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Review

Physiological Effects of Microgravity (Weightlessness) on Bone, Muscle, Immune and Endocrine Systems: A Narrative Review

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Abstract

The human body is evolutionarily adapted to function under the constant presence of Earth's gravitational field. Consequently, outside this environment, the transition to the microgravity of spaceflight triggers a cascade of physiological and cellular adaptations. At the cellular level, the absence of gravitational loading disrupts fundamental mechanotransduction pathways. This review synthesizes current evidence on how these altered biophysical conditions provoke profound biological remodeling, drawing on four complementary sources of evidence: human spaceflight, human ground-based analogs such as head-down tilt bed rest and dry immersion, animal spaceflight experiments, and ground-based simulated microgravity in vitro. Specifically, we highlight how the unloading of weight-bearing tissue accelerates progressive bone demineralization and muscle fiber atrophy. Furthermore, gravity-dependent cephalad fluid shifts and disrupted sensory inputs contribute to acute neuro-vestibular disturbances, including space motion sickness and compromised spatial orientation. Beyond structural and sensorimotor degradation, this paper examines broader systemic responses, such as immune system dysregulation, chronic inflammation, and persistent endocrine dysfunctions involving stress hormone elevation and compromised fertility. Elucidating how these microgravity-induced adaptations transition from acute compensatory responses to chronic maladaptive changes is essential for developing countermeasures, ensuring astronaut health during long-duration deep space exploration, and advancing space biology.

Keywords: microgravity; physiological adaptation; deep space exploration; bone loss; skeletal muscle atrophy; immune dysregulation; endocrine adaptation; mechanotransduction; countermeasures

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1. Introduction

Human survival and performance in space are challenged primarily by three factors, namely altered physical forces, exposure to cosmic radiation, and psychological and chronobiological stressors. First, the weightlessness condition, alongside altered electromagnetic conditions, perturbs biological systems at all scales, from molecular signalling pathways to whole-body physiology [1]. Microgravity disrupts

mechanotransduction, accelerates musculoskeletal degradation, alters cardiovascular dynamics, and compromises sensorimotor integration (Figure 1). These multisystem perturbations represent one of the central biomedical challenges of long-duration spaceflight [2].

Second, the presence of ionizing radiation from cosmic rays can induce DNA damage, genomic instability, inflammation, and a cumulative carcinogenic risk. Radiation exposure could become increasingly critical during potential missions to Mars and other deep-space destinations, where shielding may be limited and transit times could extend over months to years.

Finally, physical isolation, confinement, and monotony, combined with disrupted light/dark cycles, pose significant threats to behavioural health and cognitive performance. Dysregulation of fundamental circadian rhythms affects sleep architecture, mood stability, hormonal homeostasis, and overall mission readiness. These psychological stressors may interact synergistically with physiological challenges, amplifying their impact on crew well-being [2].

Gravity is the only environmental parameter whose magnitude and direction have remained essentially constant throughout the evolutionary history of life on Earth; other major physical determinants of life, such as the intensity, spectral composition and distribution of solar radiation, have varied substantially over geological time [3]. For this reason, gravity has profoundly influenced biological evolution, which is still an ongoing process. Its effects impact all levels of biological organization, from molecular interactions to cells, tissues, organs and whole organisms, and extend to the interactions among organisms of the same or of different species. Notably, both real microgravity and ground-based simulated microgravity have been shown to alter cytoskeletal architecture, cell morphology, gene expression and protein synthesis, although the degree of concordance between them varies considerably across cell types and endpoints [4–6]. However, the precise mechanisms by which gravity influences biological systems remain a subject of active debate [7].

Specific gravity-sensing mechanisms have been identified in plants [7]; however, in mammalian cells, neither specialized gravity-sensing organelles nor dedicated cellular structures have been conclusively identified. From a physical perspective, theoretical models initially predicted that alterations in gravity would not directly affect cellular processes, given that gravitational forces are several orders of magnitude weaker than those governing macromolecular interactions [8]. Consequently, early interpretations mistakenly attributed cellular responses to gravity to indirect effects mediated by changes in the surrounding physical environment, such as fluid dynamics and mass transport [9].

Accordingly, during the early phases of space exploration, the sensitivity of living structures to gravity was largely ascribed to indirect responses to altered macroscopic biophysical conditions rather than to direct, cellular-based gravitational sensing mechanisms [2]. To date, no definitive evidence has been provided to explain how isolated cells could directly detect gravitational accelerations within the 0–1 g range. Physics-based models continue to suggest that reduced gravity alone should exert negligible direct effects at the cellular scale.

Nevertheless, experimental evidence obtained in both real and simulated microgravity demonstrates that reduced gravitational loading induces significant biological changes, including alterations in cell shape, signal transduction pathways, cell division, gene expression, DNA integrity, and cytoskeletal organization [4,10,11]. It should be stressed that these two classes of evidence are not equivalent. Spaceflight experiments expose cells to genuine free fall, but also to launch and re-entry accelerations, ionizing radiation and prolonged storage before analysis; ground-based simulators

eliminate the confounders but never eliminate gravity while introducing shear stress of their own [12].

