1988; Swenson and Maggiorini 2002). It is not completely understood that genetic predisposition is linked to the increased endothelin production in HAPE susceptible patients with lower nitric oxide production, yet several other studies have reported nitric oxide modulations and their correlation with HAPE. A study at Author's lab demonstrated that dietary nitrite attenuates oxidative stress and activates antioxidant genes in rat heart during hypobaric hypoxia (Singh et al. 2012). HAPE is differentiated from AMS on the grounds of exhaustion, hypothermia, hyponatraemia, migraine, dehydration, infection, carbon monoxide poisoning, drug and alcohol intoxication, hypoglycaemia or severe hyperglycaemia, transient ischaemic attack or stroke and acute psychosis, possibly related to intake of corticosteroids.

3.6 High Altitude Cerebral Oedema (HACE)

HACE is a potentially fatal neurological condition that is known to develop after hours to days in high altitude travellers post AMS or HAPE. HACE is considered as a terminal clinical manifestation of AMS, it is not well understood, however, that HACE is always preceded by AMS, or HAPE and can occur independently without any clinical evidence of HAPE. Clinically it is correlated, by ataxia and hallucinations, and accumulation of fluid in the brain. Coma and death are eventual results if HACE is left untreated. The clinical diagnosis of HACE is based on its cardinal features such as a change in consciousness and ataxia (Sutton 1992). Mental status changes may include irrational behaviour that rapidly progresses to lethargy, obtundation, and coma. Other physical indications of HACE useful in clinical diagnosis are bleeding retinal veins (retinal haemorrhage), palsies of cranial nerve palsies, and cognitive deficits. The exaggerated form of these clinical conditions leads to brain herniation which causes death in HACE patients (Hultgren 1996; Yarnell et al. 2000; Hackett 1999). The increased intracranial pressure is one of the signs that can also be imaged using MRI. The underlying cause behind the oedema of the brain is the elevation of intracranial pressure, which is the overperfusion of blood vessels in response to global vasodilation mediated by nitric oxide and other related molecular events. However, there is also a possible role of other factors such as radicals and radical-induced adaptive signalling causing the pathology of HACE.

3.7 High Altitude Related Cardiac Perturbations

Although it is well-known that pulmonary oedema that appears during high altitude sickness is primarily of non-cardiac origin. However, cardiac effects are mostly retrospective in the occurrence of high altitude sickness. It is reported that cardiac or pulmonary diseases are at a much higher risk of high altitude sickness. Nevertheless, compared to patients with coronary heart disease, hypertension or bronchial asthma have lesser ill effects, while patients with chronic obstructive pulmonary disease (COPD), pulmonary hypertension or interstitial pulmonary disease might be impacted to a greater extent (Fischer 2004). As we have discussed above in the mechanism of high altitude sickness, one of the key signals that impact the heart is the activation of sympathetic systems due to chemoreception of acute hypoxia. A special condition of acute mountain sickness that is known to impact the heart to a great extent is known as adult sub-acute mountain sickness (SAMS). Poduval in his clinical assessment of SAMS has reported that individuals stationed above 5000 m when evaluated for the signs of congestive cardiac failure using simple chest X-ray and electroencephalography. Exertional dyspnea and bilateral pedal oedema were observed as the most common sign in experimental patients. Moreover, some patients also showed signs of deep venous thrombosis (Poduval 2000).

The risk of myocardial ischemia is enhanced by an elevation in cardiac work during the first few days at altitude but reduces significantly as the cone relieves the cardiac work possibly by rest and lower physical activity.. Exercise-mediated

coronary flow reserves are known to be significantly reduced at 2500 m in patients with coronary disease leading to coronary spasm mediated by sympathetic activation and alkalosis. The synergistic effect of hypoxia also with exercise is a tremendous stressor for the heart and pulmonary system. However, the cases of deaths occurring due to exercise at altitude are limited. Alkalosis of blood mediated by hyperventilation poses an indirect threat to the cardiac system, especially for diuretics. Patients with uncontrolled hypertension which are administered diuretics may need a rescheduling and revised dosing at high altitude. Also, they should avoid visiting altitude until their blood pressure is controlled (Bärtsch and Gibbs 2007).

