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REVIEW

AstroOphthalmology: Basic and Pathophysiological Concepts of Space-Induced Ocular Changes

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Abstract: Long-duration space missions pose a considerable risk to eye health, and visual dysfunction is recognized as a primary health concern for astronauts. Hence, we have developed a series of review reports to study the effects of space on the eye, called AstroOphthalmology (including Basics, Ocular Anterior Segment, Ocular Posterior Segment). This report serves as the first report of our series, and integrates the current insights into the pathophysiological consequences of the space environment on the eye. The two key space-specific stressors include microgravity and cosmic radiation. Both stressors are the interconnected pathways of oxidative stress and mitochondrial dysfunction, which inflict damage on cellular components and disrupt the function of essential ocular tissues. Microgravity triggers a cephalad fluid shift, which leads to vascular congestion, changes in hemodynamics, and increased intracranial pressure. The aforementioned changes are considered to be culprits in the onset of spaceflight-associated neuro-ocular syndrome (SANS). Exposure to galactic cosmic radiation and solar particle events presents a substantial risk for the formation of cataracts, retinal cotton-wool spots, and optic neuropathy. This review indicates that ocular damage during spaceflight is influenced by multiple factors, resulting from the synergistic interaction of fluid shifts and radiation. In addition to pathophysiology, we summarize the current in-flight evaluations such as optical coherence tomography and fundoscopy. Future research should focus on assessing combined countermeasures and establishing predictive biomarkers to mitigate these risks, which is imperative for the success of future lunar and Martian missions.

Keywords: space, spaceflight, microgravity, radiation, eye, ophthalmology

Introduction

Long-duration spaceflight (LDSF) has a profound effect on the human body due to extraordinary conditions, including microgravity, radiation, and hypercapnia. It is acknowledged that LDSF induces multi-systemic effects, including bone demineralization, muscle atrophy, cardiovascular deconditioning, vestibular and sensory imbalance, alterations in metabolic and nutritional status, and dysregulation of the immune system. LDSF also has the potential to induce structural and functional changes in the eyes, posing risks to both the safety and success of space missions.[1] Wernher von Braun, a German-American space engineer, once remarked, “Man is not made for space. But with the help of biologists and medical doctors, he can be prepared and accommodated.” This viewpoint underscores the importance of medical proficiency to establish a microcosm of human existence in a challenging environment.[2]

The influence of microgravity and cosmic radiation exposure ultimately leads to a decline in the health of the ocular system, which may pose significant acute and chronic risks to astronauts. National Aeronautics and Space Administration (NASA) has considered visual impairment as a high-priority risk for future exploration class missions, acknowledging its potential to affect crew performance during critical operations such as landing, docking, and extravehicular activities.[3,4] Visual changes were reported by 23% and 48% of astronauts on short-duration and long-duration missions, respectively.[5]

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The space environment can impact both anterior and posterior segments of the eye. A collection of findings, initially termed spaceflight-associated neuro-ocular syndrome (SANS), revealed structural and functional changes in astronauts. These ocular manifestations include optic disc edema, globe flattening, chorioretinal folds, and hyperopic refractive shifts.[6] Chorioretinal folds are a prominent structural characteristic of SANS, consisting of undulations in the choriocapillaris, Bruch's membrane, and the retinal pigment epithelium above.[7,8] While SANS is the most recognized and unique effect of spaceflight on eyes, the other conditions and concerns during or after spaceflights such as dry eye disease, cataract, glaucoma, and trauma present specific challenges and require distinct attention.

Given the scarcity of in-flight experimental opportunities, much of the mechanistic insight into ocular changes caused by space has been obtained through ground-based analogues. The head-down tilt bed rest, dry immersion, and animal irradiation models have been essential in isolating the roles of cephalad fluid shift and radiation in ocular pathophysiology.[9] However, considerable knowledge gaps still persist; the relative contributions of cephalad fluid shift, altered cerebrospinal fluid dynamics, radiation-induced damage, and their synergistic effects are not fully elucidated. Furthermore, early and reliable biomarkers for SANS are lacking, and the long-term effects of partial-gravity exposure on the lunar and Martian surfaces remain uncertain. Hence, we have decided to develop a series of AstroOphthalmology—studying the effects of space on the eye—which will contain several review reports (including Basics, Ocular Anterior Segment, Ocular Posterior Segment) to cover different aspects of space travel on ocular health.

Although numerous narrative reviews have described the clinical features of SANS or summarized potential countermeasures, few have tried to comprehensively integrate the molecular and cellular pathways that connect the two dominant stressors—microgravity and radiation—to specific ocular tissue responses. This review article, as the first report of our series, offers a meticulous overview of the environmental factors that impact the eyes in space, as well as the basic biological mechanisms that are hypothesized to underlie these events. Herein, we aim to provide a comprehensive synthesis of the current understanding of how microgravity and space radiation impact the eye. Specifically, we examine the fundamental biological mechanisms—particularly fluid redistribution, oxidative stress, and mitochondrial dysfunction—that underlie ocular pathology induced by space conditions. We also summarize the current in-flight screening protocols and highlight the emergence of new diagnostic tools. By integrating these diverse lines of evidence, this review serves as a roadmap for researchers and clinicians dedicated to protecting astronaut vision in the forthcoming era of deep-space exploration.