Organisms sense and adapt to changes in gravity through two distinct pathways: either by feeling it directly through built-in biological sensors, or indirectly by reacting to changes in their physical environment.

Direct mechanisms involve specialized structures capable of detecting changes in the gravity vector, such as statoliths, mechanosensitive ion channels, and vibratory cilia, which are present in plant cells and in specific mammalian sensory organs, such as the cochlea.

Indirect mechanisms stem from gravity-dependent physical changes, including altered sedimentation rates, reduced or abolished shear stress, diffusion-limited nutrient transport, changes in osmotic pressure, suppression of hydrostatic gradients, and hypoxic microenvironments.

Human exposure to the space environment triggers a cascade of physiological adaptations driven primarily by microgravity. To understand these multisystem perturbations, this review will examine specific readaptations, including musculoskeletal degradation marked by bone demineralization and muscle atrophy; immune system dysregulation leading to chronic inflammation and cellular senescence; and profound endocrine alterations characterized by fluid-shift-induced stress hormone elevation, insulin resistance, and compromised fertility.

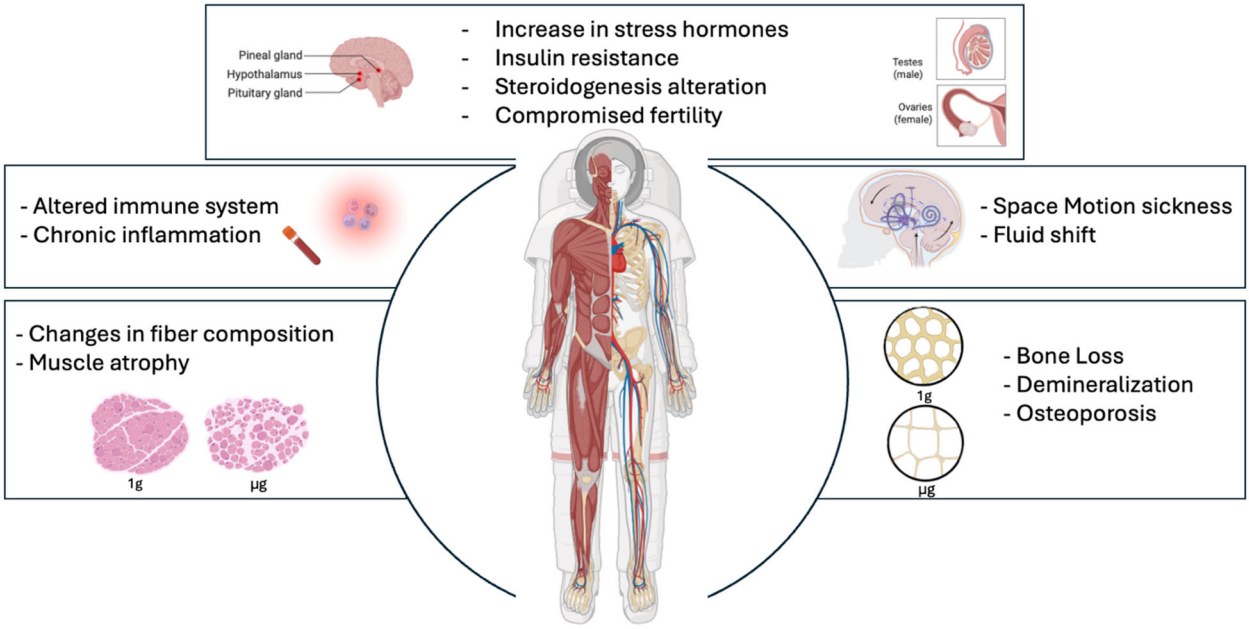


Figure 1. Exposure to microgravity perturbs human biological systems at multiple structural and functional levels. The altered physical forces disrupt mechanotransduction and induce a cephalad fluid shift, which contributes to neuro-vestibular disturbances and space motion sickness. The unloading of the musculoskeletal system accelerates degradation, leading to progressive bone demineralization and muscle atrophy. Furthermore, the combination of weightlessness and other spaceflight stressors triggers broader physiological responses, including immune system alterations, chronic inflammation, insulin resistance, and endocrine dysfunctions such as increased stress hormone levels and compromised fertility. Effects shown are drawn from different experimental platforms and are not all documented in humans in flight: bone demineralization, muscle atrophy, cephalad fluid shift, and space motion sickness are established from human spaceflight; insulin resistance and low-grade inflammation are supported by human spaceflight and human ground-

based analogs; alteration of fertility rests on rodent spaceflight and on simulated microgravity in vitro.

The systems examined in detail below—bone, skeletal muscle together with the neurovestibular system, the immune system and the endocrine system—are those for which the withdrawal of mechanical loading can be identified as the proximate cause of the observed adaptation, which is the unifying argument of this review. Other systems undergo substantial and clinically relevant change in weightlessness, in particular the cardiovascular system, the central nervous system and the gastrointestinal tract; these are summarised in a dedicated section below, and the reader is referred to the specialised reviews cited there for a full treatment.

