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Effects of High Altitude Related Oxidative Stress on Intraocular Pressure and Central Corneal Thickness – A Research Model for the Etiology of Glaucoma

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1. Introduction

Glaucoma is a progressive optic neuropathy resulting in axonal death and is a leading cause of blindness. Several factors play a role in this progressive cell loss.

Hypoxia and oxidative stress are among the risk factors for glaucomatous changes. Tissue stress is also very crucial in glaucoma. This fact is evidenced by stress proteins and heat shock proteins in glaucoma models (Tezel & Wax, 2007). A relatively undiscovered field, namely high altitude related oxidative stress has recently gained attention in glaucoma research.

High altitude, which is usually regarded as an altitude over 2,400m, has various effects on the human body. Mountaineers, outdoor sports enthusiasts, military as well as other personnel working at high altitudes are at risk and the detrimental effects caused by high altitude hypoxia can reduce their performance.

At high altitudes, atmospheric pressure gradually falls and the oxygen partial pressure decreases. The resultant hypobaric-hypoxia with an oxygen partial pressure < 60mmHg is the culprit for detrimental effects of high altitude. High altitude may lead to a constellation of symptoms including acute mountain sickness, or in extreme cases, high altitude pulmonary edema or high altitude cerebral edema. At high altitude, hypoxia, ultraviolet rays, cold and increased energy need are amongst other contributing factors.

The human eye is also affected by hypoxia at high altitude and extensive research is being carried out by various teams all around the world. Erciyes University Medical Faculty is located at the skirts of Erciyes Mountain (3,917m), Kayseri, Turkey. Inspired by the Turkish ophthalmic surgeon, Dr. Bozkurt Ergör (1927-2009), who had practised ophthalmology in Kayseri, served as the president of Turkish Mountaineering Federation and climbed to numerous peaks all over Turkey and the world, we carried research on high altitude ophthalmology at Erciyes University Medical Faculty Department of Ophthalmology (Ergör, 2011; Karakucuk et al., 2000, 2004, 2010). (Figures 1 & 2).

In this chapter, effects of high altitude on central corneal thickness and intraocular pressure will be reviewed and the topic discussed in the light of the relationship of these parameters with high altitude related oxidative stress.

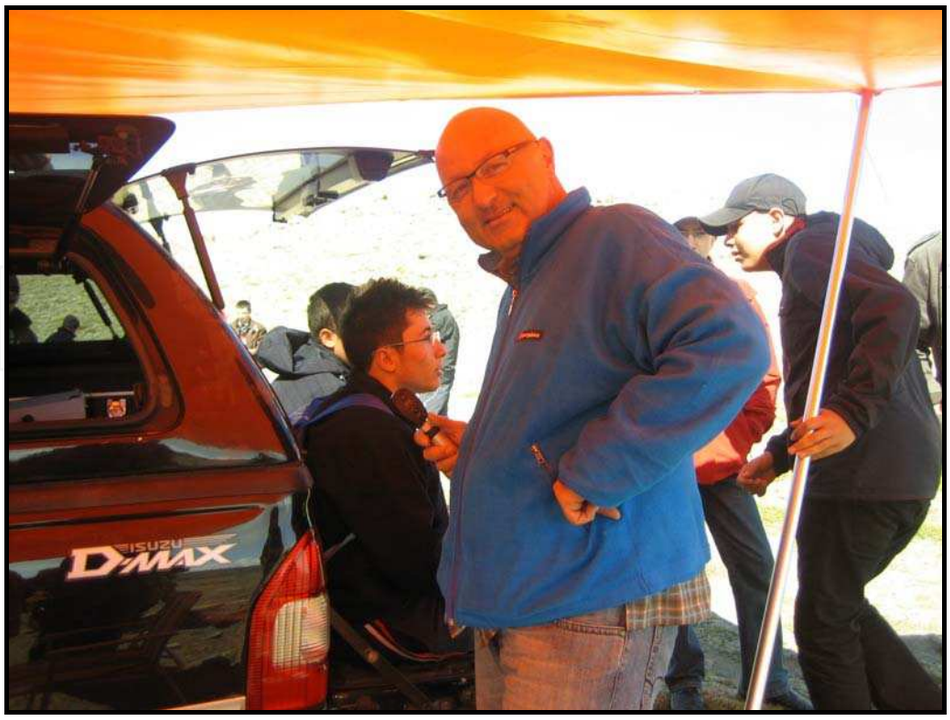

Fig. 1. Ophthalmoscopic examination is being made by the author at 2800m, (Mt. Erciyes, Kayseri, Turkey, Heine beta 200- direct ophthalmoscope). (Karakucuk et al., 2010)

