Review Article

Impact of flight and equivalent short-term high-altitude exposure on ocular structures and function

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ABSTRACT

Background: Exposure to high-altitude conditions during flight or similar activities affects many aspects of visual function, which is critical not only for flight safety but for any altitude-related activity. We aimed to summarize the available literature pertaining to ocular changes during flight or equivalent short-term high-altitude exposure (e.g., hypobaric chamber, effortless ascent lasting ≤ 24 h) and to highlight future research priorities.

Methods: Using the PubMed/MEDLINE and Web of Science/ISI Web of Knowledge databases with structured search syntax, we conducted a systematic review of the literature spanning a 40-year period (January 1, 1983, to October 10, 2023). Articles pertaining to ocular changes during flight or flight-equivalent exposure to altitude were retrieved. The reference lists of retrieved studies were also searched, and citations of these references were included in the results.

Results: Of 875 relevant PubMed and ISI publications, 122 qualified for inclusion and 20 more were retrieved from the reference lists of initially selected records, for a total of 142 articles. Reported anterior segment changes included deterioration in tear film stability and increased dry eye incidence, increased corneal thickness, discomfort and bubble formation in contact lens users, refraction changes in individuals with prior refractive surgery, decreased intraocular pressure, and alterations in pupillary reaction, contrast sensitivity, and visual fields. Photoreceptor–visual pathway changes included alterations in both photoreceptors and neuro-transduction, as evidenced in dark adaptation, macular recovery time, reduction in visual field sensitivity, and optic neuritis (likely an element of decompression sickness). Retinochoroidal changes included increases in retinal vessel caliber, retinal blood flow, and choroidal thickness; central serous chorioretinopathy; and retinal vascular events (non-arteritic ischemic optic neuropathy, high-altitude retinopathy, and retinal vein occlusion).

Conclusions: The effect of short-term high-altitude exposure on the eye is, in itself, a difficult area to study. Although serious impairment of visual acuity appears to be rare, ocular changes, including tear film stability, contact lens wear, central corneal thickness, intraocular pressure, contrast sensitivity, stability of refractive surgeries, retinal vessels, visual fields, and macula recovery time, should be considered in civilian aviators. Our report provides guidance to climbers and lowlanders traveling to altitude if they have pre-existing ocular conditions or if they experience visual symptoms while at altitude. However, key outcomes have been contradictory and comprehensive studies are scarce, especially those pertaining to the choroid and retina. Such studies could not only deepen our understanding of high-altitude ocular pathophysiology, but could also offer valuable information and treatment possibilities for a constellation of other vision-threatening diseases.

KEYWORDS

airplane, aviation medicine, national aeronautics and space administration, atmosphere exposure chamber, anoxia, oxygen deficiency, altitudes, altitude hypoxia, atmospheric pressures, corneas, refractive surgery, intraocular pressures, optic nerves, macula luteas, ora serrata, retina, choroids

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INTRODUCTION

Exposure to high-altitude conditions during flight or similar activities affects many aspects of visual function—a critical parameter not only for flight safety, but for any altitude-related activity [1, 2]. For pilots, the intensive environmental awareness and cockpit interaction produce a substantial cognitive and visual load [1, 2].

In a survey of health-related symptoms among commercial airline crews [3], ocular symptoms were the third most frequent (11%), less frequent than generalized fatigue (21%) and nearly as frequent as nasal symptoms (15%). Exposure to high altitude also imparts the risks of hypobaric hypoxia, altitude decompression sickness, hypothermia, intensive ultraviolet radiation exposure, and spatial disorientation [4]. Cabin conditions, such as temperature, humidity, and airflow, can also affect visual function. Most of these changes are benign and reversible [5, 6].

Published research pertaining to this issue is relatively scarce. A large proportion of articles represent case reports [7-12], while original studies exhibit remarkable inhomogeneity in methodology and instrumentation [13-16]. Likewise, existing reviews have reported a combination of both short- and long-term exposure or the effects of spaceflight on ocular structures [17-19], or they have focused on a single parameter or effect [20, 21]. Meta-analyses, if relevant, are rare and restricted to a single effect [22].

In this systematic review, we summarize the available literature pertaining to ocular changes during flight or equivalent short-term high-altitude exposure, such as a hypobaric chamber or effortless ascent lasting ≤ 24 h, and to highlight future research priorities.

METHODS

A comprehensive literature search was conducted using PubMed/MEDLINE and ISI Web of Science Core Collection (all editions, with the Exact Search option activated) to identify original studies conducted during the last four decades, January 1, 1983, to October 10, 2023, pertaining to ocular changes during flight or flight equivalent exposure to altitude without language restriction or study design filter.

The PubMed/ISI (TS i.e. Topic field tag selected) search syntax was structured as follows: (((ocular changes) OR (eye) OR (ophthalmic changes) OR (refractive changes) OR (cornea) OR (anterior segment) OR (intraocular pressure) OR (contact lenses) OR (IOP) OR (contrast sensitivity) OR (visual fields) OR (VEP) OR (ERG) OR (retina) OR (macula) OR (choroid)) AND ((air flight) OR (hypobaric chamber) OR (hypobaric hypoxia) OR (altitude) OR (atmospheric pressure changes))). The reference lists of retrieved studies were also searched, and citations of these references were included in the results.