2. Methods: Literature Search and Selection Strategy

A comprehensive literature search was conducted utilizing the PubMed database to identify peer-reviewed articles focusing on the physiological adaptations of the musculoskeletal, immune, and endocrine systems under microgravity and weightlessness conditions. This is a narrative review and was not conducted as a systematic review; no PRISMA protocol was registered. Searches were run in PubMed/MEDLINE, covering the period from 1960 to 2026 and restricted to publications in English, and were last updated in October 2026. The search combined three concept blocks with the Boolean operator AND: an exposure block (weightlessness OR microgravity OR "simulated microgravity" OR spaceflight OR "space flight" OR "head-down tilt" OR "bed rest" OR "dry immersion" OR hypogravity); a system block (bone OR "bone resorption" OR osteoclast OR osteoblast OR osteocyte OR muscle OR "muscle atrophy" OR vestibular OR "motion sickness" OR immune OR lymphocyte OR inflammation OR endocrine OR cortisol OR thyroid OR testosterone OR "parathyroid hormone"); and, for the mechanistic literature, a mechanism block (mechanotransduction OR cytoskeleton OR "signal transduction"). The reference lists of the retrieved reviews were screened manually for further sources. To construct a rigorous and historically grounded narrative, the search and selection criteria integrated two complementary tiers of literature:

- Foundational Benchmark Studies: Seminal and historical works establishing the core physiological responses and theoretical frameworks of space biomedicine (e.g., early cell mechanics, classic endocrine and fluid shifts, and foundational bed-rest/spaceflight data published between the late 1980s and the 2000s).
- Contemporary Advancements: Recent peer-reviewed articles, consensus papers, and systematic reviews published over the last several years to capture modern insights into cellular mechanobiology, molecular pathways, and multi-system dysregulations.

Articles were selected based on thematic relevance, methodological rigor, and their specific contribution to understanding the core targeted systems (bone, muscle, immune, and endocrine). Studies lacking peer-reviewed validation or addressing physiological systems outside our primary scope were excluded.

Throughout the manuscript, the terminology recommended by Herranz et al. is used: "microgravity" is reserved for spaceflight and free-fall platforms, "simulated microgravity" for ground-based devices such as random positioning machines, clinostats and magnetic levitation systems, and ground-based analog" for human unloading models such as head-down tilt bed rest and dry immersion. "Partial gravity" refers to lunar and Martian gravity levels [12]. Where a finding derives from a single class of platform, this is stated in the text and in the table and figure legends.

3. Multisystem Effects of Weightlessness: Time Course of Adaptation

In a human orbital spaceflight, during the initial phase of microgravity exposure (<3 weeks), a pronounced cephalad fluid shift occurs due to the absence of hydrostatic gradients, meaning that fluids shift up toward the head. This redistribution increases central venous pressure and intracranial fluid volume, contributing to facial edema, altered ocular morphology, and potential elevations in intracranial pressure. Concurrently, disruption of the vestibular apparatus results in neuro-vestibular disturbances, including spatial disorientation, impaired sensorimotor integration, and space motion sickness. In addition, the unloading of the musculoskeletal system initiates bone demineralization through an imbalance between osteoblastic and osteoclastic activity.

With continued exposure (3 weeks to 6 months), these alterations become systemic. The cardiovascular system undergoes progressive deconditioning, characterized by decreased plasma and stroke volume, impaired baroreceptor sensitivity, and orthostatic intolerance upon return to 1 g.

During long-duration missions (≥6 months), these physiological perturbations may evolve into chronic and potentially mission-limiting conditions.

Yet, although gravity-dependent physiological effects are of relevant clinical importance, perturbations at the molecular level also play a significant role. As previously shown, 24 h of exposure to microgravity on a random positioning machine results in disruption of cell shape uniformity, leading to the emergence of diverse morphological phenotypes [13,14]. Changes in a cell phenotype occur under the influence of external and internal stimuli of a biochemical and/or physical nature, including gravity [15].

4. Theoretical Framework: Gravity as a Physical Constraint on Cell Fate

The paragraphs that follow set out why gravity may be treated as a physical constraint on cell fate rather than merely as a mechanical load, and why the withdrawal of that constraint allows biological systems to access organizational states that are not available at 1 g. This argument underlies the system-specific sections that follow, in which the loss of gravitational loading is the common starting point.

Living organisms are systems far from thermodynamic equilibrium that can spontaneously self-organize into structures that exhibit oscillations, waves, and patterns [16]. Pattern formation is at the core of relevant biological processes like differentiation, morphogenesis, and even cancer transformation. In all of these conditions, when the system approaches a bifurcation point, which in principle would allow access to different phenotypes, the critical role of the forces that are expressed by the field becomes prominent and can drive the overall process into a deterministic outcome [17].

