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Trabajo Fin de Grado

Grado en Farmacia

Physiological adaptation to altitude. Possible therapeutic implications.

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Summary

High altitude is characterised by hypoxia; low levels of oxygen in the atmosphere create a deficiency in oxygen reaching the tissues. Hypoxia creates a stress in all aerobic bodies, leading to physiological, metabolic and genomic changes to adapt to this new environment.

As there are some high-altitude adapted populations, we are going to make a difference between adaptation and acclimation. Adaptation is referred as the long-term evolutionary changes which affect the whole population and acclimation are the short-term changes which lowland adapted newcomers undergo to adapt to a new environment.

In this final degree work, we will identify the main changes produced by hypoxia and other altitude-related factors in different states of the human body. We will resume physiological changes, deleterious effects in other pathologies, altitude training, as well as a review of the actual treatment and prophylaxis of the unpleasant symptoms lead by an incorrect short-term adaptation to hypoxia.

We will speak about pathologies and special situations like pregnancies, hypoxic adaptations lead to changes in these illnesses situation, some of them get improved and some of them get aggravated by altitude's hypoxia.

Recently, high-altitude and hypoxia are seen as a new pathway for the treatment of some pathologies such as obesity, diabetes, cancer and cardiovascular diseases and can open up some new fields for future studies.

1. Introduction

Most of the humanity is adapted to lowland environments; however, powered by curiosity and desire of knowing their own world they started exploring their surroundings from the very beginning of history. Soon they noticed some unpleasant effects while gaining altitude, and also, that native populations from high altitude didn´t suffer from those.

Whereas lowland environment is characterised by high partial pressure of oxygen (PO_2), highlands have lower PO_2, which is perceived as uncomfortable. There are some unpleasant symptoms linked to this low PO_2 such as fatigue, dizziness, dyspnoea, headache, nausea, ear-ringing, blistering and venous dilatation, which leads to swelling and oedema.(1–3)

All these symptoms are not present in local populations; regions such as Tibet in Asia, Andes in America and Ethiopia in Africa have been permanently inhabited for millennia, so natural adaptation has happened in these populations. Other highland populations are settled in the Rocky Mountains in Colorado (United States of America), however, only for 150 years, so it is believed that adaptation has not occurred as much as in the other populations yet.

The term “adaptation” is defined as any features of structure, function, or behaviour that increase the ability to survive and reproduce in a given environment. Adaptation occurred in different ways, such as the phenotypic traits acted by natural selection.

Adaptation is different to “acclimation” or the time-dependent changes such as the rise in ventilation, haemoglobin concentration, heart rate, and redistribution of blood flow that serve to restore arterial O_2 content and preserve the O_2 delivery to vital organs. (2)

2. Objectives

In this final degree project, we will identify altitude effects, seen by adaptive changes, athletic performance in altitude, altitude sickness's physiopathology, altitude effects on pre-existing pathologies and finally its effects on pregnancy and post-natal period.

Secondly and finally, we will describe treatment of altitude alterations and altitude as a treatment for previous pathologies.

Summing up, the objectives pursued in this final degree work are:

1. Identification of altitude effects over the human body,
    a. Adaptive changes
    b. Deleterious changes in pre-existing pathologies and pregnancy.
2. Description of therapeutic matters on altitude
    a. Treatment of altitude alterations
    b. Altitude as a treatment

3. Development

Comparing to sea level, in the lower Colorado resorts in the Rocky Mountains there is ¼ less available oxygen, at the Everest Base Camp (5300m) there is ½ of available oxygen and on the summit of Mount Everest there is only ⅓ of available oxygen.

High altitude environment is organised into stages according to the physiologic stress and the resultant pathology (Table 1):

- Intermediate altitude (1520-2440m): there is a decrease in the exercise performance and increased ventilation that keeps the blood oxygen saturation over 90%.
- High altitude (2440-4270m): hypoxia starts to occur, oxygen saturation values drop to less than 90%. This hypoxemia worsens during exercise and sleep. Most high altitude illness (HAI) occurs at this range.
- Very high altitude (4270-5490m): a period of acclimation is required to prevent High Altitude Illness (HAI) and abrupt ascent is dangerous.
- Extreme altitude (>5490m): there is great hypoxemia and hypocapnia. This hypoxic stress leads to progressive physiologic deterioration that eventually overwhelms the body's ability to acclimatize. There is no possible human habitation at this stage. (3)

Table 1: Effects of increasing altitude on respiratory physiology.

Table 1
Effects of increasing altitude on respiratory physiology

Altitude	Equivalent	Pb (mm Hg)	Estimated Pao_2 (mm Hg)	Estimated Sao_2 (%)	$Paco_2$ (mm Hg)
Sea level	—	760	90–100	97–99	38–42
5280 ft (1610 m)	Denver	623	65–80	93–97	32–42
8000 ft (2440 m)	Machu Pichu	564	45–70	88–95	31–36
12,000 ft (3660 m)	La Paz, Bolivia	483	42–53	80–89	24–34
17,500 ft (5330 m)	Everest Basecamp	388	38–50	65–81	22–30
29,000 ft (8840 m)	Everest Summit	253	28–32	54–62	10–14

Pressures expressed in mm Hg.
Abbreviations: Pb, barometric pressure; Sao_2%, arterial oxygen saturation.
Adapted from Roach CR, Lawley JS, Hackett PH. The physiology of high altitude. In: Auerbach PS, editor. Wilderness medicine. Philadelphia: Elsevier; 2016. p. 3.