Eligible studies were selected if they fulfilled the following inclusion criteria: 1) studies were conducted at simulated (hypobaric chamber) or real flight conditions and 2) studies concerned rapid ascent to altitude (≤ 24 h) (when deemed relevant). We excluded reports involving non-hypobaric hypoxic exposure, long-term changes, flying against medical advice (e.g., hypobaric expansion of intravitreal gas bubbles), and animal studies.

RESULTS

Figure 1 displays the PRISMA flow diagram of study inclusion. During the initial search, 859 PubMed and 1343 ISI articles were retrieved, totaling 2202 articles. After the initial screening, 875 articles with full text available were re-evaluated, and 753 of these did not meet the inclusion criteria (e.g., not hypobaric chamber or flight studies, prolonged stay at altitude) and were excluded. A manual search of the remaining 122 articles yielded 20 additional articles, bringing the total number of articles to 142 (S. P. and K. E.) (Figure 1). The full text of each included article was reviewed and relevant data were summarized (K. M., T. S., and G. P.).

A relatively small number of participants and a high degree of heterogeneity were noted regarding key aspects of these studies, including height and duration of exposure, means of exposure (military versus civilian aviation, hypobaric chamber, effortless ascent to altitude by driving or cable car), rate of ascent, measurement instrumentation and methodology, and evaluation of different environmental parameters. Probable sources of selection bias included the sex and age of participants, as in many cases they were young, active, male military aviators. Therefore, the considerable heterogeneity in study populations, type and duration of exposure, measuring techniques, measured parameters, as well as the presence of selection bias, rendered the prospect of meta-analysis impossible.

Based on outcomes of the included studies, we classified the results into three major categories: 1) anterior segment changes, 2) photoreceptor–visual pathway changes, and 3) retinochoroidal changes.

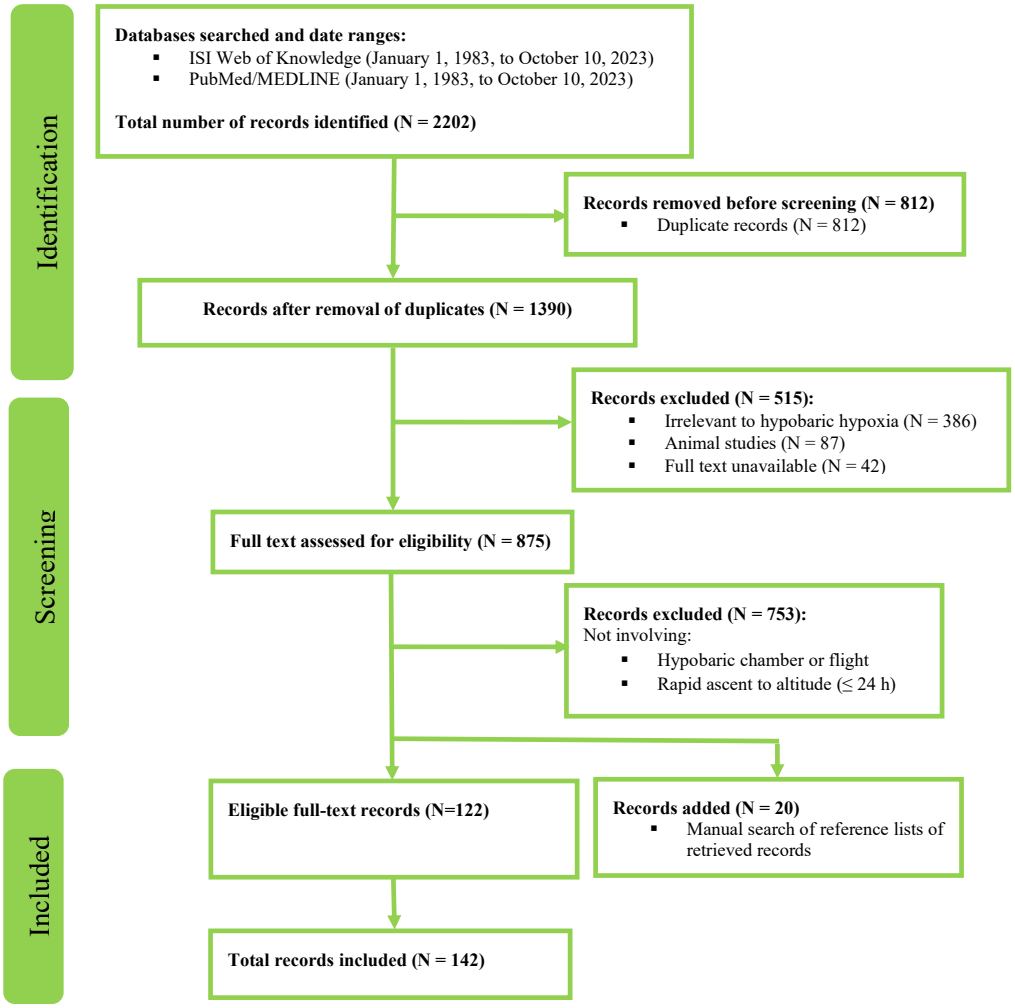

Figure 1. PRISMA flowchart illustrating the search strategy, screening, and selection of eligible records for this review. Abbreviations: N, Number of records

1) Anterior segment changes

Tear film stability–dry eye: Dry eye is frequent among flyers, affecting 72.3% of pilots [23] and 95% of flight attendants [24]. Associated factors include cabin conditions [25], older age, use of spectacles or contact lenses, flight duration and altitude [23], and especially for pilots, increased blink rate [26, 27] due to the effects of life-stress .