Space-Specific Stressors

Microgravity

The role of gravity in ocular health is critical, as it regulates intraocular pressure (IOP), aqueous humor dynamics, and aids in the alignment of the eyes. It also supports the structural integrity of the eye. Exposure to microgravity can lead to disturbances in these well-adjusted mechanisms.[10] Microgravity is defined as a reduced gravitational force (compared to normal 1 g), resulting in a sensation of weightlessness for the body. Spaceflight conditions do not represent the total absence of gravity; rather, the gravitational force is significantly decreased to values that fall between 0.0001 and 0.000001 g.[11] This can have a substantial impact on blood circulation, the lymphatic system, intracranial pressure (ICP), and cerebrospinal fluid (CSF) hemodynamics.[10]

Blood Circulation

The absence of gravitational forces from Earth results in numerous adaptations and maladaptations in blood circulation.[12] Studies have underscored the physiological responses to microgravity, which include diminished venous pressures, a reduction in plasma volume, and orthostatic intolerance. In space, the absence of blood pressure gradients that are usually present under Earth's gravity leads to a redistribution of mean arterial pressure, ultimately causing facial swelling and a decrease in volume in the lower limbs.[13] At 1g, the arterial pressure in the head is lower (approximately 70 mmHg), while the blood pressure in the feet is considerably higher (around 200 mmHg). Within a few minutes of being in a microgravity environment, roughly 2 liters of blood are redistributed from the lower body to the cephalic area (Figure 1). Consequently, blood pressure in the upper body rises, heart rate diminishes due to the activation of neck baroreceptors, vasodilation is observed, and mean arterial pressure decreases.[14] A further impact of microgravity on

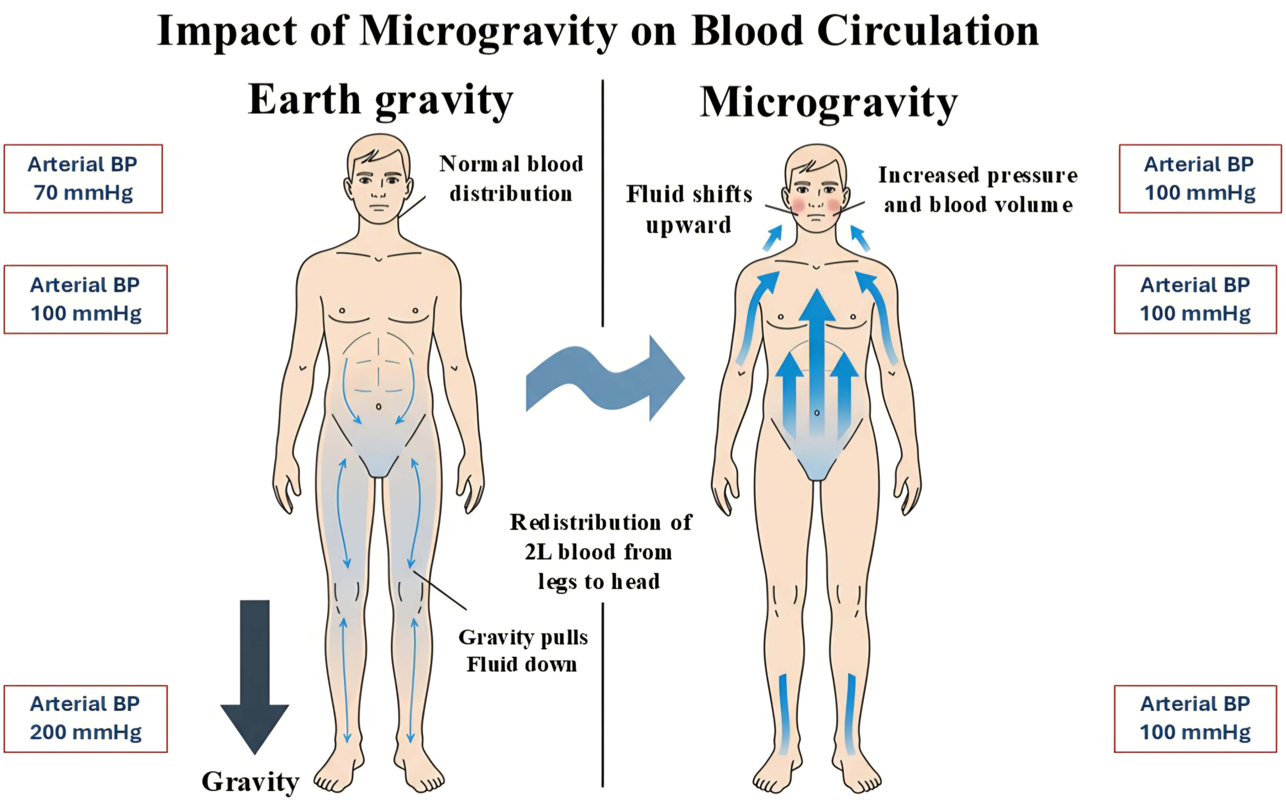

Figure 1 Impact of microgravity on blood circulation.

venous adaptations is the heightened coagulation in the cephalad venous system.[15] The lack of Earth's gravitational force results in increased venous pressure and decreased cranial venous drainage. This situation can lead to venous distension, endothelial damage, and a risk of hypercoagulability.[15] Moreover, microgravity affects the migration of endothelial cells, which are vital for maintaining the structure and stability of vascular cell walls. Microgravity conditions effectively decrease the compression of blood vessels from the surrounding tissues throughout the body, which in turn lowers central venous pressure (CVP).[16]

In microgravity, the stasis of cerebral venous blood due to cephalad fluid shifts may lead to interruptions in nutrient delivery and metabolic activity.[17] This can result in impaired adenosine triphosphate (ATP) generation, which may subsequently decrease Na^+/K^+ ATPase activity. The inability to maintain the physiologic low levels of intracellular Na^+ can lead to the occurrence of edema. Areas with a higher demand for ATP, such as the optic nerve head that contains unmyelinated nerve fibers, may be more severely affected by this stasis, resulting in optic disc edema in SANS.[18]

Lymphatic System

The lymphatic system is essential for the prevention and resolution of edema, the maintenance of normal tissue fluid volume, and the facilitation of immunologic responses. Furthermore, it plays a significant role in the clearance of CSF from the cranial region.[19] Disruption of CSF drainage into the lymphatics during spaceflight could be correlated with several pathological issues, such as SANS.[19,20] Microgravity conditions hinder lymphatic function due to various deconditioning mechanisms, including the loss of hydrostatic pressure, decreased sensory information, reduced mechanical stimulation, and changes in Starling-Landis pressure.[16] However, the significance of the ocular glymphatic pathway is an emerging and largely unverified concept. There is a deficiency of direct evidence regarding impaired glymphatic clearance in astronauts, with the majority of data originating from rodent models or indirect measurements. As a result, this hypothesis should be interpreted as provisional and in need of further validation.