We are going to make a difference between adaptation and acclimation. In local population, we are referring to adaptation, long-term evolutionary changes to adjust to its habitat that usually affect the whole population, which is the result of fertility and/or mortality. In

newcomers, we refer to acclimation, a short-term adaptation with physiological adjustments that an organism undergoes when it is transferred to a different habitat.

The term adaptation is the summation of both genetic, developmental adaptation and natural selection. During the postnatal phase, low partial pressures of O_2 lead to hypoxia, which induce lung growth, and tissue remodelling to increase O_2 diffusion. (1,2)

3.1- ADAPTIVE CHANGES TO ALTITUDE

Acclimation is the process or result of becoming accustomed to a new climate or to new conditions, a temporary adaptation to gradual changes in the natural habitat.

Acclimation by organ system:

- Pulmonary: there is increased ventilation modulated by hypoxic ventilatory response (HVR) and limited by respiratory alkalosis. And pulmonary vascular remodelling, which consists on a vasoconstriction that leads to the reduction and muscularization of precapillary arteries. (4)
- Renal: bicarbonate diuresis counteracts alkalosis.
- Cardiovascular
    - Increased sympathetic tone elevates the systemic blood pressure.
    - Increased heart rate and decreased stroke volume
    - Overall cardiac output increase
- Hematologic: hemoconcentration followed by increased red cell mass.
- Brain: increased cerebral blood flow.

Above 5500m there is inevitable weigh loss due to catabolic loss of fat and lean body mass. There is also intestinal malabsorption, impaired renal function, polycythemia leading to microcirculatory sludging, right ventricular strain from excessive pulmonary hypertension, fragmented sleep, and prolonged cerebral hypoxia. (3)

To sum up, these changes ensure the body's capacity to develop or undergo given tasks or exercises at high altitude. The increase in ventilation, cardiac output, blood pressure, heart rate, red blood cells mass and cerebral blood flow guarantee the O_2 and nutrients arrival to all vital cells. Nevertheless, at extreme altitude, there is a deterioration of almost all human systems.

3.2- ALTIDUDE AND ATHLETIC PERFORMANCE

The Mexican Olympic Games, in 1968, revealed the effect of Athletic performance at high altitude. In general terms, short distance athletes performed better due to the reduced air density, but middle and long distance athletes had worse times than expected. Athletes who lived or trained at high altitude performed better than their lowland competitors.

Due to the low oxygen content at high altitude and its consequent lower arterial oxygen pressure ((PaO_2) and reduced haemoglobin-oxygen saturation curve, there are several adaptations taking plate to compensate this hypoxia.

At this point, athletes and their coaches started considering training at high altitude to benefit from the physiological changes due to adaptation to high environments. There are many studies trying to elucidate the inside mechanisms of adaptation, however they are mostly unknown.

The hypoxia-inducible factor (HIF) is a transcription factor that regulates oxygen homeostasis. In normal conditions HIF is degraded by the ubiquitin-proteosome pathway, but in presence of hypoxia it is not degraded, leading to a longer half-life. The presence of HIF and its longer half-life leads to the transcription of its target genes, such as erythropoietin (EPO) and other molecules. As a result, there is an improved tissue oxygenation and the hypoxic damage is limited. (5)

Ventilatory effects:

Hypoxic ventilatory response (HVR) is the elevation in respiratory rate induced by hypoxia, to increase the intake of oxygen and is very important during exercise at high altitudes. This hyperventilation leads to a low $PaCO_2$, and produces a respiratory alkalosis.

This alkalosis shifts to the left the oxygen-haemoglobin dissociation curve (ODC), which allows greater load of oxygen in the lungs. However, it reduces oxygen release in tissues, worsening tissular hypoxia.

The elevation of 2,3-diphosphoglycerate (2,3-DPG), shifts the ODC to the right and improves the oxygen unloading in the tissues during exercise.

Ventilatory adaptations fail to compensate completely the hypoxia because of two reasons: the increased mismatching in ventilation-perfusion and the limitation in oxygen transfer by diffusion during exercise.(5)

Cardiovascular effects:

Hypoxia produces a sympathetic response, a vasodilatation to maintain oxygen perfusion to the tissues and avoid this way hypoxaemia.

Maximal cardiac output (CO_{max}) during exercise is ultimately reduced at acclimatized individuals, probably to reduce hypoxic damage to heart and brain. Due to the reduced peak muscle blood flow there is a restriction in oxygen delivery, and reduces maximal oxygen uptake (VO_{2max}).

Training intensity is therefore limited by reduced cardiac output and reduced VO_{2max} and can result in “detraining” effect. (5)

Haematological effects:

Hypoxic conditions induce HIF1, which is a transcription factor that increases the gene transcription of erythropoietin (EPO). EPO is produced in the kidneys and stimulates erythropoiesis in the bone marrow. This way blood capacity of carrying oxygen is improved.

In general, the maximum concentration of serum EPO happens from day 1-5 after the hypoxic exposition, but this is very variable among athletes. And when athletes in altitude training return and adapt to lowland environments, they reduce their red cell mass, due to EPO suppression, reduced iron takeover, and mainly haemolysis of young circulating red blood cells (neocytolysis). This is the reason why training should be timed so that the loss of red blood cell mass does not coincide with competitive performance.