The low relative humidity of the cabin (≤ 30%) decreases tear break up time (BUT) and increases lens debris deposition [5]. Rapid altitudinal ascent has also been correlated to increased tear osmolarity [6]. Pre-existing tear film instability [28] may also increase Baylor scale corneal staining and decrease BUT. Increased tear matrix metalloproteinase-9 and interleukin-6 levels and decreased epidermal growth factor levels have been documented under simulated flight conditions [29]. Moreover, the increased cabin ozone concentration appears to correlate with dry eye symptoms [30-32].

Corneal thickness: Corneal swelling under hypobaric hypoxic conditions is well documented. In simulated hypobaric conditions (25 000 feet [ft]), the mean (standard deviation [SD]) corneal thickness measured 564.64 (16.5) μm versus 555.14 (14.7) μm at sea level [33]. A meta-analysis of five studies reported a 13.4-μm [22] mean central corneal thickness (CCT) increase after a 12-h high-altitude exposure or hypobaric chamber equivalent of 2500 m. Only one study reported no changes in CCT at sea level versus 2234 m (548.3 versus 549.4 μm, respectively) [14].

CCT is linearly correlated to oxygen partial pressure [34]. CCT decreased by 1.3 μm per unit increase in oxyhemoglobin saturation level (SpO_2; pulse oximetry]) [35]. Notably, under hypobaric hypoxic conditions, intraocular pressure (IOP) and CCT appear non-correlated [15, 36]. Studies with rapid (2 h) ascent to altitude

(including trekking and an effortless ascent using car or cable car) also produced an increase in CCT [37], without significant changes in ocular outflow structures by anterior segment optical coherence tomography (OCT) [38]. Interestingly, healthy highlanders seem to have thinner corneas compared to lowlanders [39, 40].

Hypobaric hypoxia-induced CCT changes are age dependent. In a hypobaric chamber (30 000 ft), younger healthy pilots (mean [SD] age, 22.8 [0.6] years) demonstrated less CCT increase than older pilots (32.1 [2.8] years), with mean (SD) CCT values of 566.0 (33.7) μm versus 576.9 (28.5) μm, respectively [41].

Contact lenses: Contact lens behavior in the dry hypoxic cabin environment is important owing to the high percentage of ametropic aviators (22% in the US Army) [42]. Time-dependent subjective (irritant or foreign body sensation and slight blurring) and objective findings (ciliary injection, corneal erosions, transient stromal opacities, and tear film debris) can develop in at least one eye after a 4-h exposure to hypoxic conditions at 4000 m [43] or 0.5 atm [44].

Limbal sub-contact lens bubbles, originating from expansion of gas nuclei, affect both gas-permeable soft and hard lenses (at altitudes of 25 000 ft) and impermeable polymethyl methacrylate lenses (at 40 000 ft), in the latter case remaining for longer periods after descent. With hard lenses, bubbles primarily occur centrally, affecting corneal epithelium and visual acuity [45].

A United States Air Force (USAF) survey of contact lens wearers revealed foreign body sensation and lens decentration at 5 – 15% relative humidity, more commonly with hard gas-permeable than with soft lenses [46]. An abrupt relative humidity drop (47% to 11%) within 30 min after departure of a commercial flight [47] affects primarily hydrophilic soft lenses, which are more amenable to dehydration-related fitting problems [48].

Still, the occurrence of measurable visual acuity degradation is negligible [43, 45, 49]. A study of Royal Air Force Pilots reported a 67% incidence of contact lens-related symptoms, which did not result in a single flight safety incident for a whole year [50], in contrast to 5% for spectacle-related incidents. Moreover, contact lenses are compatible with the modern helmet-mounted pilot equipment [50, 51].

Refractive surgery: Oxygenation of corneal endothelium is accomplished through ambient oxygen diffusion. In hypoxia, endothelial dysregulation in intact corneas results in a uniform increase in corneal thickness, while transparency and anterior corneal contour (i.e., refractive power) are maintained [20, 37, 52, 53].

Laser in situ keratomileusis (LASIK): LASIK is currently the most prevalent refractive surgery technique, offering faster rehabilitation and less discomfort [20]. After its approval by the USAF in May 2007, over 2200 aircrew underwent LASIK in 2010 [54]. Studies on LASIK eyes exposed to short-term hyperbaric hypoxia revealed only minor refractive changes, as presented in Table 1 [55- 58].

Photorefractive keratectomy (PRK): Devoid of incisions, PRK causes uniform hypoxic swelling in corneas, resulting in stable anterior corneal curvature and refraction [59] (Table 1).

Laser epithelial keratomileusis (LASEK) and EPI-LASIK: Although no studies regarding LASEK/EPI-LASIK corneas are available, it is rational to assume a similar response to hypobaric hypoxia [20].