Intracranial and Intraocular Pressures

The reduction in CVP impacts the ocular transmural pressure. An equilibrium is present between ICP, which pushes against the eye, and the IOP, which counters this force. The decrease in CVP due to microgravity leads to an increase in ICP. It has been hypothesized that a disproportionate elevation in ICP in comparison to IOP results in a decrease in the translaminar pressure gradient (TLPG) across the posterior part of the eye, leading to compression at the back of the eye.[21,22] Nonetheless, this hypothesis is still a subject of ongoing debate. A number of studies have found no reliable correlation between ICP estimates and the severity of SANS, and some have reported optic disc edema even in cases where significant ICP elevation is not present. Moreover, alternative (and potentially complementary) hypotheses have been suggested, such as impaired drainage of cerebral veins and venous stasis within the vortex veins, modifications in ocular glymphatic clearance, and variations in scleral compliance.[23] Therefore, SANS is probably a multifactorial condition where increased ICP is a contributing factor, though it may not be the sole causative element.

In terrestrial settings, choroid plexus is the primary site for the production of CSF, which drains into the lower pressure cervical venous system.[24] The drainage of CSF, lymphatics, and vasculature is enhanced by the influence of gravity. In microgravity conditions, the increase in venous cross-sectional area and alterations in blood flow velocity indicate potential for venous congestion.[25,26] The internal jugular veins (IJV) are the main outflow pathway. Such venous congestion may compromise the outflow from cerebral and ocular veins, including the vortex veins, which facilitate the majority of ocular blood drainage. A decrease in venous outflow may lead to reduced CSF outflow, resulting in increased ICP and transmission along the optic nerve sheath (ONS). The choroid is the primary blood supply to the ocular tissues.[27] The significance for ocular function is that a localized increase in choroidal thickness at the posterior globe may lead to foveal displacement, resulting in a hyperopic shift and an increase in IOP.[28,29] Various studies have demonstrated that acute exposure to both simulated and actual microgravity environments result in an increase in IOP. In the initial 15 minutes of exposure to microgravity, IOP shows a 92% increase relative to baseline measurements.[30] The reasons for this increase after acute exposure to microgravity may include increased choroidal thickness, elevated episcleral venous pressure, and a narrowing of the anterior chamber angle.[31–33] It was later noted during the flight that IOP returns to levels that were similar to pre-flight baselines. The decrease in IOP with chronic exposure may be linked to an increase in the drainage of aqueous humor and a reduction in its synthesis, which may be a consequence of dehydration.[3]

Radiation

While the magnetic field in low Earth orbit (LEO) offers a degree of protection against radiation, astronauts venturing beyond LEO are no longer shielded by the magnetosphere, thus facing exposure to solar particle events (SPEs) and galactic cosmic radiation (GCR) that originate from outside the solar system (MM). SPEs are largely constituted of low linear energy transfer (LET) protons, with levels surpassing 10^6 protons/cm^2.[34] These protons are relatively easy to shield against using spacecraft hulls, but they can pose risks during extravehicular activities (EVA).[35] On the other hand, GCR is composed of high LET protons (87%), alpha particles (12%), and a small fraction of high charge and energy ions (1–2%).[36]

Studies have established that radiation exposure can result in injury to eye structures, contributing to conditions like dry eye, cataract, retinal detachment, glaucoma, madarosis, abnormal vascularity, and optic neuropathy.[37] Astronauts on International Space Station (ISS) are exposed to radiation doses that are nearly 200 times higher than those on Earth. When on the surfaces of the Moon and Mars, they will experience even greater radiation exposure, estimated at around 2.6 and 3.5 times the radiation levels on the ISS, respectively.[38] Research has shown a correlation between the radiation dose a subject receives and the development of ocular complications.[39–42] The latest NASA standards impose a limit of 600mSv for radiation exposure over the career of American astronauts, whereas other international space agencies allow for exposure levels up to 1000mSv.[43] Although the majority of ISS missions operate well below this limit, a Mars mission spanning 1 to 2 years may exceed it.[44]

Cataract

Research has shown that radiation can lead to the destruction of aromatic and sulfur-containing amino acids, as well as aggregation, crosslinking, dissociation, fragmentation, and partial folding. Specifically, crystallins, which are the primary protein components of the lens, are significantly influenced by the aggregation of proteins and the degradation of aromatic amino acid residues. This results in a dose-dependent reduction in fluorescence intensity, which alters the structure of aromatic compounds. Consequently, these changes impact lens transparency and heighten the likelihood of cataract formation.[45] In light of the elevated radiation doses encountered during deep space missions, investigations are being carried out to assess the effects of low- and high-dose radiation exposure on the crystalline lens. Results from Phase 2 of the 5-year NASA Study of Cataract in Astronauts (NASCA) revealed that the progression rate of cortical cataracts was related to the amount of space radiation exposure. However, no association was identified between space radiation and nuclear or posterior subcapsular cataracts.[46]

