Original Article

Journeying beyond the gravity and interstellar space: Unveiling the Health Challenges in space missions – An extensive review

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ABSTRACT

Background

Currently, space exploration and settlement are considered the future of humanity. It is significant to be aware of the risks and dangers that may arise and attentively plan the precautions before journeying to space. The effect of space stressors on humans is evolving research with implications for the future of space exploration and the well-being of astronauts. There have been space missions, and astronauts have taken initiatives to perform exercises and intense workouts to keep themselves healthy, but still, there were terrible consequences of prolonged exposure to the space environment. Therefore, the present review contemplates the short-term and long-term effects of space flights. This review also highlights that the well-being of astronauts or other personnel heading to space can lessen the long- and short-term impacts of exposure to space stressors. It comprehends and analyzes the advancement of medical knowledge in the area of space medicine.

Conclusion

The challenges will always be there for someone accustomed to the earth's atmosphere, but if these concerns are remembered and further research is conducted, would be beneficiary to the astronauts. Since the first space mission, the impacts of these pathological and physiological alterations have been recognized, even though the processes underlying them are unknown

Keywords

Astronauts, space journeying, space mission, space flight hazards, cosmonauts

Abbreviations used in this article

ASPP - Active Shielding Particle Pusher code
ATOH1 - Atonal bHLH transcription factor 1
ATLS - Advanced Trauma Life Support
BTAR - Bilateral tactile adhesive removal task
CBF - Cerebral blood flow
CLDN1 - Claudin 1
CSF - Cerebrospinal fluid
DCS - Decompression sickness
DLCO - Diffusing capacity for carbon monoxide
EEG - Electroencephalography
ELF3 - E74 like ETS transcription factor 3
EMG - Electromyography
EVAs - Extravehicular activities
FABP2 - Fatty acid-binding protein 2
HDBR - Human Developmental Biology Resource
ICP - Intracranial pressure
iDESIGN - iDESIGN Advanced WaveScan Studio
ISS - International Space Station
LBNP - Lower body negative pressure

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LDSF - Long-duration spaceflights
LEO - Low-Earth orbit
LASIK - Laser-Assisted In Situ Keratomileusis
MCA - Middle cerebral artery
MinION - Nanopore sequencing
MMP1 - Matrix Metallopeptidase 1
MRI - Magnetic resonance imaging
MUC 2 - Mucin 2
NO - Nitric oxide
OCT - Optical coherence tomography
SANS - Spaceflight Associated Neuro-ocular Syndrome
WMH - White matter hyperintensities

INTRODUCTION

Effect of the peculiar atmosphere and conditions in space compel astronauts to compromise their health, lifestyle, and emotional, psychological, and physical needs. Therefore, transitions are detected within the body, which develop because of the body systems responding differently in space compared to when on Earth. Space travel can lead to life-threatening symptoms such as hypoxia, blood redistribution, tachycardia, and cardiac issues. Understanding physiological responses is crucial for safety in high-altitude and space travel, necessitating precautionary measures[1].

Space stressors like microgravity, radiation, confinement, isolation, and sleep deprivation pose significant challenges to astronauts and cosmonauts during long and short-duration space flights (Figure-1). These stressors can cause complications in various systems, including cardiovascular, central nervous, digestive, reproductive, musculoskeletal, lymphatic, respiratory, and psychological (Figure-2). However, there is a lack of information on solutions to overcome these challenges. Space stressors challenge life's survival and adaptation. The International Space Station (ISS) uses omics technologies to study microorganism diversity and physiology. Multi-omics techniques like genomes, transcriptomics, proteomics, and metabolomics help understand microbes' reactions. Real-time monitoring of microbial populations, like nanopore sequencing (MinIOn), provides insights into stress responses and virulence factors[2].