The gravitational field provides the physical constraints that can prevent the emergence of chaotic behavior and finalize the biological process toward a specific, stable attractor. This has been demonstrated in animal and human cells lines exposed to simulated microgravity on RPM, in which the population segregated into two distinct phenotypes: adherent and floating cells. Because the RPM does not abolish gravity but randomizes its direction, and because it generates shear stress and convection within the culture chamber, this symmetry-breaking observation requires confirmation in orbital flight before it can be attributed to weightlessness as such [5,18].

Building on the theoretical framework established by the physical chemist Ilya Prigogine (awarded the 1977 Nobel Prize in Chemistry for his work on non-equilibrium thermodynamics) and the chemist Dilip Kondepudi, complex systems can be evaluated far from equilibrium.

According to Kondepudi and Prigogine, a system that potentially can be partitioned into two distinct attractors collapses into a unique configuration when exposed to gravity that "selects" from two possibly accessible states [19]. A symmetry-breaking transition is such that in the absence of an external driving force, such as gravity, each of many possible final states can be reached with equal probability [16,20]. Microgravity can be conceptualized as a unique physical condition in which a fundamental constraint (belonging to the field in which living organisms operate) has been modified, allowing biological systems to explore alternative organizational states.

A practical example of fluctuation is represented by cytoskeletal dynamics, whose structural properties have been described through mechanical models of eukaryotic cells, including their viscoelastic response, power-law stress relaxation, and fluidization under mechanical load. Within this theoretical framework, the cellular system is defined as out-of-equilibrium and dissipative. A bifurcation parameter has been identified, enabling the prediction of qualitatively distinct deformation scenarios within a representative cell volume, which may correlate with phenotype changes observed in vitro following exposure to simulated microgravity [21].

Alterations in cytoskeletal architecture can disrupt numerous cellular processes, including signaling, proliferation, and apoptosis [1,22]. Under microgravity conditions, such perturbations may contribute to wide-ranging biological adaptations, including adaptive phenotypes that are incompatible with survival during spaceflight. Importantly, these cellular and molecular changes scale upward to affect tissue integrity, organ function, and ultimately astronaut health and mission performance. Indeed, quantitative risk assessments indicate that while early space missions such as the Apollo program achieved crew survival probabilities exceeding 98% and mission success rates of approximately 75%, projections for long-duration interplanetary missions revealed substantially higher risks. In particular, proposed Mars mission profiles showed mission success probabilities below 10% and crew survival chances under 50%, with early estimates of cancer mortality risk associated with space radiation ranging from 400% to 1500% (meaning astronauts could face a 4- to 15-fold higher risk of dying from radiation-induced cancer compared to the terrestrial baseline risk of unexposed populations) [23].

In light of these projections, it is critical to anticipate the biological impact of prolonged exposure to the space environment and to identify effective mitigating strategies prior to the implementation of long-distance, long-duration space travel.

Accordingly, this review examines the available literature on human spaceflight experiments, summarizes current knowledge on the effects of living in space across both short- and long-duration missions, and discusses existing countermeasures as well as future directions for medical research in space [24].

5. Bone

The musculoskeletal system has adapted to Earth's gravity throughout evolution; therefore, any change in the gravitational environment has a direct impact on bone and muscle structures, which attempt to compensate and adapt to altered external stimuli. At normal gravity, bone remodeling is a tightly regulated process in which bone resorption and bone formation are balanced to maintain skeletal homeostasis [25]. Maintaining bone mass depends on the equilibrium between osteoblast-mediated bone formation and osteoclast-mediated bone resorption during the normal bone remodeling cycle. This equilibrium is disrupted in the space environment [25].

At the cellular level, osteocytes, the primary mechanosensory cells embedded within the bone matrix, rely on fluid shear stress through the lacunocanalicular network to detect mechanical loading. In microgravity, this fluid flow is severely diminished, triggering a cascade of molecular shifts that uncouple the bone remodeling cycle [26].

This lack of mechanical signaling alters osteocyte gene expression, simultaneously hyperactivating osteoclasts and suppressing osteoblasts through two primary pathways:

- The RANKL/OPG Axis: Microgravity upregulates the expression of Receptor Activator of Nuclear Factor Kappa-B Ligand (RANKL) in osteocytes and osteoblasts, while simultaneously downregulating its decoy receptor, Osteoprotegerin (OPG). This shifts the RANKL/OPG ratio heavily in favor of osteoclastogenesis, dramatically accelerating bone resorption [25–27].
- The Wnt/β-catenin Pathway: Osteocytes in microgravity significantly upregulate the expression of the SOST gene, which produces sclerostin. Sclerostin is a potent secreted glycoprotein that binds to LRP5/6 receptors on osteoblasts, actively antagonizing the Wnt/β-catenin signaling pathway. The suppression of Wnt signaling directly inhibits osteoblast proliferation, differentiation, and survival, effectively shutting down new bone formation [26,28].

The interaction via the above-described pathways is schematized in Figure 2.