Cotton Wool Spots

Retinal cotton wool spots (CWSs) have been extensively recorded following LDSF and are thought to be indicative of radiation exposure. After LDSF, CWSs were documented in four astronauts, three of whom had engaged in EVA during their missions. Since EVA suits provide less radiation shielding than the ISS, these astronauts may have been exposed to higher radiation levels. In another case, one astronaut exhibited a single CWS surrounded by a superficial retinal hemorrhage after an ISS mission, suggesting concurrent localized vascular damage. CWSs are a well-known side effect of radiation therapy, which typically involves short bursts of high-dose radiation that far exceed the prolonged low doses encountered by astronauts, and their appearance may be delayed for months to years following radiation exposure. It is hypothesized that the CWSs observed in astronauts may represent the cumulative outcome of a relatively low but prolonged radiation dose.[3] However, the small number of cases limits the ability to draw definitive conclusions. It remains uncertain whether CWSs are a result of cumulative radiation exposure, an interaction with microgravity-induced vascular changes, or an individual susceptibility. Furthermore, the occurrence of CWSs is not universal among astronauts with similar mission profiles, which underscores the necessity for larger, controlled studies.

Optic Neuropathy

Radiation exposure has been shown to significantly affect the optic nerve, with a substantial body of literature highlighting an increased risk of optic neuropathy following external beam radiation therapy. Through these investigations, it has been determined that the maximum radiation dose to the anterior visual pathway is a key factor influencing the development of radiation-induced optic neuropathy, with evidence suggesting that this pathway can tolerate no more than 50Gy of cumulative radiation in fractions of less than 2 Gy.[47–50] The inquiry into whether chronic, low-dose, mixed-field radiation from deep space can cause clinically significant optic neuropathy remains an open question. Currently, the risk is extrapolated from radiotherapy data and has not been verified in the context of space missions.

Phosphene

During deep space missions, astronauts participating in the Apollo program observed flashes of light, known as phosphenes, in their vision which are thought to be caused by high energy radiation particles impacting the retina. Astronauts aboard the ISS have similarly reported experiencing these flashes. Investigations indicated that these phosphenes result from GCR and SEPs interacting with the retina, optic nerve, and occipital cortex.[51] Comparable phosphenes are also noted in ocular oncology and in radiotherapy treatments directed at the head and neck area. The most frequently observed phosphenes manifest as either moving or stationary white dots or lines. Nevertheless, only a small number of astronauts have reported seeing blue phosphenes.[52–54]

Hypercapnia

The atmospheric CO_2 concentration on Earth is 0.04%, with PCO_2 of 0.3 mmHg at an atmospheric pressure of 760 mmHg. In contrast, the PCO_2 levels aboard the International Space Station vary significantly, ranging from 1 to 9 mmHg, and are usually found between 2.3 and 5.3 mmHg. Additionally, while air convection occurs on Earth, it is absent in space, which may lead to localized regions with particularly elevated PCO_2 levels.[55] While these levels are not high enough to result in CO_2 toxicity, they can still impact vascular tone, as shown by a greater frequency of headaches.[56] CO_2 serves as a powerful vasodilator for systemic arteries, which leads to an increase in cerebral blood flow. This rise in flow is likely a contributing factor to the increase in ICP, worsening issues related to cranial venous congestion and facilitating the emergence of SANS.[57,58] It has been concluded that the elevated PCO_2 experienced during spaceflight, potentially exacerbated by stagnant PCO_2 around the mouth in microgravity, may be linked to optic disc edema, particularly when the air circulator is ineffective or when an individual remains in a static position for extended periods. Nevertheless, the observed increases in peripapillary retinal nerve fiber layer thickness are believed to be primarily driven by hypoxia rather than hypercapnia.[59]

Pathophysiological Pathways

Oxidative Stress

Oxidative stress induced by spaceflight may result in certain visual abnormalities in astronauts.[60] The body's antioxidant defense mechanisms may become overwhelmed in microgravity, leading to oxidative damage in tissues, including the eyes. Oxidative stress occurs when there is an imbalance between the production of reactive oxygen species (ROS) and the body's antioxidant defenses.[61] ROS are molecules that can damage cellular components like DNA, proteins, and lipids. Antioxidants are molecules that help protect the body from oxidative damage by neutralizing ROS. The eye is particularly susceptible to oxidative stress due to its high metabolic rate and exposure to environmental stressors, including light and oxygen.[62] The levels of various biomarkers in the blood and urine of astronauts were evaluated in a study conducted before, during, and after space missions. The results demonstrated that the levels of 8-hydroxy-2′-deoxyguanosine (8-OHdG), a known marker of DNA damage, were significantly elevated during spaceflight when compared to pre-flight levels and were closely correlated with telomere length.[63] This indicates that the increased oxidative stress experienced during spaceflight may play a role in the development of SANS.[63]

The retinal layer is highly sensitive to oxidative injury due to its elevated oxygen consumption, the presence of oxidizable unsaturated lipids, and its limited antioxidant defenses.[64] The oxidative damage may result in cell death, at least partially through apoptosis, causing morphological changes in the inner nuclear and ganglion cell layers, which may eventually result in a decline in retinal function.[65] A mouse experiment has shown various impacts on the retina as a result of spaceflight.[66] These impacts include a decrease in retinal thickness, a reduction in cone photoreceptor count, and an increase in oxidative stress. Additionally, there was a noted rise in 4-hydroxynonenal (4-HNE), a marker of oxidative damage to the retina, which was found to be elevated in cone photoreceptors, the retinal inner nuclear layer (INL), and the ganglion cell layer (GCL) after spaceflight relative to terrestrial control mice.[66] In another study, ten-week-old male C57BL/6 mice were transported to the ISS aboard Space-X 24 for 35 days and returned to Earth alive.[67] Immunofluorescence evaluations showed an increase in retinal oxidative stress and apoptotic cell death after the spaceflight. The electroretinography (ERG) data indicated that the average amplitudes of the a- and b-waves were significantly reduced (by 39% and 32%, respectively) compared to habitat ground controls. These findings imply that the conditions of spaceflight induce oxidative stress in the retina, which may lead to damage in photoreceptor cells and impair retinal function.[67]