Astronauts on low-Earth orbit missions face sleep challenges due to lack of a 24-hour cycle, external stressors, noise, temperature fluctuations, microgravity effects, noise disturbances, work stress, and regular use of sleep-promoting drugs[3]. Sleep in space is crucial for astronaut health and productivity, but it is influenced by radiation, microgravity, and circadian rhythms. NASA studies show insufficient sleep and disrupted circadian rhythms increase operational risks. On-orbit sleep monitoring uses subjective and objective approaches, with subjective evaluations providing information about the quantity and quality of astronauts' sleep and objective examinations using technology like eye movement tracking, EEG, EMG, and physical activity monitors like Actiwatch offer more accurate physiological data[4] .

Early adaptations like Space Adaptation Syndrome can cause symptoms like nausea and fluid redistribution. Long-term effects include musculoskeletal atrophy, cardiovascular changes, and neuro-ocular syndromes due to prolonged exposure to radiation and microgravity. Spaceflight occupational health risks include radiation exposure, exposure to harmful compounds, and physical demands of extravehicular activities (EVAs). Space suits increase the risk of decompression sickness (DCS) due to lower internal pressure[5]. Astronauts' exposure to high-energy cosmic radiation can lead to cancer, neurological diseases, neuroinflammation, behavioural issues, motor dysfunction, and cognitive decline. Antioxidants like selenium are being investigated for reducing oxidative stress[6] . Artificial microgravity can downregulate DNA repair and cell cycle, overexpress transcriptional regulation genes, and interfere with cancer cell cycles, suggesting potential therapeutic uses.

The aim of this review is to prioritize the wellbeing of an astronaut or other personals heading to space can lessen the long- and short-term impacts of exposure to space stressors. It also comprehends and analyses the advancement of medical knowledge in the area of space medicine and to provide evidence concerning the alterations that occur in astronauts while being exposed to severe conditions in space.

METHODS

All peer-reviewed online articles published until 2024 in indexed journals are referenced and utilized in this review.

Inclusion criteria: We have considered all articles published in the indexed journals in English that include observational studies, case reports, and experimental studies.

Exclusion criteria: We have contemplated the articles published in other languages, personal opinions of other astronauts, vlog posts, scientific articles which are published in non-indexed journals are excluded in our study.

Effect on Lymphatic System

Body fluids of cosmonauts collect in greater amounts towards the head and central regions forcing them to develop a puffy face due to their lymphatic system being impaired[7]. Physiological changes observed in this phenomenon are, the jugular vein transforms to having a turgid appearance, the subclavian vein's pressure is elevated, and the cerebral blood flow (CBF) rises brought on by an increase in transmural venous pressure. Increased fluid accumulation in the head and central region of the body also causes dehydrated extremities [8]. This is due to an impaired lymphatic system, causing fluid redistribution and increased cerebral blood flow. Space stressors also cause edema due to fluid movement shifts[7].