Erythropoietin response is very variable; we can classify athletes as “responder” or “no-responder” phenotype due to a specific EPO gene polymorphism. Also, other factors such as illness or iron deficiency may also affect. The increase in EPO is only present in Andean athletes, whereas native Ethiopian and Himalayans athletes don’t have significant increases in EPO, haemoglobin or oxygen saturation compared to lowland athletes.

There is insufficient evidence to establish a cause-effect relationship between erythropoiesis and enhance athletic performance. It is difficult to compare haematological effects in different studies because of great variations in terms of hypoxic exposure, training content, detection methods and level of ability of subjects.(5)

Skeletal muscle effects:

When in altitude, intramuscular oxygen is reduced because of hypoxia and when the reduced intramuscular O_2 is maintained in time, it induces muscle fibre atrophy. In short term hypoxia

there are specific changes in gene transcription, metabolic economy and pH buffering capacity.

Gene transcription: There is an elevation in GLUT-4 transporter, which facilitates glucose uptake during exercise. An upregulation of angiogenin, interleukin-8 and vascular endothelial growth factor stimulates the formation of new capillaries and improves muscular blood flow.

Metabolic economy: There is an improvement in the metabolic economy in muscle cells. There is an elevation of mitochondrial density and oxidative enzymes, so that there is an increase in muscle oxidative capacity. There are some phenotypical changes creating more slow-twitch muscle, but it is unclear if they improve endurance performance or not.

pH Buffering capacity: there is an upregulation of monocarboxylate transporters and carbonic anhydrases enzymes, that handle lactate and hydrogen/bicarbonate respectively. This all produce a muscle acidosis, that has not an important enhancing effect on athletic performance, so it makes it questionable if the buffering capacity improves endurance performance or not. (5)

Immune suppression:

Due to hypoxia, there is an autonomic activation with high levels of cortisol, which leads to a particularly weak host defences and an increased probability of infection.

Athletes should be healthy when training in altitude and maintain good hygiene and nutrition. They should avoid maximum exercise on the first days of high altitude training and may need to reduce interval workout training and increase recovery time between sessions.

Altitude sessions should not be longer that 8 weeks at one time and short intervals of altitude training can prevent excessive fatigue.(5)

3.3- ALTITUDE SICKNESS PHYSIOPATHOLOGY:

Hypobaric hypoxia resulting in hypoxemia is the pathogenic stressor that leads to all forms of high-altitude illness.

High altitude illness (HAI) is a spectrum of conditions that occur at elevation as a result of hypoxia, and includes acute mountain sickness (AMS), high altitude cerebral edema (HACE) and high altitude pulmonary edema (HAPE).(3)

Acute mountain sickness (AMS):

Diagnosis of AMS is purely clinical, with non-specific symptoms, often described as an ethanol hangover. Classic symptoms develop after several hours but can be delayed till the next day.

For AMS diagnosis it is necessary a headache in addition to at least one of the following symptoms: nausea, vomiting or anorexia, general weakness or fatigue, dizziness or light-headedness of difficult sleeping.

With the hypoxia caused by ascent, there is a cardiovascular response, leading to vasodilatation on cerebral arteries, which results in increased cerebral blood flow and increased cerebral blood volume. This all causes the initial headache. It is unclear if this headache is due to the distension of pain-sensitive structures, to the activation of the trigeminal vascular system or due to the increase in intracranial pressure.(3)

AMS should be differenced from other possible pathologies: migraine, carbon monoxide poisoning, dehydration, lower respiratory tract viral infection, alcohol hangover, or physical or heat exhaustion. (3,5)

An early diagnosis and treatment is very important to avoid complications such as cerebral and pulmonary high altitude sicknesses. Once is identified, there should be avoided further ascents until symptoms have resolved. However, severe AMS may require descent, oxygen therapy or other more drastic treatments such as the use of a portable hypobaric chamber.

It is important to keep in mind that lowland fitness does not assure good altitude adaptation and cannot prevent from AMS.

The pathophysiology under AMS is not well known, it is though that the early development of AMS can be due to enhanced sympathetic activity. And also, oxidative stress of cerebrovascular endothelium can be a contributing factor as well. (5)

Cerebral high altitude sickness and High altitude cerebral edema (HACE)

After this initial headache present in AMS, blood flow is restored to baseline, with the eventual resolution of illness spontaneously.

If the cerebral blood pressure is not restored to normality the illness progresses and intracranial pressure progressively increases, that can lead to death.

Both AMS and HACE share the initiation, being HACE the extreme end result. It is unclear how AMS progresses to HACE, but it is though that there is a disruption in the blood-brain

barrier from mechanical to biochemical insults, cytotoxicity due to intracellular edema, and perhaps obstruction of the venous outflow.

Classic findings of HACE include altered mental status and ataxia. Early symptoms are drowsiness and subtle psychological and behavioural changes, including apathy and social withdrawal.

Diagnosis of HACE is based on the setting, symptoms and findings. Other pathologies that can be mistaken with HACE are: hypoglycaemia, hyponatremia, hypothermia, CNS infection, postictal state, psychosis, stroke, CNS space-occupying lesion, intracranial haemorrhage, carbon monoxide poisoning, and others such as drugs, alcohol or toxins. To exclude the diagnosis of these pathologies there are imaging studies and laboratory analysis, such as electrolytes test, complete blood count, glucose, ethanol level, carboxyhaemoglobin level and toxicology screen.(3)

Pulmonary high altitude illness and high altitude pulmonary edema (HAPE)

HAPE is an accumulation of edema fluid in the lung due to a leak in the pulmonary blood-gas barrier. The classic HAPE victim is a young, healthy person, usually male, who is fit enough to ascent rapidly to high altitude but doesn't acclimatize at the same pace.