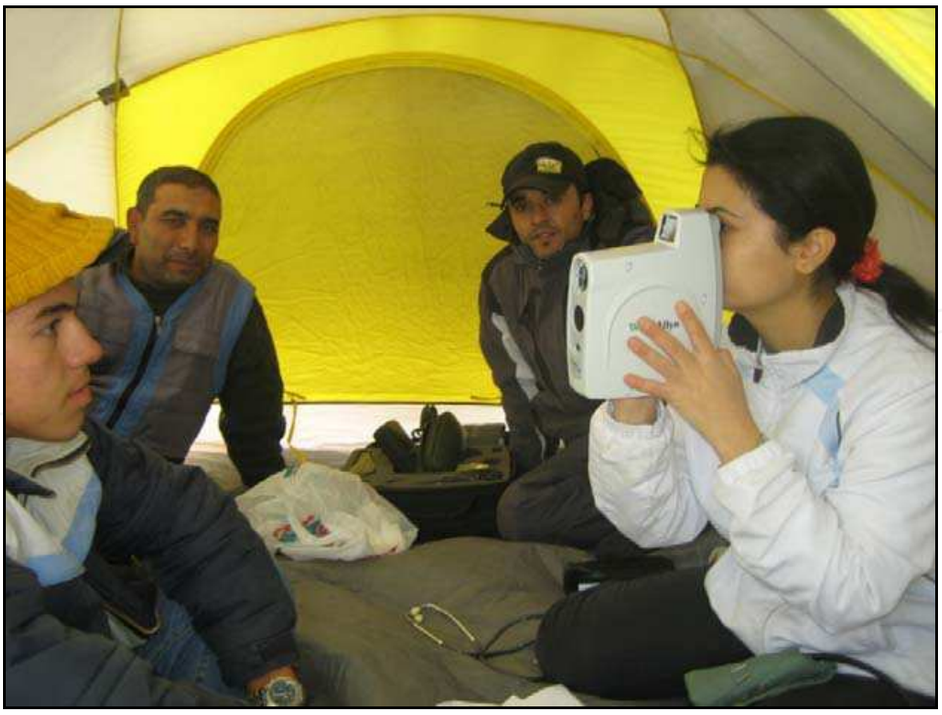

Fig. 2. Refractive changes are being evaluated inside the tent at 2800m (Mt. Erciyes, Kayseri, Turkey; Welch Allyn suresight). (Karakucuk et al., 2010)

The topic will be discussed as follows:

1. High altitude related oxidative stress and antioxidant defense mechanisms of the human body
2. Possible relationship of high altitude hypoxia with the etiopathogenesis of glaucoma
   i. Intraocular pressure changes at high altitude
   ii. Central corneal thickness changes at high altitude
   iii. Possible relationship of high altitude with pseudoexfoliation, cone cell sensitivity and visual fields
   iv. Future issues: Space travel and intraocular pressure

2. High altitude related oxidative stress and antioxidant defense mechanisms of human body

The capability of the defense network of the human body may be challenged by environmental conditions. High altitude related hypoxia is one of these great challenges. If the sea level O2 concentration is accepted as 100%, this ratio gradually decreases with increasing altitude. For example, in La Paz, Bolivia (3,660m), air pressure is 2/3 of the sea level, at Everest base camp, (around 6,000 m), air pressure is half the sea level and at the peak of Mt. Everest, the highest terrestial elevation (8,848m), air pressure is 1/3 of the sea level. In military or civil aviation, the performance of flight personnel heavily relies on the adaptive capacity of their body systems at high altitude. High altitude is usually regarded as an altitude over 2,400 m; cabin pressure during flight is usually kept around this 'safe' altitude. However, unpressurized flights, such as in small planes, military carriage aircrafts, or helicopters usually surpass this altitude and therefore occasionally detrimental effects can be seen on the personnel. There are several guidelines in worldwide aviation with regard to this matter; for example, according to the Turkish Airforce Commandership, only up to 2 hours of flying is allowed at 12,000 ft (3,657 m) when the cabin pressures are maintained at levels equivalent to the external atmospheric pressure (Bayer et al., 2004).

Despite well-defined regulations in aviation, hypoxia related incidents have been documented. A recent report stated that 3 fatal hypoxia incidents in US airforce have been observed during flights between 2001-2011 (Shender et al., 2011). In another study, hypoxic syncope in a helicopter pilot was reported at 18,000 feet (3,600 m). Although autonomic dysfunction did not cause any symptoms for this pilot during daily living, conduction block and vasovagal syncope developed at this high altitude (Chiang et al., 2011).

Temme et al., based on results from instructor pilots in a flight simulator, proposed that flight performance can be affected by hypoxia (Temme et al., 2010). This may necessitate oxygen monitoring via several methods such as pulse oximeter or near infrared spectroscopy during flight (O'Connor et al., 2004; Terry et al., 2004; Dillard & Bansal 2007). There are a number of guidelines for the pre-flight assessment of patients with pulmonary and/or cardiac diseases. However, these data are based on small studies. Therefore, Mortazavi et al. suggested that oxygen supplementation during air travel may be needed for individuals at risk (Mortazavi et al., 2003).

In light of the aforementioned facts, it is possible to say that the human body can be severely affected during flight even at moderate altitudes. In an attempt to reveal the effects of high altitude on the immune system, circulating cytokine levels were investigated by Burian et al. They searched for the changes in the levels of interleukin-1beta, interferon-gamma and tumor necrosing factor-alpha during flight, found that at a moderate altitude such as that felt inside the cabin, there is a subtle response compared to extreme altitudes (Burian et al., 2011).

Oxidative damage has also been the focus of interest at high altitude since high altitude also affects enzymatic as well as non-enzymatic systems in the body. (Chao et al., 1999; Imai et al., 1995). Reactive oxygen species are formed during stress conditions in the human body. When an extremely low availability of oxygen occurs, such as during ischemia or exposure to very low oxygen pressure, (for example at an altitude over 6,000 m), reactive oxygen species can exceed the capability of the defense mechanism, causing oxidative damage to lipids, proteins and to DNA. During heavy physical exercise such as mountaineering, different organ damage can occur as a result of oxidative challenge. High altitude exposure leads to altered activity of reactive oxygen species, which in turn leads to oxidative damage (Dosek et al., 2007).