Radial keratotomy (RK): RK involves four to eight incisions (90% of corneal thickness) in the mid-periphery, leaving the central 3 mm untouched [20, 60, 63]. During hypoxia, the weakened mid-peripheral cornea swells preferentially, resulting in a hyperopic shift correlated to the residual refractive error, accommodative reserve, and extent of the RK-treated area (number, length, and depth of incisions), rendering the corneal area amenable to overexpansion [60-62]. Notably, the cornea remains transparent and the hyperopic shift manifests after at least 12 (up to 24) h of exposure, long enough not to affect aviators [20, 63]. Studies on the effects of hypobaric hypoxia on RK corneas [63-65] are presented in Table 1.

Intraocular lenses (IOLs): Cataracts (posterior subcapsular) affect pilots at relatively young active-duty ages owing to ultraviolet light exposure [66]. IOL implantation in active aviators had no impact on flight vision requirements [67-69]. Related studies in military and civilian aviation [70, 71] are presented in Table 1.

Intraocular pressure (IOP): Conclusions in the literature are not unanimous, owing to conflicting study parameters and instrumentation differences. Dynamic contour tonometry (DCT) measurement of IOP (relative to atmospheric pressure) is less amenable to barometric changes than Goldmann applanation tonometry, resulting in higher DCT readings with increasing altitude (average increase of 1 mmHg per 673 m elevation above sea level) [13, 14]. The results of studies regarding IOP changes after short-term altitude exposure [15, 33, 72-77] are summarized in Table 2.

Pupillary reaction – acute angle closure glaucoma: Two pupillometry studies on healthy volunteers with rapid ascent to altitudes of 4559 to 4770 m reported a significantly reduced initial pupillary diameter [78, 79], while amplitude, relative amplitude, and light contraction velocity were significantly increased in one study [78] and reduced in the other [79]. Three cases of acute angle closure glaucoma during long-haul flight, attributed to dimmed cabin lights, have also been reported [80].

Table 1. Refractive surgery- and IOL implantation-related visual changes in hypobaric hypoxia

Surgery	Author (Year)	Methods	Results
LASIK	**Aaron et al. (2012)** [55]	HC: 35 000 ft (5000 ft / min), 30 min at altitude (100% oxygen mask), 24 eyes (mean 2.6 months post-LASIK).	Minor but significant changes in high and low contrast visual acuity, keratometry (≤ ± 0.25 D), and refractive error (≤ - 0.25 D).
	Stanley et al. (2008) [56]	HC:25 000 ft, 2.5 h Low relative humidity (0% and 30%) One week post-LASIK	No significant changes in refraction, best corrected visual acuity, and contrast sensitivity.
	Nelson et al. (2001) [57]	Non hypobaric hypoxia: 2 h Nitrogen filled goggles 40 post-LASIK eyes versus 40 myopic controls	Clinically negligible, but statistically significant - 0.31 D myopic shift.
	White and Mader (2000) [58]	A 52-year-old climber man post LASIK both eyes	He experienced a noticeable myopia after spending two nights at 18 000 feet, and his vision cleared after returning to 10 000 feet.
PRK	**Mader et al. (1996)** [59]	14 100 ft, 72 h 12 bilateral PRK eyes 6 – 12 months post-PRK	No changes in refraction and corneal curvature were detected, and peripheral corneal thickening normalized upon return to sea level.
RK	**Mader et al. (1995)** [63]	12 000 and 17 000 ft, 24 h 2 cases 18 – 36 months post-RK	The cornea remains transparent, and there was a manifest hyperopic shift after at least 12 h (up to 24 h) exposure.
	Ng et al. (1996) [64]	HC: 12 000 ft, 6 h, 17 RK corneas versus 7 controls 12 months post-RK	Decreased CCT. Found no significant differences in refraction, keratometry, or IOP. There was a time shift between altitude exposure and CCT changes.
	Winkle et al. (1998) [65]	20% O_2 versus 100% N_2 goggles, 2 h 20 RK eyes 10 – 36 months post-RK	The hyperopic shift was present only in the hypoxia hypoxia-exposed eye.
IOL	**Loewenstein et al. (1991)** [68]	Israeli Air Force pilot Three years, 100 flying h 5% of the time under high gravity stress	IOL did not dislocate, and no complications were observed.
	Moorman et al. (1992) [69]	23 USAF aviators Mean age of 43 years 28 eyes, 24 of which with ECCE	Eight aviators have flown since surgery.
	Mader et al. (1987) [70]	8 USAF aviators At least 6 months post-IOL implantation	Only minor visual disturbances occurred after an average of 2700 post-op flight hours.
	Kagami et al. (2009) [71]	105 Japanese native civilian aviation pilots were found to have cataracts in their annual evaluation.	All were deemed fit to fly after successful cataract surgery, and 59 pilots had bilateral cataract surgery.

Abbreviations: IOL, intraocular lens; LASIK, laser in situ keratomileusis; HC, hypobaric chamber; ft, feet; min, minutes; D, diopter; h, hours; PRK, photorefractive keratectomy; RK, radial keratotomy; CCT, central corneal thickness; IOP, intraocular pressure; O_2, oxygen; N_2, nitrogen; IOL, intraocular lens; USAF, united states air force; ECCE, extracapsular cataract extraction.

Contrast sensitivity (CS): Introductory screening of military pilots for CS has been suggested [81]. Despite the intuitive notion that CS should decrease in hypoxia, in a hypobaric chamber study (5500 m), baseline SpO_2 (98.4%) gradually decreased (74.3% within 15 min), revealing a significant negative correlation between SpO_2 and CS at low and medium spatial frequencies [82].