Mitochondrial Dysfunction

Mitochondria are fundamental cellular organelles that are responsible for energy generation through oxidative phosphorylation.[68] They are crucial in regulating apoptosis and ensuring cellular homeostasis, neuronal excitability, and synaptic transmission.[68] In the eye, mitochondria play a vital role in the transmission of visual information from the retina to the brain, and they are densely packed in the axons of retinal ganglion cells. The inner segments of retinal photoreceptors are rich in mitochondria, which are essential for the renewal of outer segments and the process of phagocytosis.[69] The phenomenon of microgravity and the augmented exposure to galactic cosmic radiation during spaceflight are well-documented to exert considerable effects on mitochondrial function.[68] Recent investigations utilizing multi-omics and systems biology, which analyzed data from 59 astronauts and mice, along with findings from NASA's GeneLab, have shown that mitochondrial stress is a common phenotype observed in spaceflight. This notable study illustrates the significant repercussions of spaceflight on mitochondrial function, leading to altered gene expression, weakened antioxidant defenses, and increased oxidative stress.[70] While this finding is noteworthy, it is derived from a single multi-omics analysis and has not yet been independently validated through dedicated ocular tissue studies. Mao et al explored the consequences of spaceflight on mitochondrial function and oxidative stress in mice, indicating that the spaceflight environment resulted in mitochondrial dysfunction and an increase in oxidative stress.[71] The research highlighted changes in the expression of genes related to mitochondrial function, as well as shifts in antioxidant levels and markers of oxidative damage observed in the study mice. This included significant rises in the levels of 4-hydroxynonenal (4-HNE) protein, a marker for lipid peroxidation, in the retina following spaceflight, along with notable modifications in the genes associated with a mitochondria-related apoptotic pathway in the ocular tissue of mice after spaceflight compared to ground-control mice.[71] The correlation between systemic mitochondrial changes and specific ocular pathologies, such as SANS or cataracts, remains to be established; functional validation in retinal and choroidal cells under real or simulated space conditions is still required.

Immunologic and Inflammatory Responses

Crucian et al studied the dynamics of plasma cytokine levels in astronauts during prolonged space missions aboard the International Space Station (ISS).[72] The research involved collecting plasma samples from 28 crewmembers at multiple time points: pre-flight, in-flight, and post-flight, with a focus on understanding the changes in the immune system and the potential health risks related to space travel.[72] Samples were collected at various intervals, including before, during, and after the flight, to capture the fluctuations in cytokine levels. It was found that while baseline cytokine levels were generally low, spaceflight caused significant increases in certain cytokines, especially IL-8 and TNFα, indicating a mild inflammatory response.[72] Elevated levels of chemokines such as CCL2, CCL4, and CXCL5 further supported the notion of chronic inflammation during spaceflight.[73] Notably, plasma levels of IL-1ra, an inhibitor of the proinflammatory effects of IL-1, were consistently elevated during spaceflight. This increase may represent an adaptive physiological response to inflammatory stress. The research highlights the importance of monitoring cytokine levels as biomarkers for assessing immune system health and the potential health risks associated with extended space missions.[72]

The alterations caused by microgravity can lead to a reduction in lymphocyte and monocyte counts, thus impairing immune function.[74] Studies have indicated that spaceflight results in decreased cytokine production, which makes astronauts more prone to infections.[75] This was brought to light in research by Rooney et al, which identified a potential relationship between stress induced by spaceflight and immune dysregulation, contributing to the reactivation of latent herpes viruses in astronauts.[76] The study observed increased shedding of these viruses in bodily fluids during and after missions, highlighting the potential health risks associated with viral reactivation upon returning to Earth.[76]

Tissue-Based Cellular and Molecular Interactions

Extended exposure to microgravity and space radiation causes significant physiological and pathological changes within human biology. At the cellular level, the predominant pathological effects of microgravity and cosmic radiation involve structural modifications resulting from free radical-mediated molecular damage.[71,77,78]

Cornea

Long-term exposure to microgravity has been associated with corneal edema, thickening, and tear film instability.[79–81] Also, GCR and SEPs are capable of inducing DNA damage, oxidative stress, and apoptosis in the cornea.[82] As the outermost layer of the eye, the cornea may face a specific challenge: lunar dust. The cornea may be detrimentally influenced by molecular changes associated with long-term exposure to low levels of dust.[37] Recent findings have revealed that even chronic exposure to low concentrations of lunar dust can elicit a molecular response in corneal tissue. As a result, lunar dust exposure may impact a variety of pathways in ocular tissues, such as oxidative stress response, mitochondrial dysfunction, fibrosis, epithelial healing, TGF-beta signaling, extracellular matrix remodeling, and cellular proliferation.[83]

Retina

In a research study, C57BL/6 mice were launched into the ISS. After completing a 35-day mission, the mice were brought back to Earth alive.[84] They were subsequently euthanized, and ocular tissues were gathered for analysis. The immunohistochemical analysis of the retina revealed that the flight mice had an increased expression of aquaporin-4

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(AQP-4) compared to the control group, which strongly indicated a disturbance in the integrity of the blood-retinal barrier (BRB). Additionally, there was a significant increase in the expression of platelet endothelial cell adhesion molecule-1 (PECAM-1) and a decrease in the expression of the BRB-related tight junction protein, Zonula occludens-1 (ZO-1). Proteomic analysis indicated that numerous key proteins and pathways involved in cell death, cell cycle, immune response, mitochondrial function, and metabolic stress were significantly altered in the flight mice when compared to ground control animals. These results suggest a complex cellular response that may affect retinal structure and BRB integrity after prolonged spaceflight.[84]