When the human body is exposed to very low oxygen partial pressure (6,000m), cells tend to generate ATP. During this process, AMP is also generated but this AMP cannot be recycled; it is instead converted to hypoxanthine and via this pathway, xanthine dehydrogenase is converted to xanthine oxidase. Xanthine oxidase is a very potent reactive oxygen species generator and likely to occur during intermittent high altitude exposure. Reactive oxygen species increase in acute hypoxia but the balance is restored during the acclimatization process. This phenomenon may have relevance to the microcirculatory alterations associated with hypoxic exposure, including acute mountain sickness and high altitude pulmonary and cerebral edema. Despite our limited knowledge on acute mountain sickness, current information suggests that reactive oxygen species are active players in the process, however it is still not clear whether they are causative or associative agents. At high altitude, UV radiation is significantly increased and this also contributes to the overproduction of reactive oxygen species (Baconyi and Radák, 2004; Dosek et al., 2007).

It was found that 6 months of intermittent 4000 m exposure decreased mitochondrial superoxide dismutase in rat skeletal muscles (Radak et al., 1994). Nakanishi et al. reported that at 5,500m simulated altitude, superoxide dismutase immunoreactivity was increased in serum, whereas it was decreased in liver. This may suggest that liver may be sensitive to high altitude related oxidative stress (Nakanishi et al., 1995).

Highlanders may have lower gluthatione peroxidase levels than lowlanders; gluthatione peroxidase controls the thiol system. At high altitude, the capacity of enzymatic/non-enzymatic antioxidation systems is decreased. Ilavazhagan reported that Vitamin E supplementation reduced high altitude induced increase in lipid peroxidation during an experimental setting at 7,576 m (Ilavazhagan, 2001). Reactive oxygen species are not easy to measure because of reactivity, however, it is possible to measure them by several methods (Tarpey et al., 2004). For example, in a detailed experimental study by Maiti et al., rats were subjected to either 3 or 7 days of exposure to 6.100 m and increased reactive oxygen species and lipid peroxidation levels in brain tissue were detected (Maiti et al., 2006). Free radicals (mainly H_2O_2) were measured spectrofluorimetrically with the supernatant using 20,70-dichlorofluorescein-diacetate according to the modified method of Robinson et al. (Robinson et al., 1998); nitric oxide was measured by the accumulation of nitrites (NO2_) in supernatant from different brain regions, a method described elsewhere (Barrias et al., 2002; Mendoza et al., 1998); lipid peroxides are measured by quantitating the amount of malondialdehyde formed by 2-thiobarbituric acid reaction as thiobarbituric acid reactive substances using the method of Utley et al. (1967). It was also found that the magnitude of increase in oxidative stress was more in 7 day-exposure group as compared to 3 day-exposure group. (Maiti et al., 2006; Radák et al., 1994).

High altitude and strenuous exercise alone can result in oxidative challenge; the combined effect leads to aggravated oxidative damage. Increased physical activity at HA increases the

vulnerability of the body to oxidation (Bakonyi & Radák 2004). Møller exposed 12 healthy subjects to 4.559m; this caused significantly increased DNA strand breaks in urine. Another important factor is cold weather, which is frequently observed at high altitudes and this also increases the damage. For example, when people were simultaneously exposed to cold, the level of urinary lipid peroxides and DNA damage increased significantly (Møller et al., 2001).

In a study by Araneda, mountain bikers performing maximal cycloergometric exercise were first tested at 670m, then 2,160 m; soldiers climbing at 6,125 m in the Andes mountains of Northern Chile were also tested during the same study. In both groups, exhaled breath contained significantly more H_2O_2 levels and lipid peroxides compared to low altitudes. The pathology at the tissue level may be caused by localized free radical-mediated vascular damage, membrane permeability changes and the generated inflammation (Araneda et al., 2005).

On the other hand, at lower altitudes, for example at 1,860m, oxidative stress markers did not change in cyclists (Wilber et al., 2004). Lipid peroxides were found as elevated at high altitude; Joanny et al. reported that at 6,000m, lipid peroxides increased by 23% and at 8,848 m, by 79%. (Joanny et al., 2001). In experimental animal settings, it was found that a minimum of 3 months' exposure to high altitude was necessary to observe increased levels of lipid peroxides. At 13 months, the balance was found as normalized. (Dosek et al., 2007; Vij et al., 2005). Sinha et al. investigated antioxidant and oxidative stress responses of temporary residents at high altitude in different climatic temperatures. They found that oxidative stress markers exhibited higher levels in those with lower climatic temperature than the higher temperatures. They also concluded that chronic exposure to hypoxia in moderate climatic temperature has a potential preconditioning effect on the antioxidant system, but exposure to both cold and hypoxia causes greater oxidative stress due to altered metabolic rate. (Sinha et al., 2009).

Hagobian et al. researched the cytokine response at high altitude (4,300 m) and also investigated the effects of exercise and antioxidants at this altitude. They also aimed at detecting any alterations in plasma cytokine levels, such as interleukin 6 and C-reactive protein after antioxidant supplement, which composed of beta-carotene, alpha tocopherol, ascorbic acid, selenium, zinc, for three weeks. Although there was no increase in oxidative stress markers, elevated plasma levels of interleukin 6 and C-reactive protein was not attenuated by the antioxidant supplement, suggesting that this increase was independent from the oxidative stress pathway (Hagobian et al., 2006).

Kaur et al. found that a very short exposure of rats to 8,000m increased melatonin level in blood; it is important to note that melatonin acts as antioxidant (Kaur et al., 2002). On the other hand, natriuretic peptides were tested in 10 healthy lowlanders during an acute ascent to 5,200m Atrial natriuretic peptide levels did not changed significantly. (Toshner et al., 2008).