Effect on Gastrointestinal System

The lining of the gastrointestinal tract acts as a barrier to

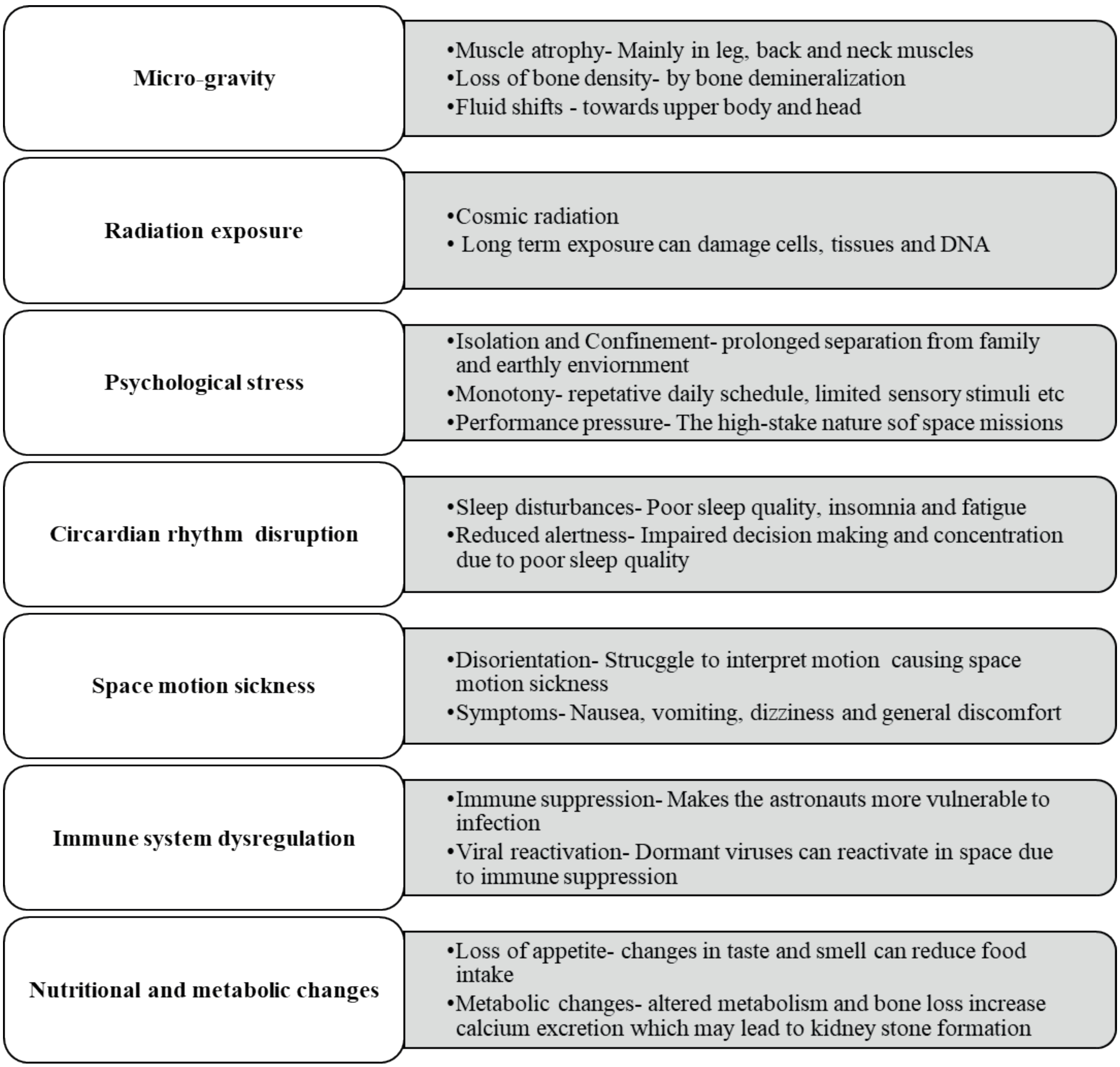

Figure 1. Types of Space stressors observed in space and its possible consequences on health

keep harmful substances out of the bloodstream. When this barrier is breached by external stressors, dysbiosis and increased intestinal permeability result[9] . Space inconveniences pose a significant threat to astronauts' gut, potentially leading to microbiome imbalances and increased vulnerability to hazardous substances. Gene expression and levels can help prevent disruptions. The downregulation of two proteins, ATOH1 and ELF3, is crucial for producing the mucus layer in the gastrointestinal tract[10].

The decrease in ATOH1 and ELF3 expression during spaceflight disrupts astronauts' gut barrier function, leading to a marginal reduction in MUC2 expression. Post-flight upregulations of MUC2, ATOH1, and ELF3 were observed, but the CLDN1 gene coding for Claudin-1, an essential gene to form tight junctions in the epithelial lining of stomach, drastically diminished on detection[11]. During spaceflight, astronauts may experience leaky gut due to increased intestinal lining porosity and decreased CLDN1 transcript (Figure-3).