3.8 High Altitude Related Perturbations in Muscles

Not much has been explored about the changes in muscles by acute high altitude exposure. However, it is likely to be highly diverse based on the duration of stay, altitude, degree of physical activity, and prior histology of muscles. Nevertheless, on the biochemical grounds, hypoxia at the tissue level (still needs to be completely validated for muscles) is a possible cause of switching of muscle to glycolytic mode. Some studies confirmed the upregulation of glycolytic enzymes in muscle post-hypoxic exposure. It is also evident that the muscles of high altitude dwellers have elevated expression of glycolytic enzymes in comparison to lowlanders (Rosser and Hochachka 1993, Green et al. 1998). Reynafarje B in their study in the early 1960s has also reported a significantly higher level of myoglobin in high altitude dwellers compared to lowlanders (Reynafarje 1962). Yet, these differences between high altitude natives and lowlanders are not a correlative measure of the effects of high altitude and acute exposure of hypobaric hypoxia on human muscles. Moreover, hypoxic cachexia, which is a well-described anatomic and physiological perturbation in hypoxia, remains poorly understood at the mechanistic level. Additionally, chronic hypoxia is also known to affect the fibre composition and enzyme activities in muscles primarily by shifting them from slow oxidative to fast glycolytic metabolism (Rosser and Hochachka 1993).

3.9 High Altitude Related Perturbations in Kidney

Physiologically, kidneys are voracious consumers of oxygen accounting for about 10% of the entire body's oxygen consumption despite only 0.5% of the mass. The presence of intra-renal hypoxia in several diseases such as diabetes is an indicator of the relation between hypoxia and kidney functions at the pathological level. There is evidence of the increased prevalence of nephropathy in diabetic patients staying at high altitudes. Laustsen et al. have recently elaborated this discussion and provided pieces of evidence on alteration of renal oxygen availability and explored the metabolism of pyruvate which was shifted to a higher side towards lactate and alanine rather than oxidative fate (Laustsen et al. 2014). More recently, it has been studies that humans living at high altitudes are at greater risk for developing

high-altitude renal syndrome (HARS), which is symptomised by polycythemia, hyperuricemia, systemic hypertension and microalbuminuria (Hurtado et al. 2012). The primary reason for such renal perturbations at high altitudes is mainly attributed to acute systemic hypoxia as well as prolonged renal hypoperfusion.

In an attempt to study the physiology of the renal system under hypoxia, a study by Handitsch et al. leaves some impressive footprints by providing data on changes in important renal indicators after hypoxic exposure. They observed an initial decrease in glomerular filtration rate that became significant after 48 h which returned to normal after approximately a week Moreover, a sustained erythropoietin production was observed above an altitude of >2100 m which is suggestive of renal remodelling. As kidneys are also important organs performing the renal compensation for the hyperventilation and hypoxia-induced respiratory alkalosis, the sodium excretion rate and fractional excretion of sodium is recorded inconsistent (Haditsch et al. 2015).

3.10 High Altitude Related Perturbations in Liver

The liver is one of the busiest organs of the body in terms of metabolic pathways and also a site of control of many intermediate metabolic processes. After the brain and kidney, it is the largest consumer of oxygen, therefore hypoxia of various origins may affect its anatomy as well as physiology. Very limited research has been conducted and therefore scanty data is available on evidence of liver injury or dysfunction in individuals travelling to extreme altitudes of 5000 m or above. It is evident that, while the patients with liver transplants may not be affected by high altitude exposure, the travellers with cirrhosis require careful pre-travel evaluation. It is important to identify the predisposition to high altitude particularly in cirrhotic liver cases especially for mitigating the illness at those altitudes (Luks et al. 2008). While the book was being written, no evidence was available about the long-term risk of chronic liver disease, while staying at high altitudes or travelling to altitudes for a much longer period in months or years.

3.11 Conclusion

Hypoxia as it appears is a major physiological threat to a significant portion of the human population either travelling or dwelling at extreme altitudes. Despite decades of efforts the exact nature of physiological perturbations and pathological manifestations are not completely resolved at the mechanistic level. Albeit, research has provided suitable and safe regimens for altitude ascent in terms of adaptive measures and acclimatization methodologies. Rapid descent and oxygen supplementation have emerged as immediate remedies of high altitude sickness. Moreover, some prophylactic pharmaceuticals such as acetazolamide and dexamethasone have been proposed. Also, some therapeutic recommendations such as nifedipine, acetazolamide, sildenafil, and tadalafil have been established. A lot more evidence is

warranted at the system level and organ level changes in physiology to prevent any unlikely mortality and relieve the discomfort on the rapid ascent to high altitude.

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