Magalhaes et al. investigated 6 mountaineers during a 3-week study. The study was carried out between 5,250-7,161 m. In their study, total antioxidant system, sulfhydryl groups, superoxide dismutase and glutathione peroxidase were studied. They concluded that a period of severe high altitude exposure during a Himalayan expedition constituted a systemic oxidative stress even to acclimatized climbers, with deleterious consequences such as quantitative changes in erythrocyte antioxidant enzyme activity and membrane fatty-acid profile. Erythrocyte antioxidant enzyme activity is determined by measuring superoxide dismutase, glutathione peroxidase and glutathione reductase; fatty acid profile is determined by measuring monounsaturated fatty acids, polyunsaturated fatty acids, saturated fatty acids and trans fatty acids (Magalhaes et al., 2005). It is known that

Fig. 3. Blood is drawn at 2800m, Mt. Erciyes. (Karakucuk et al., 2010)

Fig. 4. Blood samples are analyzed and records made at 2800m; Mt. Erciyes. (Karakucuk et al., 2010)

although many Sherpas live at high altitudes for their entire lives, some of them surprisingly can manifest symptoms of acute mountain sickness during mountaineering at extremely high altitudes. Based on these findings, an interesting study was made by Droma et al.; they searched for the presence of hypoxia-inducible factor and von Hippel-Lindau tumor suppressor protein, which are putatively hypoxia sensors that control cellular responses to hypoxia. However, their study did not reveal such an association. Maybe another set of genes, or genetic mechanisms determines the susceptibility of individuals to high altitude (Droma et al., 2008).

Diet and oral antioxidant supplements may have a role in the body's response to high altitude. For example, Indians living at high altitude consume trichopus zeylanicus, which is an antioxidant, as a protection against the detrimental effects of high altitude (Tharakan et al., 2005). In one study, Schmidt et al. investigated the importance of antioxidant supplementation during high altitude related oxidative stress; they used a mixture of supplemented antioxidants such as Vitamin E, beta-carotene, ascorbic acid, selenium, alpha-lipolic acid, N-acetyl L-cysteine, catechin, lutein and lycopene at high altitude and reported that that this was effective (Schmidt et al., 2002). On the contrary, in some studies, antioxidant supplementation did not attenuate high altitude related oxidative stress (Subuthi et al., 2004).

Antioxidants in the human body can be measured from biological fluids which contain numerous compounds with chain breaking antioxidant activity, including urate, ascorbate, bilirubin, and thiols in the aqueous phase and alpha-tocopherol, carotenoids, and flavonoids in the lipid phase. Instead of measuring each antioxidant seperately, it is possible to measure the total antioxidant activity using the thiobarbituric acid reactive substances method described elsewhere (Koracevic et al., 2001). Total antioxidant level in normal healthy controls was reported as 2.42mmol/L in control subjects. (Olisekodiaka et al., 2009)

Since there is no single universal marker for protein oxidation, some macromolecules can be used as markers of oxidative stress; advanced oxidation protein products are among such macromolecules and can be analyzed using commercial kits with an Abbott C-16000 autoanalyzer, according to a method described elsewhere using spectrophotometry. Advanced oxidation protein products levels were expressed as micromolar chloramine-T equivalents (µmol/L) (Witko-Sarsat, et al., 1996; Baskol et al., 2008).

	1080m	2800m	p
Total oxidative system	3.32µmol H2O2 equiv/L (0.92-18.41)	7.02µmol H2O2 equiv/L, (0.49-22.07)	0.04*
Total antioxidative system	2.13µmol H2O2 equiv/L (1.65-2.90)	2.22µmol H2O2 equiv/L (1.72-2.77)	0.30
Advanced oxidative protein products	195.58µmol/L, (84.77-663.16)	220.74µmol/L, (103.81-667.35)	0.03*

Table 1. Oxidation and antioxidation parameters at normal (1,080) and high (2,800m) altitude; Mt. Erciyes. (Karakucuk et al., 2010; *statistically significant)

In one study, we measured blood levels of total antioxidant system, total oxidative system and advanced oxidative protein products as oxidative stress markers at 1,080 m and at 2,800 m in a group of 40 healthy individuals after an unacclimatized ascent to 2,800 m from 2,200 m at Erciyes Mountain. The results showed that there was a significant increase in levels of total oxidative system at 2,800m compared to 1,080 m ($p=0.04$). Advanced oxidative protein products also significantly increased at high altitude($p=0.03$). There was not a parallel increase in the total antioxidant system ($p=0.30$), suggesting that during acute unacclimatized ascent, antioxidant system cannot counterbalance the detrimental effects of the oxidant system (Karakucuk et al., 2010; Dolbun et al., 2010).

3. Possible relationship of high altitude hypoxia with the etiopathogenesis of glaucoma

Fast ascent during outdoor sports such as glacier skiing, heli-skiing, paragliding and parachuting has caused short acclimatization, making acute mountain sickness likely to occur with its consequences. This effect not only concerns skiers, skydivers, paragliders, and balloon travelers, but also participants in aviation and aerospace activities, particularly when unpressurized travel is to be made, such as helicopter or small aircraft flights. It is very important to note that results obtained in experimental settings, such as hypobaric high altitude chambers, do not always reflect geographical conditions; because in the real environment, strenuous exercise, cold and wind further complicate the issue.

3.1 Intraocular pressure changes at high altitude

Results with regard to the intraocular pressure (IOP) changes at high altitude are varying and somewhat confusing.