With hypoxia there is a pulmonary vasoconstriction, when this reduction in arteries diameter is uneven, then HAPE occurs. The capillary beds that are not protected by the vasoconstriction have high microvascular pressure, which leads to a leak of fluids.

Other factors are as well, inadequate ventilatory response, increased sympathetic tone, inadequate production of endothelial nitric oxide and impaired clearance of alveolar fluid.

Symptoms are usually developed on the second night at high altitude. Without intervention, symptoms quickly progress from dyspnea with exertion to dyspnea at rest. Fever is common but is not a diagnostic factor. Oxygen saturation is often 10-20 points lower than healthy individuals.

As HAPE develops there is a worsening tachycardia, tachypnea, lassitude, productive cough and cyanosis. Eventually it progresses to altered mental state and coma, which can be the result of profound hypoxemia or even of HACE.

It should be differentiated from other similar pathologies such as asthma, bronchitis, heart failure, mucus plugging, myocardial infarction, pneumonia and pulmonary embolus. (3)

3.4- ALTITUDE EFFECTS ON PRE-EXISTING PATHOLOGIES

Pre-existing pathologies can carry problems for patients when they try to go on altitude, some of them are life-threatening and altitude should be avoided at all costs and some of them just need to be controlled and supervised.

Cardiovascular problems:

High blood pressure (HBP): It is common for lowland visitors with a history of HBP to experience temporarily high blood pressure even with good medical control at sea level. This is explained due to the higher levels of adrenaline or cortisol hormones released by hypoxic conditions.

Generally, it is not needed to change blood pressure medication dosage. Usually, the initial HBP returns to baseline after 1-2 weeks at altitude.

Heart disease (coronary artery disease): Cold in combination with hypoxia and exertion may produce even more strain on the heart.

Patients with coronary disease will likely do well at moderate altitude following some instructions such as: be used to exercise at low altitude, reduce exercise at high altitude specially the first days, stay on regular medication, bring a copy of a recent electrocardiogram, avoid coldness and spend 1-2 extra days acclimatizing to avoid altitude illness.

Arrhythmias: Many patients with irregular heart rhythms such as supraventricular tachycardia (SVT) or atrial fibrillation travel to high altitude locations safely. Although, it is unknown if these conditions are aggravated by high altitude, arrhythmias should be controlled at sea level before travelling to high altitude locations and keep doctors informed of these travelling plans.

Congenital heart problems: such as ventricular septal defect (VSD), atrial septal defect (ASD), patent ductus arteriosus (PDA) or tetralogy of Fallot partially corrected. These conditions may increase symptoms at altitude and predispose to HAPE.

A right to left shunting is an increase in lung's blood pressure which pushes blood flow of the heart through holes. It potentially contributes to altitude symptoms as there is less blood oxygenation. These patients should take cautions when considering high altitude exposure.

Heart failure: At altitude, there is fluid retention with or without AMS. These heart failure patients have increased sensitivity to fluid retention, so altitude can worsen their heart condition.

These patients can safely travel to high altitude carefully with some recommendations like: regular medical tests, control weigh daily, continue taking medications regularly and consider taking prophylaxis to speed up acclimation.

Pulmonary hypertension: patients with pulmonary hypertension have higher risk of developing HAPE and need to consider this risk before travelling to altitude. These patients should take supplemental oxygen and Nifedipine as a prophylactic. (6–8)

Pulmonary diseases:

Asthma: contrary to some opinions, there is a better control of asthma in long-term visitors at high altitude than at lowland environment. However, the outcome of short-term visitors is not as clear as long-term visitors suggested. In short trips to altitude, it has been reported a 20% worsened control of asthma that included some asthma attacks in these patients.

The reason of these outcomes can suggest a complex interplay of several factors that affect asthma control, including less pollution, lower allergen burden (no dust mites live at high altitude), lower humidity, cold air, hypoxia and air density. These factors suggest that some types of asthma, especially the allergic type can do better at altitude than at sea level.

Medications should not be suspended and patients should carry a relief inhaler just as they would do at sea level.

Emphysema: these patients have difficulties transporting oxygen from their lungs to their blood stream, so at high altitude, they usually perform worse. And there are studies showing higher death rates in people living at high altitudes with emphysema than those living at low altitude.

Those patients with emphysema that want to travel to a high altitude should discuss with their doctor to optimize their condition and take additional oxygen.

Cystic fibrosis: These patients should generally avoid high altitudes. Some of them may be able to visit moderate altitude with supplemental oxygen, chest physiotherapy, mucolytics and aggressive care with other medications such as antibiotics. (6–8)

Neurologic conditions

Migraine: A recent study shows that low oxygen levels can trigger migraines. These patients do not have higher risk of developing altitude sickness. However, when a migraine appears at high altitude it is difficult to distinguish it from an altitude headache, although migraine has an aura and is unilateral.

Patients should take their regular medications and if it is not effective use oxygen supplementation with other treatments for AMS.

Stroke/Transient ischemic attack (TIA): there is no evidence that suggest that the risk of stroke is increased, but occasionally, stroke-like symptoms such as weakness on one side of the body or partial symptoms have been reported in young healthy persons at very high altitude. This symptoms resolve with oxygen or returning to lower altitude.