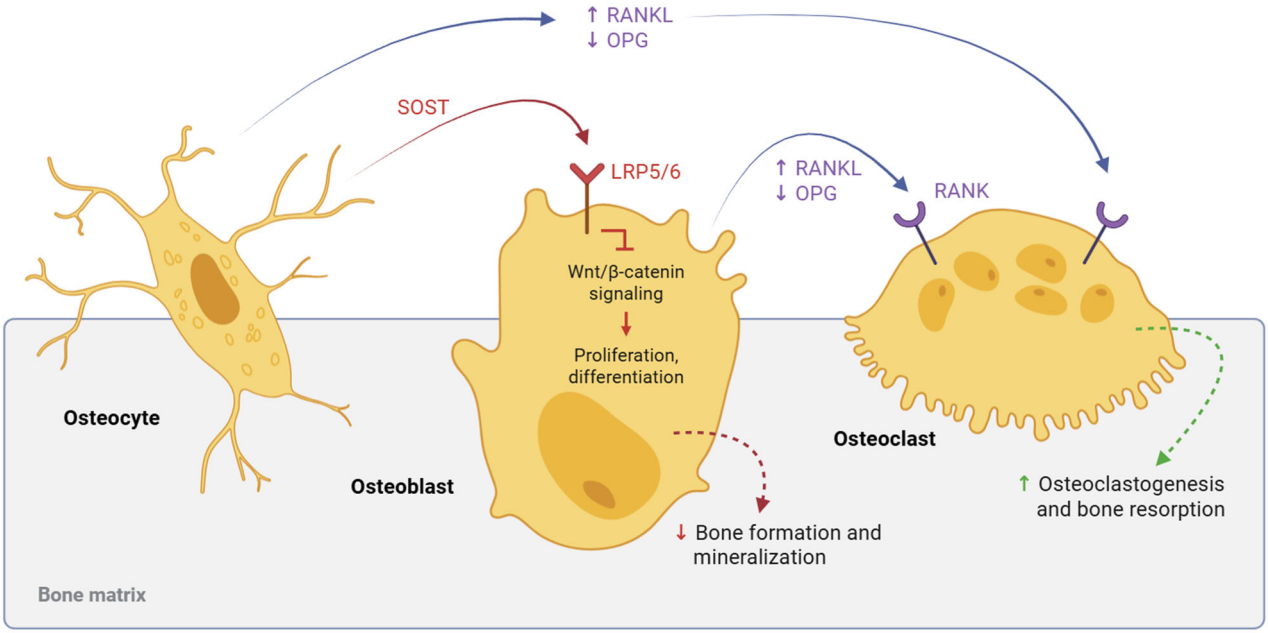


Figure 2. Microgravity effects on bone remodeling: osteocytes alter osteoblast and osteoclast activity via the specific RANKL/OPG and Sclerostin/Wnt molecular pathways.

Bone loss is a well-documented phenomenon occurring in humans during both short- and long-term spaceflights. The main consequence of prolonged exposure to real microgravity is a bone loss of approximately 1–2% per month in astronauts [29]. The impact of microgravity on the skeletal system mimics osteoporosis, a condition characterized by reduced bone mass and altered bone microarchitecture. However, in microgravity, these changes occur more rapidly due to disuse of the skeletal–muscle system.

Spaceflight-induced bone loss preferentially affects the weight-bearing skeleton of the lower limbs and the spine because of the substantial reduction in mechanical loading; as set out below, it should not be equated with terrestrial osteoporosis. Under normal conditions on Earth, bones are constantly exposed to mechanical stimulation through static gravity-induced weight-bearing, opposing ground reaction forces, and dynamic loading generated by muscular contractions during locomotion. Because of this, physical exercise is essential for increasing or maintaining bone mass and strength on Earth [30]. In contrast, weightless conditions in space reduce mechanical loading on weight-bearing

bones, resulting in adaptive changes that increase bone resorption and inhibit bone formation [29].

Bone resorption is particularly exacerbated during the first two weeks of spaceflight, as evidenced by increased urinary concentrations of bone resorption markers such as N-telopeptide and pyridinium crosslinks. Concurrently, urinary calcium excretion increases, indicating reduced calcium retention in astronauts. Because bone formation is unchanged or decreased, this leads to an overall negative calcium balance that contributes to bone loss in space [28]. Consistently, bone mineral density (BMD) studies in astronauts demonstrate significant decreases in weight-bearing bones such as the tibia, whereas non-weight-bearing bones like the distal radius remain largely unaffected [26].

Because spaceflights are infrequent and costly, on Earth, head-down tilt (HDT) bed rest at a 6° angle, corresponding to approximately 0.1 g, has become the standard human-based ground analog for spaceflight deconditioning, and dry immersion is increasingly used as a complementary model that additionally reproduces supportlessness. These are analogs of the physiological consequences of weightlessness [31,32].