Ersanli et al. measured IOP in 34 healthy pilots at 792m and a simulated altitude of 9,144m. First, the subjects breathed 100% O_2 (hypobaric normoxia) at high altitude. Immediately after the measurement, the subjects removed their masks and IOP measurements were repeated with an inspired oxygen partial pressure of 47 mmHg (hypobaric hypoxia). Measurements were made by tonopen-XL. IOP at ground level in 68 eyes of 34 subjects was 12.31 ± 2.98 mmHg. It rose significantly to 16.75 ± 4.14 mmHg for hypobaric normoxia ($p = 0.003$). The value declined slightly to 14.37 ± 3.44 mmHg following mask removal at altitude, a value that was not significantly different from either the initial value ($p = 0.323$) or the mask-on value ($p = 0.195$). Following return to ground level, IOP was 12.81 ± 1.74 mmHg, statistically insignificant from the initial value. The authors concluded that healthy subjects whose baseline IOP is in the normal range experience only a small, temporary elevation of IOP during passive exposure to high altitude with either normoxia or acute hypoxia. The small rise in IOP seen in the healthy subjects might be much greater in older persons or those with limits on aqueous drainage, such as preexisting ocular hypertension or glaucoma. In addition, factors such as exercise and dehydration might alter the picture in mountains, especially when people are transported rapidly to a high elevation and then required to undertake various activities like heliskiing or paragliding. These results can also lead to the conclusion that during climbing to high altitude with oxygen masks, intraocular pressures can rise to significant levels and this may be important for climbers with ocular hypertension or glaucoma (Ersanli et al., 2006).

We also reported a nonsignificant rise in IOP at 3,932 m on Mount Kackar; in that study the measurements were made by Schiotz tonometer (Karakucuk & Mirza, 2000) (Figure 5). This type of tonometer is gravity dependent and therefore may not always be suitable for high altitude environments. The Tono-Pen XL, on the other hand, has been used in hypobaric environments and has been suggested to be unresponsive to changes in atmospheric pressure. In our following studies, we continued our intraocular pressure measurements with Tonopen and again obtained a similar rise (Karakucuk et al., 2010).

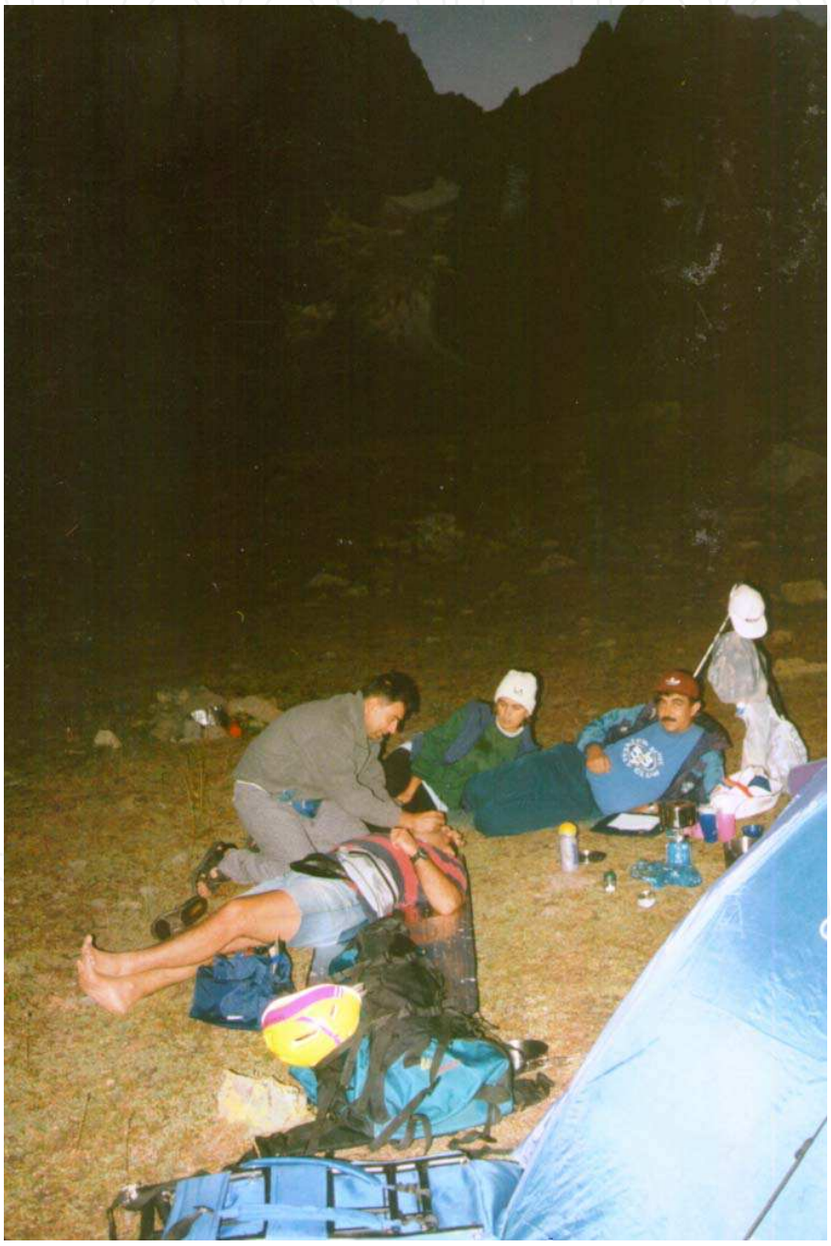

Fig. 5. IOP is being measured at Kaçkar mountains; Black Sea-Turkey. (Schiotz tonometer, Riester, Germany) (Karakucuk & Mirza, 2000)

Bayer et al. reported that in an unpressurized aircraft at 3,048 m, healthy subjects showed no significant change in IOP (Bayer et al., 2004). Another study also suggested that flying seems not to alter IOP in normal subjects. (Ayala et al., 2010).