Brain tumors: tumors or cysts in the brain can produce more symptoms at altitude such as headaches.

Seizures: if this pathology is controlled it is considered safe to travel to high altitude. However, it may unmask a seizure disorder in apparently healthy individuals, due to a combination of stress of altitude, cold, overexertion, alcohol and lack of sleep. (6–8)

Other

Anemia: courses with lower haemoglobin levels, which reduces oxygen transportation capacity, affecting acclimation.

If there is a history of anemia, before travelling to high altitude, should diagnose the aetiology, check haemoglobin and red blood cells levels and take additional iron supplements.

Blood clotting disorders: there is no evidence that shows that there is an increased risk of blood clots in lungs (pulmonary embolus) or legs (deep venous thrombosis).

Carbon monoxide: CO poisoning at high altitude is way more serious due to the lower oxygen levels. A CO detector can be life-saving.

Carotid surgery: It is not recommended travelling to high altitude with carotid artery surgery; these patients should be less able to acclimatize because of a less sensitive oxygen variation measurement that starts the compensatory effects of high altitude. If it is necessary, supplemental oxygen can be administered and tight control on the hypoxic ventilatory response.

Delayed wound healing: Increased stress hormones and lower oxygen delivery to the tissues make the wounds and cuts take longer to heal and get infected more easily.

Visual problems: they include retinal haemorrhages, increased cerebral edema, brain swelling, increased cerebral pressure, snow blindness and corneal edema.

Immunosuppression: as hypoxia induces an autonomic response, stress hormones lead to a weak immune system. It is important to maintain proper hygiene, hand washing to avoid infections.

Obesity: there is a slight increased risk of altitude sickness, probably caused by lower levels of oxygen due to the increased difficulty of passing into the lungs because of the weight compressing their chests. Travelling to high altitudes is not recommended for these patients, however if it is necessary, supplemental oxygen for day and night time should be used.

Sickle cell disease: Patients with this disease are not recommended to travel to high altitude, due to the risk of splenic infarction due to obstructing cells. (6–8)

Sleep disturbances (Sleep apnea): such as central sleep apnea (CSA) and obstructive sleep apnea (OSA) can lower oxygen levels during sleep.

Living at high altitude, periods of central sleep apnea occurs almost universally, and in general, its severity increases with altitude. Visitors who abruptly move to high altitude report sleep disturbances, including insomnia and restlessness, translating in daytime fatigue and cognitive impairment. This all can be attributed to sleep apnea, which fragments sleeps because of arousals and the effects of hypoxia, hypocapnia induced by hypoxia and changes in cerebral blood flow caused by altitude.

For the treatment, it is recommended de use of oxygen at night with a continuous positive airway pressure (CPAP) machine and to consider adjustments in set pressure. Also, acetazolamide is a good prophylactic treatment. There should be a daily check in patients with daytime hypoxaemia for the presence of pulmonary hypertension and treat with Nifedipine as a prophylactic. (8,9)

3.5- PREGNANCY AND POST-NATAL PERIOD

Highland women are known for giving birth to heavier-weight infants and having higher utero-placental blood flow than lowland women. However, in lowland adapted women there is a reduction in birth weight when they are in high altitude environments.

At sea level, there is an increased oxygen intake because of higher respiratory rate, blood volume and cardiac output increase, although the overall oxygen carrying capacity decreases due to hemodilution.

Maternal acclimation to high altitude is targeted towards increasing blood flow, nutrient and oxygen transport to the uterus. As they start off with 50% lower arterial PO_2 and PCO_2 values, and the increase in PO_2 is not as marked as at sea level.

This lower PO_2 is translated into hypoxia, which induces the erythropoietin gene and elevates haemoglobin levels, increases oxygen transport capacity and overall oxygen content; however it also increases blood viscosity.

At sea level, increased blood viscosity is associated with complications such as intrauterine growth restriction, pre-eclampsia and peripheral resistance. So it can be concluded that high blood viscosity is a risk factor for optimal perfusion of the placenta. (1,10)

Foetal hypoxia:

It is obvious to think that fetus at high altitude are more hypoxic than at sea level. Although there is no arterial redistribution, blood velocities are lower at high altitude than at sea level, which is particularly evident in the umbilical artery flow. This effect can be explained due to the higher fetal blood viscosity due to the higher haematocrit.

In short-term acclimatized populations such as residents in Colorado, there is an increased prevalence of intrauterine growth restriction and hypertensive disorders during pregnancy. However, mortality rates in low birth-weight neonatal and babies are lower in high altitude populations than low-altitude populations in studies taken place in Peru and Mexico.(10)

The quality of the intrauterine environment can lead to adult life pathologies, so chronic hypoxia, by different reasons, can be a possible risk factor for other pathologies.(11)

Placenta:

As a result of chronic hypoxia, there is neovascularization, with an increase in the number of tissue capillaries and increased branches of the capillaries in placental villi.

There is a reduction in uterine artery volume flow measured by Doppler ultrasound in the third trimester of pregnancy.(10)

Growth factors:

In the second half of pregnancy at high altitude, the placental hypoxia causes an increase in maternal insulin-like growth factor binding protein-1 (IGFBP-1) concentrations, due to the increase in maternal and fetal demands. This IGFBP-1 restricts the IGF-mediated fetal growth as an adaptive mechanism to prevent worsening of the fetoplacental hypoxia. (10)

Foetal nutrition:

The most important maternal fuel for the growth of the fetus is glucose. Glucose crosses de placenta by facilitated diffusion. In fetal growth restriction, maternal plasma glucose is decreased.