In contrast, no significant CS changes were detected in US Airmen wearing soft contact lenses when exposed to hypobaric chamber (25 000 ft for 75 min, or 10 000 ft for 4 h) [49]. Similar results have been reported for altitudes of 4600 ft [83] and up to 10 000 ft [84], supporting the notion that CS at upper-to-mid mesopic conditions is not affected by ambient partial oxygen pressure. In addition, no significant CS changes were detected in pilots using the aviator night vision imaging system for 30 min at simulated altitude up to 14 000 ft [85, 86].

Contrastingly, an HC study (18 000 to 25 000 ft) of 12 military aviators resulted in a CCT increase (550 μm to 600 μm) and a significant reduction in CS (1.95 log to 1.05 log on Pelli–Robson charts) [87]. Moreover, a significant decrease in Weber CS in 14 healthy individuals ascending to 4559 m (mean effect size of - 0.13 log CS), without visual acuity changes, has been reported [88].

Table 2. Intraocular pressure changes in hypobaric hypoxia

Author (Year)	Methods	Measurement Device	Results
Xie et al. (2019) [72]	HC: 4000 ft; 2 h	AccuPen Corrected-CCT	The mean ± SD IOP decreased (correlated to serum bicarbonates) from 16.4 ± 3.4 mmHg to 15.1 ± 2.1 mmHg at 4000 ft and even lower (14.9 ± 2.4 mmHg) upon return to baseline.
Bayer et al. (2008) [74]	Airplane cabin pressure equivalent: 8000 ft; 4 h Max airplane altitude 19 000 ft (40 min after departure)	Tono-Pen ® XL	Baseline mean ± SD IOP (14.0 ± 2.2 mmHg) remained unchanged at 14.2 ± 2.7 mmHg (19 000 ft, 40 min flight), decreasing to 12.3 ± 2.5 mmHg at the second flight hour and after landing (12 ± 1.7 mmHg).
Karadag et al. (2008) [15]	HC: 30 000 ft, 1 to 3 min without 100% O_2 mask 30 male pilots aged 21 – 39 years	Tono-Pen ® XL The corrected-CCT	Hypoxic mean ± SD IOP (18.23 ± 2.84 mmHg) was significantly greater than pre and post-hypoxic IOP (16.52 ± 2.84 mmHg and 17.02 ± 2.52 mmHg respectively).
Nebbioso et al. (2014) [33]	HC: 18 000 ft up to a ceiling of 25 000 ft 10% O_2 face mask Ascending /descending rate 4 000 ft / min 20 Air Force attendees, aged 32 ± 5 years	I-Care ® tonometry The corrected-CCT	Baseline mean ± SD IOP (16 ± 2.23mmHg), reduced to 13.7 ± 4.17 mmHg at 18 000 ft (ascent) to 14.5 ± 2.74 at 18 000 ft (during descent), and 12.8 ± 2.57 mmHg upon return to baseline.
Newton et al. (1963) [75]	HC: 30 000 ft (ascent rate 2000 ft / min). 60 US Aerospace medical students aged 20 – 37 years	Schiotz electronic tonometer 4 min contact time	No difference in the aqueous outflow facility at ground level and 30 000 ft.
Cymerman et al. (2000) [76]	HC: Two different settings 2 h Normobaric Hypoxia (760 mmHg, 12.8% O_2) Hypobaric Normoxia (466 mmHg, 37.3 % O_2)	Non-contact pneumatic tonometer, Model CT–20	In normobaric hypoxia, IOP decline reached significance at 2 hours, while in hypobaric normoxia, the decline was abrupt and significant at 30 min, suggesting two different pathways that hypobaric hypoxia can affect IOP.
Ersanli et al. (2006) [77]	HC: 30 000 ft, 1 to 3 min without 100% O_2 mask 34 healthy male pilots aged 26 – 39 years	Tono-Pen ® XL	The mean ± SD IOP increased at 30 000 ft both with (16.75 ± 4.14 mmHg) and without (14.37 ± 3.44 mmHg) 100% O_2, compared to baseline (12.31 ± 2.98 mmHg) and returned to baseline 30 min after leaving HC.

Abbreviations: HC, hypobaric chamber; ft, feet; h, hours; CCT, central corneal thickness; SD, standard deviation; IOP, intraocular pressure; mmHg, millimeters of mercury; min, minutes; O_2, Oxygen.

2) Photoreceptors and visual pathway changes

These include changes in photoreceptors, neuro-transduction (electroretinogram [ERG]/visual evoked potentials [VEP]), dark adaptation, macular recovery time, and visual fields. Surprisingly, these complex interactions were at first studied during World War II in the context of flight fitness of military aviators [89]. Rods, cones, bipolar cells, and ganglion cells are affected by hypobaric hypoxic exposure [90-99], as are VEP [100] and visual fields [101], which are exceptionally important for aviators and flight safety. Cases of optic neuritis [7, 102, 103] and optic nerve head edema [104] (not correlated to acute mountain sickness) after hypobaric hypoxic exposure have also been described. An outline of the existing studies is presented in Table 3.