Pavlidis et al. searched for intraocular pressure changes during high altitude acclimatization in healthy climbers between 500m and 5,050m. The mountaineers climbed with a gradual ascent, with rest stops and acclimatization days which were similar to that used by most trekkers in the Karakoram region to improve physiological acclimatization and reduce the incidents of serious acute high-altitude sickness. The climbing protocol of the expedition was as follows: day 1, from Skardu (2,286m) to Skardu lake (3,986m) by trekking and off road; day 2, transportation to Askole (2,900m); day 3, trek to Jola (3,100m); day 4, trek to Paju (3,350m); day 5, trek above Paju (3,850m) and return; day 6, trek to Urdukas (4,000m); day 7, trek to Goro II (4,220m); day 8, trek to Concordia (4,450m); day 9, trek to Ali camp (5,050m); day 10, ascent to Gondogoro La pass (5,650m). The authors reported that IOP decreased in sudden ascents of more than 200m/day and recovered, following acclimatization, for ascents up to 200m/day. They concluded that IOP changes may be related to hypoxia-induced respiratory alkalozis and that the IOP fall is proportional with the fall of oxygen partial pressure and acclimatization. They also suggested that IOP changes could reflect intracranial pressure variations and can be used for monitoring acute mountain sickness, high altitude cerebral or pulmonary edema (Pavlidis et al., 2006).

We also searched for the effects of high altitude on the IOP and various vital functions such as SaO_2, blood pressure, pulse and temperature. Systolic and diastolic arterial pressure and pulse rate increased whereas body temperature decreased and these findings were statistically significant ($p<0.05$). There were no correlations between these parameters and the IOP (Karakucuk et al., 2010) (Table 2).

Parameters	1080m (mean) (n=40)	2800m (mean) (n=40)	p
Partial arterial oxygen pressure (%)	96	92↓	<0.001*
Systolic blood pressure (mmHg)	105	114↑	<0.001*
Diastolic blood pressure (mmHg)	63	73↑	<0.001*
Pulse rate (n/min)	83	96↑	<0.001*
Body temperature (°C)	35,9	35,7↓	0,05*

Table 2. Vital parameters at low (1,080m) and high altitude (2,800m); Mt. Erciyes (Karakucuk et al., 2010; *statistically significant)

In one study, IOP was found as decreased at hyperbaric conditions. It was also suggested that swimming goggles significantly increase IOP at sea level since they may compress the eyeball (Van de Veire et al., 2008). The IOP increase observed in swimmers may be due to

goggle/face area; in one study, IOP increased while wearing goggles by a mean pressure of 4.5 mm Hg ($p<0.001$) with this pressure rise being sustained for the duration of goggles wear. A smaller goggle/face area ($p = 0.013$) was consistently associated with greater IOP elevation (Morgan et al. 2008).

In a prospective study which involved 25 healthy mountaineers who were randomly assigned to two different ascent profiles at Mt. Muztagh Ata (7,546 m/24,751 ft); group 1 was assigned to a shorter acclimatization time before ascent than group 2. IOP in both groups showed small but statistically significant changes: an increase during ascent from 490 m/1,607 ft to 5,533 m/18,148 ft and then a continuous decrease during further ascent to 6,265 m/20,549 ft and on descent to 4,497 m/14,750 ft and to 490 m. The authors concluded that hypobaric hypoxia at very high altitude leads to small but statistically significant changes in IOP that are altered by systemic oxygen saturation (Bosch et al., 2010a).

Karadag et al. searched whether IOP changes at hypobaric hypoxic exposure are related to plasma pro-brain natriuretic peptide levels. They found that IOP increased at high altitude, however, proBNP levels did not have any significant differences (Karadag et al., 2010).

Somner et al. reported that acute exposure to high altitude caused a statistically significant increase in IOP which returned to baseline levels with prolonged exposure to altitude. They concluded that observed changes in IOP may partially be explained by the change in central corneal thickness and are not predictive of symptoms of acute mountain sickness or development of high altitude retinopathy (Somner et al., 2007).

Karadag et al. reported that a short-term hypobaric hypoxic exposure caused a significant increase in IOP in healthy participants. As opposed to Somner et al., Karadag and associates concluded that this significant increase in IOP cannot be solely explained by a central corneal thickness-related overestimation error at high altitude. They also concluded that individuals with IOP-related disorders such as glaucoma should be cautious during high altitude exposure (Karadag et al., 2008).

3.2 Central corneal thickness changes at high altitude

Central corneal thickness is also shown to be affected by high altitude related hypoxia in many studies.

Bosch et al. investigated the effects of increasing altitude up to 6,265 m on healthy mountaineers. There was a statistically significant relationship between central corneal thickness increase and cerebral acute mountain sickness score. They found that adhering to a slower ascent profile results in less corneal edema. They concluded that corneal swelling is aggravated by low oxygen partial pressure. They also concluded that individuals with acute mountain sickness related symptoms had thicker corneas. Carbonic anhydrase is also found in cornea endothelium; they suggested that carbonic anhydrase inhibitors can negatively affect endothelial safety and must be cautiously used (Bosch et al., 2010b).

In our study at Erciyes Mountain, we also found a statistically significant increase in central corneal thickness at high altitude. There was a correlation with increased IOP on right eyes ($p=0.05$) whereas no such correlation was found on left eyes ($p>=0.05$; Fig. 6 & Table 3) There was not a significant correlation between central corneal thickness and any of the blood oxidation or antioxidation parameters studied (Karakucuk et al., 2010; Dolbun et al., 2010) (Fig. 6; Table 3).