At high altitude in non-pregnant native women, fasting plasma glucose is decreased, and even lower in pregnant women. This is associated with lower fasting concentrations of insulin and higher insulin sensitivity, whereas C-peptide and β-cell functions remain the same.

Pregnancy has greater energy requirements and the increase in metabolic rates at high altitude makes it more important to find an efficient source of energy. As the carbohydrate oxidation provides the highest ATP yield per mol oxygen, it is the preferred metabolic pathway at high altitude. The increased glucose uptake is due to an increase in glucose utilization and not due to higher insulin action.

Therefore, the low maternal fasting plasma glucose associated with high peripheral insulin sensitivity at high altitude may partly explain the lower birth weights at high altitude. (10)

3.6- ALTITUDE SICKNESS TREATMENT

Acute mountain sickness usually is self-limited, but high altitude pulmonary edema and high altitude cerebral edema are real emergencies that need stabilization and intervention.

There are three guiding principles for the management of all altitude sickness:

1. Never proceed to a higher sleeping altitude with symptoms of AMS
2. Patients should descent if symptoms do not improve after pharmacologic or not pharmacologic treatment.
3. In the presence of confusion, ataxia or dyspnea at rest with relative hypoxemia the management should be descent and/or treatment immediately

Descent is the definitive treatment for all forms of altitude sickness. However descent is not always possible. (3)

Prevention

There are different strategies to prevent AMS and its complications, HACE and HAPE

Pharmacological:

***Acetazolamide**:* inhibitor of the enzyme carbonic anhydrase, it reduces renal reabsorption of bicarbonate, increasing bicarbonate elimination through urine and resulting in metabolic acidosis. This metabolic acidosis neutralizes the alkalosis produced by high respiratory rate, this way respiratory rate is maintained, so it elevates O_2 diffusion in the lungs, improving this way acclimation. However, it has several side effects such as headache, nausea and also Stevens-Johnson syndrome.

***Benzolamide**:* is another carbonic anhydrase inhibitor, but more hydrophilic, so it has less central nervous system (CNS) side effects.

***Budesonide**:* is a corticosteroid hormone analog that reduces the immune system response with anti-inflammatory actions.

***Dexamethasone**:* Anti-inflammatory and immunosuppressor due to the inhibition of inflammatory cells and suppression of expression of inflammatory mediators. It is 30 times stronger than cortisol. It has numerous side effects, so that's why it is reserved for intolerance to acetazolamide or treatment of moderate or severe forms of AMS.

It can be administrated orally, intramuscularly or intravenously, depending on the available resources and physiological conditions, such as vomiting.

***Ginkgo biloba**:* there are variable results in different studies; lack of consistency between commercial gingko preparations can explain this conflicting evidence. It is a good option for individuals who prefer more natural alternatives.

***Ibuprofen**:* more studies are necessary to prove that it is efficient against AMS and not just as a treatment for headache as an analgesic.

***Nifedipine**:* blocks calcium channels in vascular smooth muscle and myocardial cells, which produces a peripheral arterial vasodilatation. This vasodilatation reduces blood pressure. It is commonly used for HAPE prevention although there are not enough data.

***Salmeterol**:* is a β2-adrenergic agonist, which leads to a dilatation in the alveolar and lung space. It is used inhaled as an adjunctive treatment with other medication such as nifedipine.

***Sildenafil and Tadalafil**:* phosphodiesterase inhibitors that prevent pulmonary hypertension due to the reduction of hypoxic pulmonary vasoconstriction. Tadalafil is used more commonly than Sildenafil due to its longer half-life. They can both cause headache as a side effect.

Non pharmacological:

***Graded ascent**:* to allow time for acclimation. Above 2500m, mountaineers and trekkers should not ascent faster than 500m/day.

Preacclimation: strategies such as intermittent exposure to hypobaric hypoxia or normobaric hypoxia with a commercial tent, chamber or mask.

Remote ischemic preconditioning: is a strategy that consists on inducing discrete episodes of isquemia-reperfusion in the extremities, usually with an inflated blood pressure cuff.

***Oxygen**:* Low-flow oxygen via nasal cannula, especially during sleep relieves the physiologic stress of hypobaric hypoxia and effectively simulates sea level if below 3000m.

In table 2 we can observe the resume of high altitude sicknesses treatment.

Table 2: Pharmacological and non-pharmacological prevention of AMS, HACE and HAPE

Prevention		AMS	HACE	HAPE
Pharmacological	Acetazolamide	**Yes**	**Yes**	
	Benzolamide	**Yes**	**Yes**	
	Budesonide	**Yes**	**Yes**	
	Dexamethasone	**Yes**	**Yes**	**Yes**
	Ginkgo biloba	**Yes**	**Yes**	
	Ibuprofen	**Yes**	**Yes**	
	Nifedipine		**Yes**	**Yes**
	Salmeterol		**Yes**	**Yes**
	Sildenafil and tadalafil		**Yes**	**Yes**
Non pharmacological	Graded ascent	**Yes**		
	Preacclimation			
	Oxygen			
	Remote ischemic preconditioning			

Symptomatic care

- *Acetaminophen, Ibuprofen, Ondansetron*

Treatment complications and pitfalls

Pharmacologic

- ***Acetazolamide**:* there should be a tolerance test before ascent, it should be avoided in individuals with previous anaphylaxis to sulpha-antibiotics,. Most commonly side effects include increased urination, paraesthesia, fatigue and gastrointestinal upset.
- *Dexamethasone:* its use should be weighed against the risk of side effects such as adrenal suppression and steroid psychosis.
- *Ibuprofen:* further study is needed.