The role of retinal pigment epithelium (RPE) is fundamental in maintaining the BRB, as it is involved in the metabolic activities of the visual cycle. Evidence from studies suggests that simulated microgravity can cause detrimental effects on human RPE cells in vitro, including alterations in the cytoskeleton and gene expression.[85,86] In a study, human RPE cells were exposed to simulated microgravity (0.01 g) for 24 hours using a rotating bioreactor designed by NASA. The analysis of these cells was performed 48 hours after the rotation to detect the levels of prostaglandin E2 (PGE2) production, which serves as a marker for inflammatory responses and is a known risk factor for RPE cells. The findings demonstrated DNA breaks in RPE cells and an increase in PGE2 synthesis. Additionally, it was found that the negative impact of simulated microgravity on RPE cells could be reduced or eliminated by pretreatment with cysteine, an agent recognized for its anti-inflammatory effects.[85] One study reported that simulated microgravity enhances the epithelial–mesenchymal transition (EMT) of a human RPE cell line known as ARPE19 and promotes the expression of vascular endothelial growth factor (VEGF). Additionally, they demonstrated that the antioxidant Ishophloroglucin A could effectively inhibit EMT triggered by microgravity or VEGF by lowering VEGF–VEGFR2 signaling.[87]

The ARPE19 cell line was employed in experiments using the Random Positioning Machine system to simulate microgravity conditions. The outcomes indicated adverse effects on the cells, such as diminished cell viability, increased rates of apoptosis, disruption of the S-phase of the cell cycle, and oxidative stress.[88] In another study, the clinorotation technique within a bioreactor that mimics microgravity was applied to cultivate the human ARPE19 cell line. A comparison of the outcomes with the 1 g control in a static 2D culture indicated the formation of multicellular spheroids, a decline in cell migration, an increase in intracellular ROS levels, mitochondrial dysfunction, activation of autophagic pathways, and stimulation of ciliogenesis.[89] In contrast, in one investigation, ARPE-19 cells were relocated and grown for 3 days on the ISS.[90] It was found that a 3-day incubation of ARPE-19 cells on the ISS did not affect their proliferation rate nor induce apoptosis.[90]

The endothelial vascular cells of the human retina and choroid are another population of retinal cells that show significant sensitivity to microgravity effects. Zhao et al cultured these cells for a period of 3 days under simulated microgravity. At the cellular level, the cells displayed a reduced cell body size, chromatin condensation and vacuolization, mitochondrial cavitation, and apoptosis. It was also noted that the simulated microgravity effect on choroidal vascular cells results in changes to the cellular ensemble, a reduction in the number of F-actin microfilaments, and the activation of the Bcl-2 apoptosis pathway along with the PI3K/AKT pathway.[91]

Some evidence suggests that cosmic rays induce cell death in the outer nuclear layer of rats that have been flown in space.[92] In addition, research indicates that microgravity enhances apoptosis in astrocytes.[93] A significant rise in apoptosis in the photoreceptors of spaceflight mice compared to ground-control mice was observed in another study.[94] In a controlled in vitro experiment on primary Müller glia cells from adult rats, the natural antioxidants aloin and ginkgolide A flavonoids were assessed to clarify their protective role in the cultivation of Müller glia cells that were exposed to cosmic radiation. This radiation was simulated using cosmic galactic rays at the Brookhaven NASA Space Radiation Laboratory. The results revealed a favorable effect of antioxidants on the viability of Müller glia cells, as indicated by a decrease in ROS production within these cells.[95]

Although rodent models are invaluable for dissecting molecular pathways—including oxidative stress, blood retinal barrier disruption, and mitochondrial dysfunction—they are inherently limited for studying the pressure-induced structural hallmarks of SANS, such as choroidal folds and globe flattening. Rodents lack a robust, collagenous lamina cribrosa comparable to that of humans and non-human primates; consequently, their optic nerve head (ONH) does not experience the same translaminar pressure gradient mechanics that are thought to drive posterior globe deformation and folding of the chorioretinal layers in astronauts. Larger animal models that possess a true lamina cribrosa and human-like ONH architecture are therefore essential.[96–98] Integrating data from these anatomically appropriate models with the molecular insights gained from rodent studies will be critical for a comprehensive understanding of space-induced ocular pathology.

Screening

The astronaut selection program is extremely specialized. This intensive process is aimed at identifying candidates with strong physical and mental well-being. Ophthalmic examinations are a significant part of this selection, with the purpose of preventing eye-related incidents in space. Those with existing ocular conditions face a heightened risk of both physical and mental health issues, which could be more challenging to manage during long-duration missions.[2]

NASA performs comprehensive evaluations of candidates' visual capabilities (eg., uncorrected visual acuity, refractive error, near point of accommodation, near point convergence, IOP) employing specialized devices. NASA mandates a visual acuity of 20/20 in each eye, which can be accomplished through corrective interventions such as eyeglasses or refractive surgical methods. A majority of crewmembers experience presbyopia, with about 80% utilizing some form of vision correction.[2] All crewmembers undergo yearly eye examinations in addition to pre-flight, in-flight, and post-flight assessments to explore the physiological effects of spaceflight.[2] It is advisable that a minimum follow-up period of 2 years for brain and eye evaluations become standard protocol. Higher sampling during the initial mission return phase (2–3 months) could be extended to 6- or even 12-month intervals after one year.[22]

Clinical Manifestations

Table 1 lists the different ophthalmic clinical manifestations and concerns related to space environment. These items are separately discussed in other reports of AstroOphthalmology elsewhere.