Our results are in accordance with Morris et al. who also investigated central corneal thickness at high altitude in their Apex 2 study, during which an ascent was made to Chacaltaya cosmic research center (5,200m) and ultrasound pachymetry was made. Mean central corneal thickness increased significantly from 543 to 561 microns. Endothelial dysfunction causing stromal swelling was suggested as the causative agent for stromal edema. In their study, central corneal thickness increased 3.5% on day 1, 4% on day 3, 5% on day 7 (Morris et al., 2007). In an attempt to enlighten endothelium damage seen at altitude

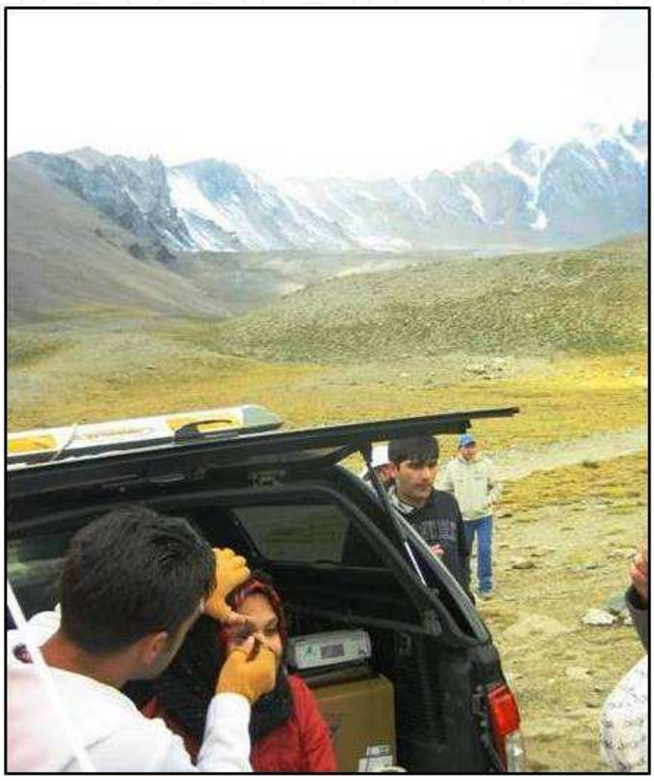

Fig. 6. Central corneal thickness measurements are made at 2800 m *(accutome-occupach5)* (Karakucuk et al., 2010)

	1080 m	2800m	p
IOP-right eyes	13.22±2.74 mmHg	14.45±3.54mmHg	=0.05*
IOP-left eyes	13.9± 3.0 mmHg	14.3± 3.6 mmHg	>0.05
Central corneal thickness-right eyes	549±31.9µm	555±31µm	<0.05*
Central corneal thickness-left eyes	550±32.4µm	554±30µm	<0.05*

Table 3. IOP and central corneal thickness changes at low and high altitude. (Karakucuk et al., 2010; *statistically significant)

related hypoxia, ultrastructural analysis of the rat cornea revealed that a 30 day-stay at 5,500m brought about no changes on epithelium; on the other hand, stroma was hydrated, thickened and endothelium was damaged. Descemets membrane was also thickened (Mastropasqua et al. 1996). In another study, increased corneal vasoendothelial growth factor and cytochrome p450 were suggested as the causative factors (Mastyugin et al., 2001).

Karadag et al. investigated 70 eyes of 35 subjects from two different age groups. Measurements were carried at 792m and at a simulated altitude of 9,144m. A short term hypobaric hypoxia exposure increased central corneal thickness significantly in the older age group (Karadag et al., 2009).

Di Blasio et al. investigated central corneal thickness measurements in hypobarism and suggested treatment of corneal edema with hyperosmotic agents. They found evidence that after 20 min of staying at 25,000ft, the decrease of barometric pressure produces a significant stromal and epithelial edema and that this can be treated with a hyperosmotic solution (Di Blasio et al., 2011) which may be of practical importance for those exposed to high altitudes.

3.3 Possible relationship of high altitude with pseudoexfoliation, cone cell sensitivity and visual fields

Kozobolis et al. suggested that a correlation between increased pseudoexfoliation prevalence and high altitude may exist since they reported a higher incidence of pseudoexfoliation in Crete highlanders (Rethymnon 27%) as opposed to lowlanders (Heraklion %11.5, Chania 13.4% and Lasithi 16.9%) (Kozobolis et al., 1997). In another similar study, Jones et al. found an increased occurrence of pseudoexfoliation in males in a Spanish American population of New Mexico and proposed a geographic climatic theory that relates pseudoexfoliation to greater solar radiation levels due to a high overall altitude (Jones et al., 1992).

Horng et al. evaluated black-and-white visual field sensitivity during acute exposure to a simulated altitude of 7,620m in fifteen healthy male pilots with an age range of 26 – 39 yr. They measured arterial oxygen saturation using transdermal pulse oximetry with an oximeter clamped to the distal phalanx of the right middle finger of the subjects, while the visual field was measured within a 30° eccentricity in the right eye by using the quick mode of an SBP-3000 computerized perimeter. The pilots breathed 100% O_2 for 30 min before and during chamber ascent, then removed their masks while measurements were performed. Mean visual sensitivity was significantly reduced; peripheral sensitivity was significantly more diminished than central sensitivity. The different resistance of the cone cell system and the rod cell system functions to oxygen deprivation might account for this finding (Horng et al., 2008).