3) Retinochoroidal changes

Peripheral fundus lesions: The only official data available are from the Furstenfeldbruck Air Force Medical Institute 1980 annual examination of 2451 pilots (aged 25 – 41 years) and 674 recruits (aged 18 – 24 years). The incidences of specific findings were as follows: lattice degeneration and snail tracks, 9.1%; round retinal holes, 1.5%; white without pressure, 11%; chorioretinal scars, 6%; paving-stone, 5%; microaneurysms, 8%; retinal pigment epithelium hypertrophy, 1.3%; and choroidal nevi, 4.2%. These incidences were similar to those of the general population [105].

Retinal vascular changes: The caliber of retinal vessels is affected by hypobaric hypoxia within minutes [106-108]. After 15 min at 8000 ft, small-artery (< 75 μm) caliber increased by 4% and larger-artery caliber increased by 7%, and the same was true at 10 000 and 12 500 ft. At 12 500 and 15 000 ft, small-vein caliber increased by 9% and 12%, respectively. Large-vein caliber did not increase until 15 000 ft was reached. A negative non-linear correlation between vessel diameter at sea level and vasodilation at altitude was also documented for both arteries and veins [109].

Table 3. Photoreceptor and visual pathway changes in hypobaric hypoxia

Author (Year)	Methods	Results
Lin et al. (2012) [94]	Inhalation of an O_2 and N_2 mixture 525 s, 7.7 log trolands white light Six healthy hikers, aged 34.0 ± 3.8 years	Hypoxic conditions (SaO_2 80%) and/or intense illumination resulted in a diminished ERG a-wave and photoreceptor bleaching on fERG.
Schatz et al. (2014) [97]	12 healthy individuals aged 25 to 54 years Cable car Ascend to 10 700 ft, then Short (2 h) ascent at 15 000 ft	ERG S-cone b-wave decreased significantly during rapid ascent to high altitude (15 000 ft).
Schatz et al. (2013) [98]	13 healthy individuals aged 25 to 54 years Cable car Ascend to 10 700 ft, then Short 2 h ascent at 15 000 ft	Combined rod-cone responses are primarily affected, thus photo-transduction and visual processing seem to be the most vulnerable sites in the visual pathway.
McFarland (1939) [95]	Pilots' reports Douglas bag laboratory experiments	Pilots complained of a dimming sensation at altitudes around 18 000 ft, which normalized rapidly after returning to sea level. Rod and cone thresholds were equally raised while the rate of adaptation remained unchanged.
Ernest et al. (1971) [91]	Inhalation of 10% O_2, 90% N_2 mixture Three healthy individuals aged 24 to 34 years Goldmann - Weekers adaptometer	Cone thresholds were increased more than rod thresholds at 5° retinal eccentricity. Peripheral rod thresholds (45° eccentricity) were increased more than on central 5°. Rod and cone dark adaptation curves were affected after the first 4 min.
Janaky et al. (2007) [93]	14 healthy men aged 18 to 52 years RETI-Port 32 ERG system The simulated altitude of 18 000 ft (15 min)	Oscillatory potentials (both OP1 and OP2) amplitude significantly decreased in hypoxic conditions. Partial OP1 and OP2 recovery occurred after termination of the hypoxia.
Singh et al. (2004) [100]	Rapid altitude ascend (14 000 ft)	Increased (still within physiological limits) N1 wave latency, attributed to synaptic delay and/or altered neuronal processing.
Horng et al. (2008) [101]	HC: 25 000 ft 30^0 automated perimetry 15 male pilots, aged 26 to 39 years	Mean ± SD of visual sensitivity reduced significantly (7.2 ± 1.6 dB), and peripheral sensitivity was significantly more affected than central.
Hecht et al. (1946) [92]	Inhalation of an O_2 and N_2 mixture O_2 concentration stepwise reduced (sea level to 17 000 feet in 7 steps)	Brightness discrimination is impaired with an increased rate at higher altitudes and inversely correlated to the light intensity (negligible in normal daylight). Rods and cones were equally affected, but the real origin seems to be in the ganglion cells.
McFarland (1940) [96]	Inhalation of an O_2 and N_2 mixture (10 000 and 18 000 ft equivalent) Shlaer Visual Acuity device	The hypoxia-correlated decrease in visual acuity is only evident under low illumination.
Connolly et al. (2006) [99]	HC: 10 000 ft and 15 000 ft Five healthy individuals aged 22 to 35 years Visual Field Analyser Mk II	Hypoxia significantly delays early scotopic sensitivity. Hypocapnia and hyperoxia hasten early scotopic sensitivity. Rods seem to be functionally hypoxic at ambient air (1 bar).

Abbreviations: O_2, oxygen; N_2, nitrogen; s, seconds; SaO_2, oxygen saturation of arterial blood; ERG, electroretinogram; fERG, flash electroretinogram; ft, feet; h, hours; min, minutes; OP, oscillatory potentials; HC, hypobaric chamber; SD, standard deviation; dB, decibel; bar, atmospheric pressure unit.

In other studies at altitudes of 6000 ft to 18 000 ft [107] and 16 000 – 19 000 ft produced an increase of 10% to 20% in retinal vessel caliber, with retinal venules dilating more than the arterioles [110]. A comparison of individuals flying 5 h at 3700 m to native highlanders revealed retinal venous dilation and a significant decrease in both arterial SaO_2 and arteriovenous difference, while venous SaO_2 and arterial vessel diameter remained stable, and subfoveal choroidal thickness increased [111].