Non pharmacologic

- HACE patients who progress to coma need an advanced airway and bladder drainage. Blood pressure monitorization is needed to avoid cerebral isquemia caused by cerebral hypotension
- Avoid rapid depressurization of portable hyperbaric chambers, which can result in middle ear squeeze
- HAPE patients usually need intravenous fluid rehydration. When there is infection too, they should be treated both.

Treatment

Table 3: Pharmacological and non-pharmacological treatment of AMS, HACE and HAPE

Treatment		AMS	HACE	HAPE
Pharmacological	Acetazolamide	**Yes**		
	Dexomethasone	**Yes**	**Yes**	
	Nifedipine			**Yes**
	Sildenafil, Tadalafil			**Yes**
Non-pharmacological	Oxygen	**Yes**	**Yes**	**Yes**
	Descent	**Yes**	**Yes**	**Yes**
	Body position		**Yes**	
	Portable hyperbaric chambers		**Yes**	**Yes**
	Environmental factors			**Yes**

Conclusions on treatment

Acetazolamide is the best choice for AMS prevention

Best treatment for all AMS is descent and/or oxygen

Dexamethasone is excellent for treating AMS and HACE

3.7- ALTITUDE AS A TREATMENT

Exposure to high altitude activates several complex and adaptive mechanisms aiming to protect human homeostasis from extreme environmental conditions, such as hypoxia and low temperatures. (12)

Epidemiological and experimental data suggest that chronic exposure to high altitude reduces cancer mortality and lowers prevalence of metabolic disorders like diabetes and obesity. Owing to modifications of a broad spectrum of physiological, metabolic and cellular programs because of acclimation to altitude, with a generally beneficial outcome for humans (13)

Obesity: is defined as an abnormal or excessive fat accumulation that presents a risk to health. Obesity and overweight are major risk factors for a number of chronic diseases, including diabetes, cardiovascular diseases and cancer.

As many people living in high-altitude regions have lower percentage of body fat and fewer obesity-related illnesses, some researchers have been applying hypoxic conditions for the treatment of obesity to test its effects.

Exposure and exercise under hypoxic conditions in conjunction with decreased appetite, improved metabolism, enhanced utilization of fatty acids, and body weight loss are considered an interesting and important therapeutic modality for obesity treatment. (14)

Appetite alterations by hypoxic conditions: natural high-altitude environment cause “altitude anorexia” which is a reduction in appetite and reduced dietary intake, this can be a consequence of acute mountain sickness (AMS) or due to hypoxemia per se.

Although the mechanism of appetite suppression via hypoxic condition has not yet been elucidated, exposure and exercise training in the hypoxic conditions seem to induce reduced appetite and energy intake via a decrease in ghrelin and increase in leptin, PYY, PP and norepirephrine hormones. (14)

Therapeutic effects of hypoxic exposure on obesity: There are very few studies on the therapeutic effects of exposure to hypoxic conditions on obese subjects. However, it has been shown that there is a reduction in body weight due to an increase basal metabolic rate, insulin sensitivity and leptin levels.

There is enhanced insulin sensitivity in tissues at rest and during exercise, so there is a decrease in blood glucose and higher glucose turnover, which leads to a greater glucose utilization. (14)

Therapeutic effects of exercise training in hypoxic condition on obesity: several studies conclude that aerobic training in hypoxic conditions compared to same exercise conditions in normoxic training, can cause changes in:

- Body composition by decreasing body fat
- Enhancing metabolic functions such as improving lipid levels
- Cardiovascular function such as lowering blood pressure, reducing arterial stiffness, increasing high-density lipoprotein (HDL-cholesterol), compared to normoxic training.

The results of hypoxic training can vary depending on hypoxic exposure and exercise condition (type, intensity, duration and time).

Intermittent hypoxic training (IHT) is the most effective and most used non-pharmacological therapy for obesity and health promotion. It consists of exercise training in an intermittent hypoxic environment, usually, 3-5 sessions of less than 3 hours per week over a 4 to 12 week period.

Also, some studies expose that exercise training in hypoxic conditions can reduce absolute exercise load and mechanical stress can be particularly beneficial for obese patients with orthopaedic comorbidities. (14)

Diabetes:

There has been documented an inverse relationship between altitude, diabetes and obesity. This is the result of genetic and physiological adaptations principally to hypoxia that favourably affect glucose metabolism, however, the contribution to financial, dietary and other life-style parameters may also be important.

In a short term exposure, there is a hyperglycaemia due to the activation of the sympathetic system. Whereas long term exposure results in lower plasma glucose concentrations, mediated by improved insulin sensitivity and augmented peripheral glucose disposal. (12)

Although regular physical activity is encouraged for individuals with diabetes, exercise at high altitude increases risk for a number of potential complications, such as anorexia, increased energy expenditure, changes in metabolic demands, insulin sensitivity, extreme weather conditions; all summing up to a deterioration of metabolic control, especially if mountain sickness occurs. (12,15)

Frequent blood glucose monitoring is imperative, and results must be interpreted with caution because capillary blood glucometer results may be less accurate at high elevations and low temperatures. (15)

At high altitude, higher haemoglobin levels and differences in glucose metabolism may influence the diagnostic performance of HbA1c for testing for diabetes. In table 4 it can be seen the differences between haemoglobin, HbA1c and fasting plasma glucose (FPG) at sea level and high altitude.