We also investigated the response of the cone cell system to altitude related hypoxia in sixteen healthy high school students, aged between 14 and 17 yr. Their color vision was examined with the Farnsworth-Munsell 100-Hue test at 1060 and 3000 m. It was found out that there was a statistically significant increase in the total number of errors ($p = 0.001$) as well as in the number of errors in sector 1 ($p = 0.007$) and sector 3 ($p = 0.013$) at 3,000 m when compared with 1,060m. We concluded that altitude related hypoxia resulted in a color vision deficit with a reduced cone sensitivity at the blue-yellow range (Karakucuk et al., 2004).

3.4 Future issues – Space travel and intraocular pressure

Microgravity is a term more or less a synonym for weightlessness and zero-gravity, but indicates that g-forces are not quite zero, just very small. It is a measure of the degree to which an object in space is subjected to acceleration. *Micro* indicates accelerations equivalent to one millionth (10^{-6}) of the force of gravity at Earth's surface. The symbol for microgravity, μg, was used on the insignia of Space Shuttle flight STS-87 because this flight was devoted to microgravity research (Harland 2011). Microgravity also has impacts on the IOP; it is known that IOP increases rapidly in microgravity. In an attempt to measure IOP through the eyelid during a space mission, a hardware, KARI was used (Jennings et al., 2010).

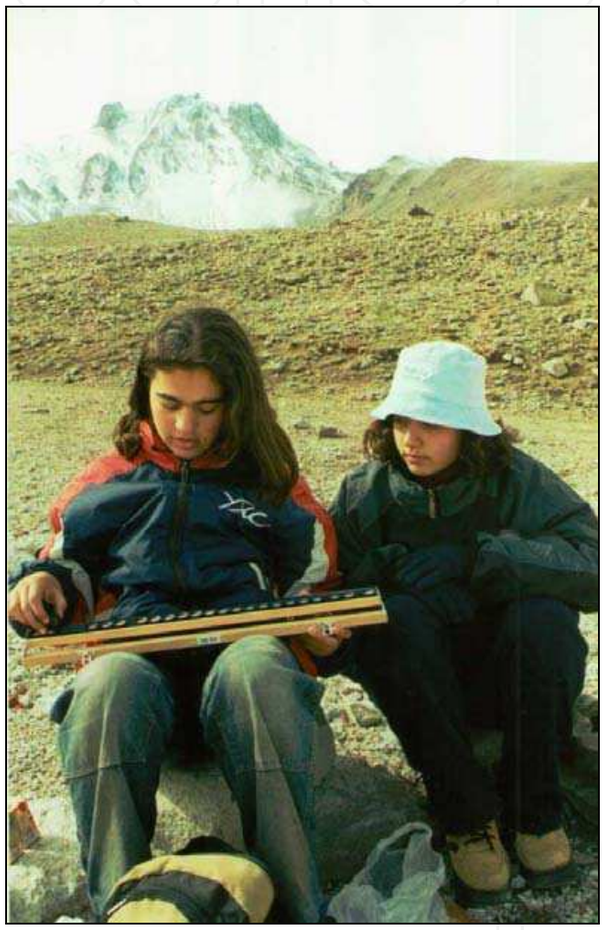

Fig. 7. Farnsworth-Munsell-100 Hue test is being performed on healthy young individuals at 3000m, Mt. Erciyes. (Karakucuk et al., 2004)

If a candidate for space travel has a potential risk for glaucoma, he or she may sustain significant glaucomatous damage during space flight likely to cause incapacitation. Currently, there is no established protocol to predict the possibility of glaucoma during space flight. Normally, head down posture, similar to that in space flight is demonstrated to increase IOP (Baskaran et al., 2006). Xu et al. modified a 'head down rest' test to predict the occurrence of ocular hypertension and glaucoma in astronaut and space tourist selection; they also investigated whether myopic subjects are more sensitive to microgravity than

normal subjects. They concluded that myopes are more susceptible to the head down position and they may possess a risk factor for developing ocular hypertension and possibly glaucoma when exposed to microgravity (Xu et al., 2010).

4. Conclusion

It is clearly seen from the above mentioned studies that oxidative stress has a deep impact on the human body and the human eye is affected by altitudes over 2,400m, commonly regarded as high altitude. In an attempt to evaluate the effects of high altitude on antioxidant parameters and intraocular pressure, as well as central corneal thickness, we found that oxidative stress markers, total oxidative system and advanced oxidative protein products are increased, along with IOP during acute exposure to hypoxic environment at high altitudes and that antioxidant system may have a limited capacity to counterbalance this effect due to acute unacclimatized ascent (Karakucuk et al., 2010).

Taken all together, despite conflicting results from various centers, it is possible to say that intraocular pressure and central corneal thickness are affected by low atmospheric pressure at high altitudes. People with preexisting ophthalmological pathologies such as ocular hypertension or glaucoma must be very cautious when they are exposed to these altitudes. Acclimatization is crucial before strenuous high altitude activities. When acute unacclimatized ascent is inevitable, either in mountaineering or aviation, functions of the human eye which rely on the integrity of color vision, visual field, intraocular pressure and corneal thickness must be cautiously evaluated. In the next era when space flights will be more accessible to the inhabitants of our planet, effects of microgravity on intraocular pressure of the human eye will probably be the main topic of interest.

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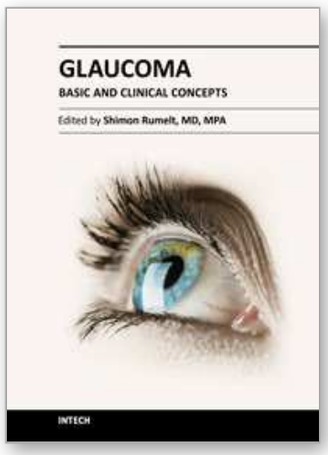

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