Increased vessel tortuosity after ascent to 3600 m has been documented [112], while retinal blood flow was significantly altered. Measurements in 9 healthy individuals (aged 20 – 40 years) who flew for 45 min from 2600 ft to 17 500 ft revealed an 89% flow increase, with concurrent narrowing of the arteriovenous oxygen difference [110]. Retinal vascular perfusion density was reported to increase after rapid ascent (24 h) from 1130 to 3800 m and was inversely related to partial pressure of arterial oxygen [113].

Choroidal vascular changes: Mountaineers rapidly ascending (24 h) from 1625 to 4559 m [114] presented a small but significant increase in choroidal thickness, unrelated to acute mountain sickness and reversible

upon return to low altitude, which was attributed to a compensatory vascular bed reaction to hypoxia [114]. A subfoveal choroidal thickness increase after a rapid ascent to 3700 m (mean [SD], 295.21 [91.81] versus 336.07 [96.31] μm) has also been observed [115].

Central serous chorioretinopathy (CSCR): A CSCR review in USAF aviators (55 eyes of 47 individuals, 8 bilateral) [116] reported 97% recovery and flight status restoration (86% with visual acuity ≥ 20/20). Among 53 additional individuals discovered by reviewing other authorities' waivers, only 11 received a permanent flying status waiver [116]. An Israeli Air Force review [117] detected 14 cases (1.3/1000 aviators per year), 6 of them recurrent. As to whether flying conditions trigger CSCR attacks, only sparse case reports exist [118].

Retinal vascular events: Under this term we include cases of retinal vascular disease that occur in correlation with short-term hypobaric hypoxic exposure, with recurrent or permanent visual consequences discussed below.

Non-arteritic ischemic optic neuropathy (NAION): A few cases were reported in the literature, such as that of a 41-year-old male USAF pilot, with "disk at risk", who developed NAION during high G-force maneuvers in an A10 fighter jet. He also suffered a NAION insult in the same eye 16 months earlier and in the fellow eye 8 months later [119]. High + Gz acceleration (associated with reversal and subsequent cessation of temporal carotid flow [120]) in conjunction with hypobaric hypoxia may have triggered NAION [119].

In another case, a 61-year-old woman with cerebral small vessel disease experienced right eye NAION within 24 h of an airplane flight. The next year, she developed left-eye NAION after remaining at an elevation of 1500 m for 10 consecutive days [121]. NAION has been described after long (15 h) flights [122], and upon airplane landing (with concurrent retinal vein occlusion) after 1 month at 8333 ft [123].

Central retinal artery occlusion (CRAO): CRAO during landing has also been reported in an individual who suffered CRAO 5 years earlier in the fellow eye during descent from high altitude [124]. These cases raise the question of individual susceptibility to microvascular events at high altitude.

High altitude retinopathy (HAR) – Retinal vein occlusion: HAR affects un-acclimatized individuals exposed to hypobaric hypoxia, presenting with venous and arterial dilatation, pre-retinal, intraretinal, peripapillary or vitreous hemorrhages, peripapillary hyperemia, and/or papilledema [125-127], and even bilateral cystoid macular edema [128]. Risk factors include higher altitude and longer exposure, increased blood viscosity, lower SaO_2, and higher baseline IOP [129-133].

Only a few cases of flight-associated HAR [12, 134] and CRVO (HC exposure) [10] have been described. Other reported rare occurrences include deep cerebral venous thrombosis with visual implications associated with long-haul flight [135] and extraconal intraorbital hemorrhage likely attributable to cabin pressure fluctuations [11].

DISCUSSION

This review aimed to offer a complete and concise summary of four decades' knowledge on visual changes during flight or equivalent short-term hypobaric hypoxic exposure, to provide a convenient guide for professional and civilian eye care, and to highlight knowledge gaps and areas in need of further investigation [4, 14, 87, 116, 136].

Anterior segment changes

Low relative humidity [5] and increased evaporation rate impair tear film stability during flight. Contact lens wearers are more vulnerable, because as ambient temperature and relative humidity decrease, the tear film becomes thinner, although the total tear volume is not affected [137]. Air humidification and artificial tears are safe and effective measures in alleviating dry eye symptoms [28, 136]. Avoidance of contact lens use during flight may be prudent [5, 137]; major concerns also include bubble formation, decentration, and corneal epithelial integrity [45-49]. Subjective dry eye symptoms, although annoying, appear not to seriously affect vision or flight safety. Visual symptoms and signs also depend on the type of lens (soft or rigid, gas permeable) [43, 45, 138].

Regarding IOP changes, conclusions are often contradictory owing to variations in study parameters, measuring equipment, and CCT correction [4, 22]. Nevertheless, there is a trend toward an IOP decrease among studies, and a plausible explanation is a decrease in aqueous humor formation either through hypobaric hypoxia-induced reduction in plasma bicarbonates [72] or pH changes and respiratory alkalosis [139, 140]. Increased aqueous outflow through the trabecular meshwork has also been proposed [33, 73]. Because normobaric hypoxia appears to result in a delayed (2 h) decline in IOP, while in hypobaric normoxia the decline is abrupt and significant at 30 min, two different pathways are possibly implicated in IOP reduction associated with hypobaric hypoxia [76].

Corneal thickening is attributed to endothelial dysfunction and defective corneal dehydration [34, 36, 41].