Observations of animals during space missions reveal their body responses to microgravity, potentially preventing catastrophic events. Mice's colons showed a decrease in Mucin glycosylation genes, suggesting the space environment alters glycosylation patterns and potentially weakens the mucosal barrier. Additionally, RR-10 mice's colons expressed lower levels of FABP2 gene, a marker used to measure gut epithelium[12].

The study by Yao et al,[13] reported that probiotic bacteria Lactococcus cremoris and Bifidobacteria lungum were less common in RR-6 mice during flight, affecting gut microbiota balance and immune system homeostasis. Similar challenges faced by astronauts include dysbiosis and inflammation due to inadequate gene expression, highlighting the need for adaptation to harsh, alien environments

Effect on Cardiovascular System

Astronauts have been observed experiencing arrhythmias or irregular heartbeats, such as tachycardia, during both long and short-duration space flights, indicating physiological changes. Space radiation and microgravity can alter heart function, leading to irregularities in the cardiovascular system during space expeditions. This can result in decreased blood volume, ventricular atrophy, arrhythmias, increased arterial stiffness, and altered blood flow distribution[14]. As

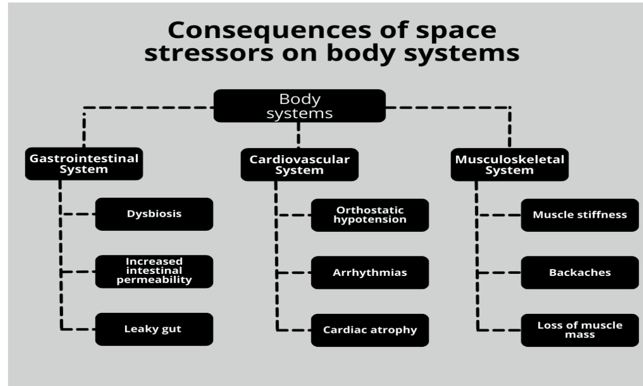

Fig.2: Consequences of space stressors on vital body systems

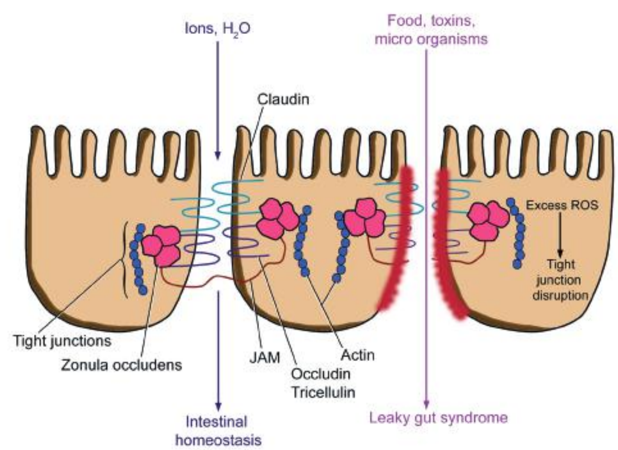

Figure 3. Schematic representation of tight junction disruption in gut epithelia and leaky gut syndrome. (JAM- Junctional adhesion molecule)

with parabolic flight, directly measured central venous pressure is also elevated during the high levels of acceleration launch period and upon assuming a launch position. However, it rapidly decreases upon entry into microgravity[15]. Astronauts experience orthostatic intolerance and hypotension upon returning to Earth, due to vascular structural changes. Approximately 83% of astronauts experience orthostatic hypotension after extended spaceflights, compared to only 20% after brief spaceflights[16].

Medications, such as statins, NSAIDs, and angiotensin converting enzyme inhibitors (ACE-Is and ARBs), are beneficial for astronauts due to their potential to heal cardiovascular diseases, reduce radiation exposure, and protect the cardiopulmonary system from damage caused by radiation. These medications can also help reduce vascular changes after radiation exposure[17].