In a 35-day bed rest study, bone density measurements performed two weeks after exposure revealed reductions in cancellous bone mass, with losses of 1% in the distal femur, 3% in the patella, and 2% in the distal tibia, while no changes were observed in the distal radius [33]. Furthermore, after 56 and 90 days of bed rest, bone mass in the distal radius remained unchanged, whereas bone mass in the distal tibia declined by 3.6% and 6%, respectively. Cortical bone thickness and density decreased by less than 2% even after 90 days of bed rest [34]. As bone loss progresses, an increased risk of kidney stone formation arises due to elevated urinary calcium excretion, both in bed rest studies and during spaceflight [35].

Furthermore, recent simulated microgravity experiments indicate that this environment directly impairs the terminal stages of bone formation. The lack of mechanical loading inhibits the differentiation of mature osteoblasts into osteocytes and disrupts the assembly of extracellular matrix components, actively preventing matrix mineralization [36]. Therefore, microgravity-induced bone loss is a dual-threat cellular response: it not only unleashes aggressive osteoclast resorption but fundamentally paralyzes the osteogenic and mineralization capabilities of bone-forming cells.

Because terrestrial osteoporosis and spaceflight bone loss share the endpoint of reduced bone mass, they are frequently compared to each other. However, there are some important differences that make this condition particular in each environment.

Terrestrial osteoporosis is a systemic skeletal disease of reduced bone mass and deteriorated microarchitecture. It affects predominantly postmenopausal women and older men, and it is an age-related decline in osteoblast function [37].

Spaceflight-induced bone loss occurs in healthy adults who are not osteoporotic and who typically return to Earth with bone density still within the normal range for their age [38,39].

It is mechanically driven rather than hormonally driven, and it is concentrated at loaded sites, such as the proximal femur, hip, lumbar spine, and tibia [40].

Countermeasures based on exercise have shown limited effectiveness in preventing bone loss during spaceflight [41,42]. However, more recent resistive exercise devices, when combined with dietary interventions, have demonstrated some promise in attenuating BMD loss [43]. Despite near-daily exercise before, during, and after missions, substantial bone loss still occurs, highlighting the challenge of providing adequate skeletal loading in microgravity. This difficulty is further compounded by shared equipment and the need for individualized training programs to preserve bone and muscle integrity [44]. Conclusively, physical activity before and during flight remains a critical, yet incomplete, countermeasure [45].

6. Muscle and Neurovestibular Systems

The effects of microgravity on neuromuscular and neurovestibular systems after long term exposure is still a major concern.

Decreases in muscle mass, strength, and endurance are primary changes that occur in individuals during long-duration space missions, with pronounced muscular atrophy in antigravity extensor muscles, such as the soleus, gastrocnemius, and quadriceps, significantly more than flexor muscles or upper body musculature. These changes are accompanied by shifts in muscle fiber composition and reduced force-generating capability [46]. Specifically, at the cellular level, microgravity induces selective muscle fiber atrophy, with slow-twitch (Type I) fibers generally exhibiting greater cross-sectional area loss compared to fast-twitch (Type II) fibers. This is accompanied by a structural shift in myosin heavy chain phenotype from slow, oxidative fibers to fast, glycolytic isoforms, which heavily contributes to reduced force-generating capability and increased fatigability [46]. Furthermore, skeletal muscle recovery after spaceflight is a prolonged process. While some functional stabilization occurs within the first few weeks back on Earth, specific data indicates that full restoration of muscle volume, fiber size, and pre-flight peak power can take anywhere from several weeks to over three months, depending on the mission's duration and the efficacy of applied in-flight and post-flight countermeasures [46].

Recent experimental data from five astronauts, assessed at multiple timepoints across a long-duration mission, provide new insight into these adaptive phenomena [47]. In this study, astronauts performed quiet standing tasks post-flight, meanwhile the center of foot pressure (CoP) was computed from three-dimensional ground reaction forces (Fx, Fy, Fz) and moments (Mx, My, Mz). Results demonstrated post-flight modifications in muscle synergies, specifically in the structure of muscle-weighting vectors, indicating that the coordination patterns used on Earth were reorganized following spaceflight. These alterations were interpreted as reflecting neurophysiological plasticity in muscle activation induced by prolonged weightlessness, rather than merely biomechanical adaptation.

On Earth, the postural control system maintains bipedal stability by modulating motor commands to counteract gravitational toppling torque. In microgravity, the absence of this gravitational constraint promotes both morphological and neurophysiological remodeling within the neuromuscular system [47,48].

Transitions from microgravity to partial-gravity environments—such as the Moon (0.16 g) or Mars (0.38 g)—place additional demands on the motor control system and may increase the risk of operational decrements or injury in settings with limited medical support. Consequently, neurophysiological biomarkers derived from muscle synergy analysis have been proposed as functional indicators for monitoring astronaut condition and for guiding rehabilitation and training following long-duration missions. [49]

In parallel with neuromuscular changes, the neurovestibular system undergoes substantial reorganization during spaceflight. Space Motion Sickness (SMS), first described during Vostok II in 1962 [50], is one of the most prevalent clinical conditions during the initial days of exposure to microgravity. Approximately 70% of astronauts experience SMS during spacecraft operations or parabolic flights, with about half of the cases rated as moderate to severe [51,52].