In-Flight Evaluations

During missions, data gathering capabilities include vision questionnaires, visual acuity testing, Amsler grid testing, fundus photography, orbital ultrasound, and optical coherence tomography (OCT) (Table 2).[99]

Teleophthalmology and Artificial Intelligence

Teleophthalmology can connect spacecraft crews with specialists on Earth, facilitating assistance for ocular emergencies through high-resolution imaging instruments, including anterior segment cameras and fundus photography devices. These systems support detailed assessments that can be transmitted for expert analysis.[100,101] However, as missions extend into deep space, communication delays of up to 20 minutes will occur, necessitating onboard diagnostic autonomy and advanced remote healthcare approaches.[102] Regarding ocular health, the integration of diagnostic systems with artificial intelligence (AI) and teleophthalmology frameworks allows astronauts to execute initial evaluations and interventions on their own when Earth-based consultations are not immediately available. AI-driven decision support enhances the capabilities of astronauts by offering customized treatment options, minimizing reliance on terrestrial expertise, and facilitating prompt handling of ocular emergencies.[102,103]

Table 1 Pathological Manifestations and Concerns Related to Space Environment

Ocular Segment	Ophthalmic Manifestations/Concerns
Anterior segment	Dry eye disease Cataract Glaucoma Corneal traumatic and emergency conditions (abrasion, foreign body, edema, keratitis, perforation, chemical burn)
Posterior segment	Spaceflight associated neuro ocular syndrome (SANS) Retinal/choroidal detachment Retinal artery/vein occlusion Solar retinopathy

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Table 2 In-Flight Evaluation Tools

Evaluation Tool	Description
Vision questionnaire	*All crewmembers are tasked with completing the questionnaire. *Visual distortion, vision in low-light environments, variations in visual acuity, depth perception, double vision, temporary vision loss, and changes in near, intermediate, and distance vision, and also type of eyewear employed are asked. *Any changes should be reported as mild (not affecting daily activities), moderate (requiring modifications to complete activities), or severe (significantly impacting or obstructing daily activities).
Visual acuity testing and Amsler grid testing	*Far visual acuity is tested for each eye, both with and without corrective lenses, using a software application that is loaded onto the OCT laptop. The astronaut is positioned 15 feet away from the laptop during the test. *Near visual acuity is tested for each eye with and without corrective lenses. This is accomplished by placing a paper-based eye chart 16 inches from the astronaut. *Similar procedure is applied for Amsler grid testing to evaluate macula.
Fundoscopy and fundus photography	*Each eye undergoes dilated fundoscopy to acquire images of the retina and optic disc. These assessments are guided remotely through the use of a fundoscope and desktop streaming software technology, enabling recording of images and short video clips.
Orbital ultrasound	*Ocular ultrasound is carried out during the flight on days 30, 90, and 30 days prior to returning to Earth. *These in-flight sessions are managed remotely by sonographers in mission control. However, this process may have some degrees of transmission delay.
Optical coherence tomograph	*OCT is carried out before, during, and after space missions to monitor changes predominantly in the posterior segment of the eye. *While in flight, the OCT scans are conducted with subjects positioning their chin on a chin rest, as the device scans the eyes, enabling ground-support personnel to access the OCT laptop remotely. *Although OCT is not the first-choice method for assessing anterior segment on Earth, it can be utilized in space to examine this structure with appropriate instructions. *Notably, in December 2018, OCT angiography (OCTA) became available on the ISS.

Discussion and Future Perspective

Various pathophysiological concepts in this area are supported by strong evidence, while others remain unproven. Well-documented findings include the presence of optic disc edema, globe flattening, and chorioretinal folds in astronauts after extended missions; the dose-dependent increased risk of cortical cataract due to space radiation; the acute rise in intraocular pressure (IOP) upon entering microgravity; and the cephalad fluid shift confirmed by various imaging modalities. Emerging yet less validated theories consist of the glymphatic hypothesis associated with SANS, mitochondrial dysfunction as a primary cause of retinal damage, the impact of hypercapnia on optic disc edema, and the gradient-wise mechanical stress model of chorioretinal folds.

Given the limited opportunities for actual spaceflight, ground-based analogues are pivotal in exploring the pathophysiology of SANS and in evaluating countermeasures. The head-down tilt bed rest, which ranges from −6° to −15°, is the most widely used terrestrial model, consistently reproducing cephalad fluid shifts, choroidal thickening, and optic disc edema.[104,105] Dry immersion, which simulates the absence of support and the fluid redistribution typical of weightlessness, further mimics the cardiovascular and ocular responses observed in orbit.[106] Additional techniques include lower body negative pressure to counteract fluid shifts, parabolic flights for brief periods of microgravity, and short radius centrifugation to generate artificial gravity as a potential countermeasure.[107,108] These analogue environments, each with unique advantages and limitations, form the backbone of experimental SANS research and are crucial for developing both diagnostic protocols and preventive strategies for future lunar and Martian missions.