Research on space radiation's impact on atherosclerosis in animals suggests long-term exposure may increase the risk of accelerated atherosclerosis through endothelial damage, pro-inflammatory reactions, cardiac dysfunction, myocardial fibrosis, and increased arterial stiffness[14]. The progress of atherosclerosis and the effect of space radiation could only be analyzed through animal studies since any compulsory examinations could be performed and its consequences could be monitored efficiently.

Effect on Musculoskeletal System

Spaceflights can cause significant injury to the musculoskeletal system, leading to bone loss and muscle mass loss, affecting astronauts' strength and future missions. Post-mission, bone loss persists for months, mainly affecting legs and spine. Back pain may develop quickly due to atrophy and disc swelling[18].

Muscle stiffness in astronauts is a common issue, but amorphous calcium carbonate, a dietary supplement on the International Space Station, can improve osteoblast and skeletal muscle function in microgravity and radiation environments, potentially preventing decreased bone density and muscle atrophy[19]. Amorphous calcium carbonate may enhance cell differentiation and performance, preventing radiation and microgravity damage to bone and muscle tissue, as demonstrated in a study by Guillaud et al[20].

Results showed that pedaling cadence changes with resistance and gravity, with higher gravity increasing cadence and lower resistance decreasing it. The CNS maintains stable motor output by fine-tuning muscular coordination. Nitric oxide(NO), derived from skeletal muscle, plays a role in muscle pathophysiology[21]. Urinary nitrogenous compound excretion increases after a few days in microgravity, which reduces muscle mass maintenance capacity.

Research shows that myostatin, an initial myokine in developing muscles, negatively regulates muscle growth. An animal study with the deficit of myostatin as in antibody-treated mice show increased muscle mass, suggesting lowering myostatin expression promotes muscle growth[22]. Myostatin depletion is thought to enhance myoblast proliferation and differentiation as well as muscle mass, according to additional research on the underlying mechanisms.

Effect on Reproductive system

When males are in an environment of microgravity, the motility of sperms decreases[23].

Female astronauts often use combined oral contraceptives for medically induced amenorrhea to manage menstrual bleeding during space flight. But these contraceptives can increase the risk of venous thromboembolism due to lower levels of serum albumin probably induced by estrogen and progesterone. During lengthy spaceflight, a female astronaut was diagnosed with occlusive deep vein thrombosis[24]. Humans exposed to 15 Gy (SI unit for radiation dose) of radiation may experience ovaries failing[25]. In males, radiation may lead to azoospermia and increased risk of genetic disorders. Microgravity affects endometrium decidualization in mice which in turn affects the implantation and pregnancy maintenance, and also embryonic stem cell growth[26]. Likewise in males the microgravity may results in lower testosterone level, and overall male reproductive health. Exposure to ionizing radiation increases sperm DNA fragmentation[27].

Effect on Respiratory system

It is essential to comprehend how microgravity affects the respiratory system in order to protect astronauts' health and safety during extended space missions. Gravity affects lung perfusion and ventilation, leading to unequal distribution in hydrostatic pressure gradients. Microgravity, experienced during parabolic manoeuvres or orbital flights, significantly changes these dynamics[28]. Fluid shifts and diaphragm compression decrease vital capacity and forced expiratory flows, but residual volume decreases over time, indicating more consistent alveolar emptying. Expectations of uniform ventilation are not met, and cardiac output changes. In microgravity, diffusing capacity for carbon monoxide(DLCO) increases, suggesting fully recruited pulmonary capillaries promote optimal gas exchange. Overall ventilation-perfusion matching becomes uniform[29].

NASA's study on astronauts' pulmonary nitric oxide (NO) levels revealed early airway inflammation that eventually subsided. Contrary to previous ideas, NO absorption in microgravity circumstances was not increased. During long-term space missions, exhaled nitric oxide levels declined significantly, with an average reduction rate of 0.55 mPa per 180 days. Tracking

NO levels is crucial for understanding astronauts' respiratory health, especially before exposure to hazardous planetary dust[30].