The main functions of the neurovestibular system are spatial orientation, maintenance of balance, and stabilization of vision through the vestibular–ocular reflexes. Although symptoms typically resolve within three days in microgravity and post-flight recovery occurs rapidly, SMS can significantly impair operational readiness. Two principal mechanisms have been proposed to explain SMS: the fluid-shift theory and the sensory-conflict theory [53]. The fluid-shift model posits that cephalad redistribution of

body fluids alters vestibular receptor responses, potentially through endolymphatic duct distension or pressure effects on the eighth cranial nerve, thereby inducing SMS. By contrast, the sensory-conflict theory attributes SMS to a mismatch among visual, proprioceptive, and vestibular inputs when the terrestrial gravity-based sensory relationships are disrupted in microgravity.

Given that the neurovestibular system governs spatial orientation, balance, and gaze stabilization, disturbances in these functions can have profound implications for astronauts' well-being and task performance.

7. Immune System

On Earth, immune cells are strongly influenced by mechanotransduction processes, which make them sensitive to gravitational forces that are converted into biochemical signals [54].

The immune system, both innate and adaptive, undergoes a profound reshaping in microgravity conditions, where these signals are disrupted, leading to altered cellular behavior and an acceleration of cellular aging. [55,56] Significant alterations are observable both after long spaceflight and during simulated-microgravity experiments, namely immune exhaustion, immune senescence, and inflammation [55].

These processes are strictly related: the continuous stimulation of leukocytes makes them less prone to react, and it will start increasing inhibition systems within the cells (immune exhaustion) [57–59].

As a consequence of inhibition, mitochondrial functionality is compromised to prevent leukocytes from replicating efficiently [58,60–62].

Finally, the persistent state of basal inflammation leads to a decline in the immune system, through a mechanism that mimics the natural decline seen in the elderly [63].

Together with leukocytes, lymphocyte activity has also been investigated under microgravity conditions. Studies performed both on-ground and using microgravity simulators demonstrated that lymphocyte activity drops significantly with suppressed production of antibodies like IgG and IgM. This effect starts at 72 h and could last up to 20 days [64].

In a study by Winer et al. [65], the immune response to spaceflight stress is characterized through specific molecular pathways and cellular subpopulations. In the adaptive compartment, a marked inhibition of T lymphocyte activation is observed, with CD4+ cells exhibiting greater sensitivity than CD8+ cells. This suppression is driven by the downregulation of CD25, CD69, and CD71 markers, reduced secretion of effector cytokines (IL-2 and IFN-γ), and attenuation of ZAP70 kinase. Concurrently, in regulatory T cells (Tregs), STAT5 signaling increases along with enhanced chromatin accessibility of FOXP3, establishing an immunosuppressive state. Intracellularly, microgravity alters the cytoskeleton by modulating Rho GTPases (such as RhoA and CDC42) and hindering the translocation of protein kinase C (PKC) and the TRIM25/RIG-I complex, thereby compromising the type I interferon response. In the innate component, NF-κB signaling promotes basal inflammation with the release of IL-1, IL-6, IL-8, and TNF, while the cytotoxicity of NK cells and the phagocytosis of neutrophils and dendritic cells decrease. Finally, although B lymphocyte homeostasis appears preserved, the humoral response shows alterations in the BCR repertoire.

Furthermore, Winer et al. link alterations in epithelial barriers and the microbiome to the widespread immune dysfunction observed in space. At the intestinal level, prolonged missions cause a reduction in beneficial genera such as Akkermansia, Lactobacillus, and Bifidobacterium, accompanied by an increase in the Firmicutes-to-Bacteroidetes ratio. This dysbiosis is directly associated with immune crosstalk, correlating with an increase in circulating pro-inflammatory cytokines and chemokines

such as CCL2, IL-8, IL-1β, and CCL4. In the skin, spatial transcriptomic analysis reveals the disruption of the epithelial barrier, activation of the KRAS pathway, impairment of interferon signaling, and reduced T cell migration. In parallel, shifts in the oral and skin microbiota, characterized by the enrichment of pathobionts such as Streptococcus gordonii and Streptococcus pneumoniae, show direct associations with gene expression in CD14+ monocytes, NK cells, and dendritic cells. These interactions alter antigen presentation (HLA genes) and JAK/STAT inflammatory pathways, reducing immune surveillance and promoting the reactivation of latent viruses (HSV-1, VZV, EBV, CMV).

Even if interest in studying immunity in space is increasing, there is still a necessity to standardize the experimental setup. Many experiments expose cells to microgravity for less than 72 h, which is too short to truly capture how cells adapt to the space environment. Furthermore, for experiments performed during spaceflight, the extreme stresses can compromise sample viability and trigger "false" immune responses that make it hard to isolate the effects of the microgravity environment itself [66].

The main effects of microgravity on the immune system are reported in Table 1.

Table 1. Summary of spaceflight-induced alterations in the immune system, associated molecular mechanisms, and clinical consequences. The "Evidence source" column states, for each row, the class of experimental platform from which the findings derive, following the terminology recommended by Herranz et al. [12].