Studies show that shifts in fluid due to microgravity result in vascular congestion and a decrease in CSF outflow, potentially leading to a state of low-grade, chronic hypoxia in the optic nerve head and retina.[13,16] A novel trend that has recently emerged in the fields of astrobiology and space physiology research is gravitational dose-response modeling.[7,109]

This quantitative framework is designed to map the relationship between progressive alterations in the gravitational vector (referred to as the "dose" of gravity) and the resulting physiological changes (known as the "response"). Rather than considering microgravity as a simple binary state, this methodology employs graded tilt paradigms (for instance, from +45° head-up to −45° head-down) to create continuous response curves for hemodynamic, autonomic, and ocular variables. The fundamental concept is that various tissues and functions display unique thresholds and slopes regarding their sensitivity to gravity. Whittle et al[109] were the pioneers in applying this methodology to cardiovascular hemodynamics, revealing a significant gravitational dependence across a spectrum of variables—including heart rate, stroke volume, cardiac output, and autonomic indices—across a tilt range from 45° head-up to 45° head-down. Following this approach, Iftime et al[7] investigated the differences in visual performance during acute exposure to a microgravity analogue. They utilized simple reaction time tasks in the central and perimacular visual fields during vertical, bed rest, −6°, and −15° head-down tilt, constructing dose-response models that associate the gravitational component with visual function parameters. Their research uncovered that the perimacular (peripheral) retina is the first region to be functionally impacted by changes in gravity, while the central retina is the last to be affected. This gradient of topographical vulnerability has direct consequences for SANS, indicating that functional testing of the extra-macular retina—especially towards the optic disc—may allow for earlier identification of SANS-related pathologies compared to standard central visual assessments alone. The application of dose-response modeling in spaceflight ocular research provides various advantages: to begin with, it identifies the gravitational thresholds at which certain ocular tissues begin to demonstrate dysfunction; next, it facilitates a quantitative evaluation of countermeasure efficacy; and ultimately, it offers a predictive framework for estimating ocular risk during partial-gravity exposures on the lunar (0.16 g) and Martian (0.38 g) surfaces —settings for which empirical ocular data is notably lacking.

Tissues that are hypoxic are more prone to damage from radiation, as the efficiency of repairing DNA strand breaks caused by radiation is diminished in low-oxygen conditions.[62,82,85] Thus, the radiation exposure experienced during a mission may exert a more severe influence on ocular tissues that have already been compromised by the fluid dynamics associated with microgravity.

Both microgravity and radiation independently cause significant oxidative stress. Microgravity disrupts the function of mitochondria and compromises antioxidant defenses, while radiation directly creates ROS. Hence, it is crucial for future research to extend beyond the study of isolated risks. Future investigations should explicitly test the combined effects of radiation and microgravity in animal models.

Numerous countermeasures are presently under investigation to alleviate SANS. Lower body negative pressure (LBNP) has been demonstrated to decrease the diameter of the optic nerve sheath during head down tilt and to partially normalize choroidal thickness, thereby addressing the fluid shift aspect of SANS. Another promising strategy involves artificial gravity produced by short radius centrifugation, with or without exercise, which may help restore hydrostatic gradients and cardiovascular tone. Pharmacological agents, including antioxidants (such as cysteine and Ishophloroglucin A), have shown protective effects on retinal pigment epithelial cells in simulated microgravity, while radioprotectors are currently undergoing preliminary testing for the prevention of cataracts and retinal damage. Venoconstrictive thigh cuffs are designed to retain blood in the lower extremities and mitigate cephalad fluid shift, although their effectiveness on ocular health necessitates further investigation. Future countermeasures should be multi-targeted, including the development of pharmacological agents that can protect against oxidative damage from radiation and vascular stress due to microgravity. Additionally, it is essential to identify early predictive biomarkers in biofluids (for example, oxidative stress markers) that can signal ocular damage before it is clinically observable. The challenges posed by communication delays that prevent real-time telemedicine in deep-space missions have rendered the establishment of fully autonomous AI-driven diagnostic systems an essential requirement. These systems must be proficient in integrating OCT-A, fundus imagery, and biomarker data to provide astronauts with diagnostic and treatment advice without the involvement of Earth-based support.

The evidence presented in this review is constrained by notable limitations. To begin with, most human data is derived from a small group of astronauts, the vast majority of whom are male; the sex-specific differences in fluid regulation and radiation sensitivity are largely unexamined. Additionally, ground-based microgravity analogues only approximate the genuine spaceflight environment and do not replicate all features of weightlessness, particularly the

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absence of tissue compression and the complete range of fluid dynamics. Moreover, many mechanistic studies rely on animal models (mainly mice), whose retinal anatomy is different from that of humans, and on in vitro cell cultures subjected to simulated microgravity or simplified radiation protocols that may not capture the complex, mixed field radiation of deep space. Furthermore, longitudinal in-flight studies are limited; the timeline of SANS development is still poorly understood, and post-flight follow-up is often too brief to assess long-term reversibility. Finally, the small sample sizes and limited statistical power of many studies complicate the detection of small but clinically relevant effects. Future research should focus on larger, more diverse cohorts, direct in-flight measurements, and rigorous validation of analog models against actual spaceflight data.

Conclusion

The human eye is highly sensitive to the environment of space. This review has gathered evidence that illustrates how extended spaceflight poses a multifaceted threat to eye health, mainly through two interconnected pathways: the mechanical and hemodynamic effects resulting from cephalad fluid shift, and the direct and indirect damage to tissues caused by cosmic radiation. At the core of both pathways is the prevalent mechanism of oxidative stress and mitochondrial dysfunction, which injures cellular components and hinders the operation of vital tissues. With aspirations directed towards lunar and Martian missions, the risk of irreversible damage that could compromise vision is considerable. The clinical significance of these changes extends beyond individual astronaut health: even mild visual impairment can degrade task performance, reduce mission safety, and limit operational capabilities during extravehicular activities or planetary surface operations. As space agencies plan lunar habitats and crewed Mars missions, unrecognized or unmanaged ocular pathology could threaten the success of these endeavors. Therefore, future research must move beyond descriptive characterization and focus on actionable solutions, including development of integrated countermeasures that simultaneously address the mechanical effects of fluid shift and the molecular damage caused by radiation, identification and validation of early predictive biomarkers to enable pre-clinical detection of SANS and other space-related eye diseases, and establishment of autonomous, AI driven diagnostic platforms capable of operating without real time Earth support, which is essential for deep space missions.

Data Sharing Statement

All data reported in this study are publicly available.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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