Effect on Central nervous system

The human body has special problems because of space exploration, especially with regard to physiological systems that control intracranial pressure (ICP) and cerebral hemodynamics. A study by Alperin et al,[31] examined that long-duration spaceflight is linked to a large increase in periventricular white matter hyperintensities (WMH) and ventricular cerebrospinal fluid (CSF) volume, but no significant alterations were found in deep WMH. An increase in ventricular CSF volume can cause high intracranial pressure (ICP) and change brain hemodynamic, altering blood flow and perfusion. These findings point to possible cognitive and visual impairments in astronauts, but the lack of deep WMH suggests that cognitive abnormalities are not largely ischemic in nature.

It is interesting to note that individuals with optic disc edema displayed a range of ICP variations, suggesting a complicated connection between ICP and space-related ocular abnormalities. Post-flight, an increase in cerebral blood velocity was also seen, which may have been affected by lower hemoglobin levels and was independent of changes in intracranial pressure[32].

Spaceflight significantly alters human brain morphology (Table-1), with effects becoming more noticeable on longer flights. The expansion of the right lateral and third ventricles occurs in the first six months of spaceflight, with ventricular enlargement plateauing after this time. Shorter recovery times may not allow the brain to fully recover. The volume of gray matter varies depending on the location, reflecting the brain's adjustment to microgravity. White matter may be more resistant to spaceflight impacts. Experienced astronauts' brain patterns of free water redistribution differ, indicating different structural reactions[33] .

EEG studies show increased alpha rhythm in parieto-occipital and sensorimotor regions in microgravity, while reduced motor cortex, vestibular system, and cerebellum rhythm are observed. Dry immersion studies confirm these findings, while the Human Developmental Biology Resource (HDBR) research shows opposing effects. Magnetic resonance imaging detects microgravity-induced changes, and long-duration spaceflight affects brain functioning and neuroplasticity[34].

The human brain's influence on emotions is fascinating, as it has been programmed from birth to contemplate the world around us. A study by Kent[35] suggests that the presence or absence of gravity can induce pessimistic or delightful feelings in an individual. A basic feature of thought and language is a preference for verticality, with "UP" being positive and "DOWN" being negative. Positive mental states, such as anxiety, hyperactivity, and mania, have less or negative value, while negative states, like sleep and relaxation, are positive. The intricacy of our experiences with verticality in the physical world is mirrored in the mental realm of verticality.

A study on 14 Russian astronauts found that 6 followed the blame-blame style, 5 were in the computing style, and 3 were in the placing style. Blamers are judgmental and quick to point out flaws, while placing blamers are timid and seek permission. Placings are emotionless and cool, expecting everyone to work effectively and follow guidelines[36] . Recent research reported that social isolation and radiation did not negatively impact fine motor skills in animals during tasks like the bilateral tactile adhesive removal task (BTAR). In some cases, the control group performed better, and Dual Flight stressors improved some deficiencies in the space radiation group[37]. However, prolonged social isolation may lead to hyper-focus or overstimulation, allowing animals to identify stickers more quickly and perform better on the BTAR. Secluding animals allowed them to focus on the task without distraction, and flight stressors improved their performance.

Effect on Special Senses

Astronauts returning from extended space missions often experience visual acuity, optic disc edema, globe flattening, choroidal folds, and hyperopic shifts, with some showing a hyperopic shift of +0.50 diopters or more[38].

Spaceflight-associated neuro-ocular syndrome (SANS) is a range of ocular abnormalities experienced by astronauts during long-term space missions. Initially, it was thought to be caused by increased venous pressures, but recent research found venous pressures in weightlessness were lower than those in supine settings on earth (Figure- 4).