Normal corneas thicken uniformly with no apparent corneal curvature change. The same is true for LASIK corneas due to the superficial nature of the surgery [59]. LASIK eyes, even when exposed to extreme altitudes under military operational conditions (exposure time ≤ 30 min), are expected to remain stable [55]. In contrast, structural changes in RK corneas result in a hyperopic shift [61-63, 141]. This shift must be considered in aviators, climbers, and those engaging in recreational activities at high altitude.

CS may also be affected by the increase in corneal thickness [87] and retinal oxygenation [84], although contradictory results are reported [49, 82-84, 87, 88].

Photoreceptors and visual pathway changes

ERG studies revealed that rods are more susceptible than cones to hypoxia at moderate altitude (4000–5000 ft), while visual degradation under photopic conditions occurs at altitudes over 10 000 ft [21]. Macular recovery consists of two phases: an initial neural phase more resistant to hypoxia (at least up to 15 000 ft) [99] and a second recovery phase evident at 2 min, representing the photoreceptor's photochemical recovery. Mesopic vision resilience in hypoxic conditions is important, as cockpit instrument illumination and military pilots' night vision goggles fall into the mesopic range [21, 84, 85].

Hypobaric hypoxic conditions at 18 000 ft and above appear to be the threshold beyond which complete macular sensitivity recovery is not achieved [90]. At this altitude, combined rod-cone responses are primarily affected [98], and a dimming sensation is reported by pilots [95], providing evidence that the dysfunction lies in the more sensitive bipolar and ganglion cell layers.

Reduced retinal sensitivity during hypoxia also manifests as a reduction in mean visual field sensitivity, which becomes more pronounced in the periphery [101]. Ganglion cells rather than photoreceptors are likely implicated in this phenomenon, as ganglion cells appear more sensitive to even mild and transient systemic hypoxia [142].

Optic neuropathy has also been observed in conjunction with hypobaric hypoxia, not as a truly classic neuritis, but mostly as part of decompression sickness, mandating emergent hyperbaric oxygen treatment. Decompression sickness typically occurs at altitudes above 25 000 ft, although exposure above 18 000 ft (especially if prolonged or repeated) is still considered a risk [143].

Retinochoroidal changes

Vasodilation, nonlinear from sea level to 15 000 ft of simulated altitude, was negatively correlated to the vessel diameter at sea level in both arteries and veins [109], primarily affecting retinal venules at an altitude of 15 000 ft. An altitude of 12 500 ft appears to be a critical point of complex interactions between hypoxia (causing vasodilation) and hypocapnia due to over-ventilation (causing vasoconstriction). Above this level, the effect of hypoxia appears to override that of hypercapnia [109]. Photoreceptors are highly oxygen-demanding cells, and retinal hypoxia plays an important role in various retinal diseases [144].

Other parameters to consider are the increased retinal blood flow velocity and/or viscosity and the depletion of endothelial nitric oxide as a result of increased oxidative stress, resulting in increased shear stress on the vessel walls [112]. In addition, abrupt, even minuscule pH changes and a redistribution between retinal and choroidal circulation may play a role, although these assumptions have not been confirmed [110].

Notably, the literature pertaining to choroidal and retinal circulation during flight is scarce, and there is a direct relation between visual function and retinal blood supply [145]. Future OCT and OCT angiography studies may not only offer knew knowledge about ocular well-being during flight [113] (of paramount importance for pilots), but may also find applications in a constellation of other serious and debilitating ocular disorders such as diabetic retinopathy [146].

Although CSCR is reported among aviators, the incidence is not high. There is only one reported case presenting a temporal association between hypobaric exposure and CSCR [147]. Active or recurrent CSCR may severely compromise flying status. Still, a relative flexibility in aeromedical waiver standards may be prudent in cases of inactive, stable disease [2].

The emergence of NAION in response to hypobaric hypoxia can be attributed to failure of retinal circulatory autoregulation in the face of decreased SaO_2 and perfusion pressure, with the concomitant increase in venous pressure. Hypoxia-induced oxidative stress, glial cell dysfunction, and up-regulation of inflammatory pathways [148, 149] have also been suggested to play a role.

Our study, although exhaustive in terms of literature search, and detailed in reporting all relative studies, has several limitations. Many of the existing studies are limited by insufficient design and methodological flaws, and many are single-case reports. We were mostly limited by the absence of strong evidence to prove causal

relationships and provide sound pathophysiological explanations for the observed changes. In light of this, a meta-analysis of these studies was impossible, and our findings are far from conclusive regarding aspects such as changes in IOP, retinal vasculature, and neurotransmission.

CONCLUSIONS

Although judicious and conservative, the conclusions of this study highlight important aspects of short-term high-altitude exposure. Although serious impairment of visual acuity appears to be rare, ocular changes, including tear film stability, contact lens wear, CCT, IOP, CS, stability of refractive surgeries, retinal vessels, visual fields, and macula recovery time, should be considered in civilian aviators. Our report also provides guidance to climbers and lowlanders traveling to altitude if they have pre-existing ocular conditions or if they experience visual symptoms while at altitude. Further investigations, preferably multicenter studies in facilities equipped with hypobaric chambers in a strictly controlled environment, are required to clarify changes in retinal vasculature, photoreceptors and neuro-transduction, visual fields, and IOP associated with short-term high-altitude exposure.

ETHICAL DECLARATIONS

Ethical approval: This was a review study and no ethical approval was required.
Conflict of interest: None.

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