Table 4: Results of haemoglobin, HbA1c and FPG measurements at sea level and high-altitude.

	Sea level	High-altitude
Haemoglobin	13.5 g/dL	16.7 g/dL
HbA1c	41 mmol/mol	40 mmol/mol
Fasting plasma glucose (FPG)	5.3 mmol/L	4.9 mmol/L

The relationship between HbA1c and fasting plasma glucose (FPG) and sensitivity of HbA1c varies between sea level and high altitude. At sea level, the relation between HbA1c and FPG is quadratic and at high altitude it is linear. The sensitivity of HbA1c is 87.3% at sea level and 40.9% at high altitude, suggesting a limitation in the performance of HbA1c to diagnose diabetes in altitude.

In conclusion, as HbA1c diagnostic performance is limited at high altitude, consequently, FPG and the oral glucose tolerance test should be used as diagnostic criteria for diabetes at high altitude.(16)

It is important to undergo pre-travel screening to rule out possible contraindications owing to chronic diabetes complications and make well-informed decisions about risks. Despite the risks, healthy, physically fit and well-prepared individuals with type 1 or type 2 diabetes who are capable of advanced self-management can be encouraged to participate in these activities and attain their summit goals. Moreover, trekking at high altitude can serve as an effective way to engage physical activity and to increase confident with fundamental diabetes self-management skills. (15)

Cancer mortality reduction:

We understand tumor formation as a competition between healthy and cancer cells with improved fitness (higher competitiveness) of healthy cells at high altitude.

Despite the permanent stress of hypoxic exposure, humans living in high altitude areas have reduced cancer mortality over a broad spectrum of cancer types. In fact, the majority of the physiological adaptive processes at high altitude might be driving force for reduced cancer mortality.

Reactive oxygen species and their detoxification as well as the hypoxia-inducible factors are especially promising targets and may be related to why cancer mortality is reduced at high altitude. There are two other aspects with a proven impact on tumorigenesis, the immune system and tumour surveillance as well as HA-induced metabolic changes. (17)

A complexity of multiple, potentially tumor-suppressive pathways at high altitude impede the understanding of mechanisms leading to reduced cancer mortality. High altitude activates multiple adaptive mechanisms (oxygen independent and dependent) sharing common pathways as well as activating counteracting pathways. Many adaptive processes at high altitude are tightly interconnected and thus cannot be ruled out that the entirety or at least some of the high-altitude related alterations act in concert to reduce cancer mortality (13,17)

There are some HA-related changes in glucose, lipid and iron metabolism that may have an impact on tumorigenesis. Additionally there are two other parameters with a strong impact on tumorigenesis, namely drug metabolism and physical activity, to support their potential contribution to HA-dependent reduced cancer mortality. Future studies are needed to resolve why cancer mortality is reduced at HA and how this knowledge might be used to prevent and treat cancer patients. (13)

There are more animal and clinical studies needed to clearly explain why cancer mortality is reduced at high altitude and to decide whether HA or hypoxia-based therapeutic approaches could be implemented for cancer treatment. (17)

Cardiovascular disease:

Whether this hypoxic chronic exposure is beneficial or detrimental to the cardiovascular system is uncertain. On one hand, multiple studies have suggested a protective effect of living at moderate and high altitudes for cardiovascular risk factors and cardiovascular disease (CVD) events. Conversely, residence at high altitude compensates developing diseases such as chronic mountain sickness and high-altitude pulmonary hypertension and worsens outcomes for diseases such as chronic obstructive pulmonary disease. Interestingly, recently published data show a potential role for severe hypoxia as a unique and unexpected therapy of myocardial infarction. (18)

4. Conclusions

The acclimation carries different changes to guarantee O_2 and nutrient arrival to all vital cells. They include increased ventilation, increased cardiac output and blood pressure, renal diuresis, increased sympathetic tone and increased red cell mass…etc.

Altitude has been used as a training method due to the increase in O_2 carrying capacity because of an increase in haemoglobin and red blood cells. However there are other detraining effects which include ventilatory mismatching, reduced maximal cardiac output, muscular atrophy and immune suppression.

When the acclimation is not correct, high altitude illnesses occur, they include acute mountain sickness, high altitude cerebral edema and high altitude pulmonary edema. They should be differenced from other similar pathologies, controlled and treated in some cases.

Some pathologies carry problems for patients when they travel to high altitudes. These patients should keep their doctors informed to control and supervise their health status.

Highland pregnant women tend to have heavier babies, however, lowland pregnant women who travel to high altitude develop small-weight babies. This is due to hypoxia, which limits foetal growth in order to keep a correct development. The placenta gets more vascularization to increase oxygen and nutrient arrival to the baby.

There are some treatments and prevention for altitude sicknesses. Acetazolamide is the best choice for AMS prevention and the best treatment is descent and/or oxygen. It is important not to gain more altitude with symptoms of AMS, if symptoms don’t improve patients should descent and if there are some risk symptoms descent and/or treat immediately.

A new line of investigation has been opened to prove the beneficial effect of hypoxia on some pathologies such as obesity, diabetes and mortality of cancer. However this field needs further studies to completely understand the underlying mechanisms and possible adaptations.

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