MATLAB-based numerical modelling research shows that astronauts with larger preflight body weights experience a decline in central venous pressure and

Table-1 Comparison of effect of space flight on brain architecture and physiology

Study	Key findings	Effects on ICP	Effects on Cerebral Hemodynamics	Implications for SANS
Alperin et al.[31]	Increased periventricular WMH and ventricular CSF volume in astronauts on long missions; no significant changes in deep WMH.	Increase in ventricular CSF likely elevates ICP.	Possible disruption of blood flow and perfusion due to increased ICP.	Cognitive disturbances in astronauts may not be related to deep WMH, indicating other mechanisms may be involved in SANS.
Ken ichi Iwasaki et al. [32]	Post-flight cerebral blood velocity increased, with lower hemoglobin levels detected. ICP variations varied between those with and without optic disc edema.	ICP reduced in astronauts without edema.	MCA increased, possibly linked to lower hemoglobin.	Suggested varying ICP impact based on individual physiological responses
McGregor et al. [33]	Brain architecture changes, including ventricle expansion, gray matter volume alterations, elevated alpha rhythm, and increased swelling of lateral and third ventricles	No significant ICP increase reported.	Changes in brain structure impact cerebral dynamics.	Most changes occur early in flight, and different brain adaptations are observed with repeated exposure.
Marfia et al. [34]	Microgravity impacts cancer cell morphology, proliferation, and apoptosis, affecting brain tissue. EEG shows increased alpha rhythms, decreased motor cortex and cerebellar rhythms, and MRI shows major changes.	Not specifically addressed in the study.	Impact on metabolic pathways and cytoarchitecture in brain tissue.	Impacted neuroplasticity is important to comprehend SANS adaptations.

ICP- Intracranial pressure, SANS - Spaceflight Associated Neuro-ocular Syndrome, WMH- white matter hyperintensities, MCA- Middle cerebral artery

intracranial pressure (ICP) during weightlessness, which is linked to the incidence of severe acute non-traumatic shock syndrome. This decrease in pressure may cause ocular remodelling and SANS symptoms. Standard techniques like lower body negative pressure may not effectively counteract SANS[39]. As part of normal health screenings for astronauts returning from long-duration spaceflights (LDSF), NASA has done systematic eye tests, including optical coherence tomography (OCT) and magnetic resonance imaging (MRI) scans, to thoroughly record SANS since its discovery[5].

Vestibular system anomalies induced by microgravity result in space motion sickness, spatial disorientation, and movement problems. Astronauts have to rely more on visual cues because there is less sensory input from Earth's otoliths in orbit[6]. Microgravity has been linked to significant changes in the neurovestibular system, including the loss of gravity perception in the otoliths, which affects vestibular nuclei and cortical projections.

Effect on Immune system

Spaceflight significantly impacts the human immune system, exposing abnormalities in both innate and adaptive immune systems. Space missions enhance innate immunity, providing a comprehensive defense, while impairing adaptive immune responses. Chronic reactivation of latent herpesviruses and extended exposure to galactic radiation exacerbate hypersensitive reactions and allergy responses. To counteract these immunological alterations, a comprehensive countermeasure plan involving dietary supplementation, exercise, and pharmaceutical therapies is necessary, including immune function support and virus reactivation prevention[40] .

Solutions to complications in space

The International Space Station's emergency plan for lunar missions could be applied to lunar missions, involving stabilizing astronauts using Advanced Life

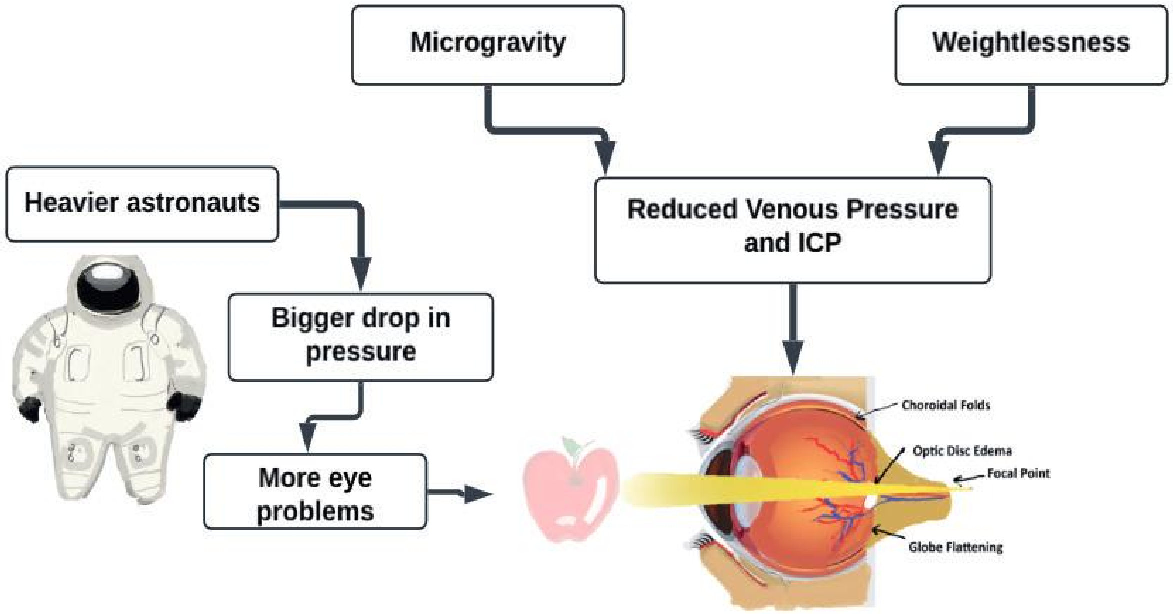

Figure 4. Mechanism of Spaceflight-Associated Neuro-Ocular Syndrome (SANS) and its relation to microgravity and weightlessness.

Support Pack and Advanced Trauma Life Support (ATLS) techniques and evacuating them back to Earth for medical care[41] . Effective nursing care in orbit requires careful planning and consideration of space environment constraints, with specialized training programs and modifying nursing practices ensuring the best care for space travellers[42] . NASA and partners created the Active Shielding Particle Pusher code (ASPP) to analyze potential active shielding architectures[43].

Viewports offer astronauts psychological comfort and physiological benefits, but also have disadvantages like financial costs, reduced station structural integrity, potential loneliness, confusion due to spin, and disruptions to sleep and wake cycles[44] . NASA's Webb Telescope has revolutionized ophthalmology by improving the accuracy and efficiency of measuring ground mirrors, while the Infrared Scanning Shack Hartmann System and iDESIGN system have improved safety and precision of LASIK procedures[45]. The Handheld Bioprinter, developed for astronauts, can treat in situ wounds in a floating in-space environment[46].

CONCLUSION

Spaceflight involves various categories with unique challenges, including Low Earth Orbit (LEO) missions, suborbital flights, exploration-class missions, and commercial spaceflight. Medical requirements ensure safety, while commercial spaceflight and space tourism follow less stringent regulations. Early adaptations can cause symptoms; long-term effects include musculoskeletal atrophy, cardiovascular changes, and neuro-ocular syndromes. Prolonged exposure to microgravity and radiation leads to gene levels falling, causing dysbiosis and leaky gut syndrome in cosmonauts until their return to Earth.

Many people hope to embark on the once-in-a-lifetime experience of space travel in the future. Humanity's aspirations extend beyond space exploration; in order to realize that goal of starting a new life in an unknown location, it is important to be aware of the risks involved in traveling beyond the speed of light and into interstellar space. For someone who is used to the earth's atmosphere, the difficulties will always exist, but if these issues are kept in mind and additional research is done, there may be no end to the problems' solutions. Although the mechanisms underlying these pathological and physiological changes are unknown, their effects have been observed since the first space expedition.

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