Immune System Component	Molecular & Cellular Alterations in Spaceflight	Physiological & Clinical Consequences	Evidence Source
Adaptive Immunity (T & B Lymphocytes)	Marked inhibition of T cell activation (CD4+ more sensitive than CD8+); downregulation of CD25, CD69, CD71, IL-2, and IFN-γ; attenuation of ZAP70 kinase. Increased STAT5 signaling and FOXP3 chromatin accessibility in Tregs. Suppressed production of IgG and IgM antibodies, alongside alterations in the BCR repertoire.	Impaired lymphocyte activation, establishment of an immunosuppressive state, and overall reduced adaptive immune surveillance.	Human spaceflight; simulated microgravity in vitro
Innate Immunity (NK cells, Neutrophils, DCs)	Decreased natural killer (NK) cell cytotoxicity, further suppressed by stress-induced elevations in cortisol and catecholamines. Reduced phagocytosis in neutrophils and dendritic cells (DCs). Altered antigen presentation (HLA genes).	Diminished primary defense mechanisms, compromised innate immune surveillance, and higher susceptibility to pathogens.	Human spaceflight; human ground-based analogs
Intracellular Pathways & Mechanotransduction	Disrupted mechanotransduction alters cytoskeletal architecture. Modulation of Rho GTPases (RhoA, CDC42) and hindered translocation of PKC and the TRIM25/RIG-I complex. Compromised mitochondrial functionality preventing efficient leukocyte replication.	Compromised type I interferon response, leading to severe immune exhaustion and accelerated immune senescence.	Simulated microgravity in vitro

Inflammatory Profile	Continuous leukocyte stimulation and activation of NF-κB signaling, promoting the release of pro-inflammatory cytokines and chemokines (IL-1, IL-1β, IL-6, IL-8, TNF, CCL2, and CCL4).	Persistent state of basal, chronic low-grade inflammation, mimicking the natural decline seen in the elderly.	Human spaceflight; simulated microgravity in vitro
Microbiome & Epithelial Barriers	Intestinal dysbiosis (decreased *Akkermansia*, *Lactobacillus*, *Bifidobacterium*; increased Firmicutes-to-Bacteroidetes ratio) and enrichment of oral/skin pathobionts (*Streptococcus* spp.). Skin epithelial barrier disruption with KRAS activation and reduced T cell migration.	Exacerbation of systemic immune crosstalk and JAK/STAT pathways, directly driving latent viral reactivation (e.g., HSV-1, VZV, EBV, CMV).	Human spaceflight (ISS missions)

8. Endocrine System

The endocrine system is fundamental for maintaining homeostasis and responding to environmental stressors; under normal gravity, it plays a crucial role in coordinating vital processes such as metabolism, growth, reproduction, and hydroelectrolytic equilibrium through a complex network of chemical messengers [67–70]. Exposure to microgravity acts as a significant stressor that forces this system into a drastic functional readaptation, generating physiological alterations that mimic—in an accelerated manner, albeit reversible upon re-entry—processes typical of natural aging [71]. In space, the displacement of body fluids towards the head (cephalic fluid shift) activates the hypothalamic–pituitary–adrenal (HPA) axis, often leading to an increase in stress hormones, such as cortisol and catecholamines, necessary to manage new metabolic demands in orbit [67–69,71,72].

This environmental condition frequently induces a "diabetogenic" state characterized by insulin resistance and glucose intolerance, similar to type 2 diabetes or metabolic aging. This condition is aggravated by physical inactivity and a state of low-grade inflammation [70,71,73]. In parallel, the endocrine system also mediates the degeneration of musculoskeletal tissues: the loss of local mechanical loading [71] reduces the secretion of anabolic hormones and alters the calcium axis with variations in parathyroid hormone (PTH) levels [67] and Vitamin D [69,71], accelerating osteopenia. In real microgravity, subclinical hypothyroidism has also been reported; structural changes in thyrocytes and loss of TSH receptors from the cell surface are documented in cell models, although the in-flight clinical picture was subsequently shown to be confounded by an environmental factor (see below) [71,74], along with marked hypoandrogenism featuring reduced plasma and salivary testosterone [75]. At the cellular level, impairment of mechanotransduction via the alteration of cytoskeletal architecture under microgravity conditions impairs mitochondrial function and intracellular signaling, triggering oxidative stress and modifying gene expression [76–78]. This level of disorganization leads to an expression analogous to the phenomenon of cellular senescence [77].

Adaptation to spaceflight imposes a drastic reconfiguration of the hydrosaline balance and stress response, triggered primarily by the cephalic fluid shift [10]. This transient phenomenon is initially interpreted by cardiac baroreceptors as an increase in central blood volume, stimulating the release of Atrial Natriuretic Factor (ANF), a hormone that promotes sodium and water excretion in an attempt to reduce plasma volume via a negative feedback mechanism. However, as the mission progresses, a new

equilibrium is established, characterized by reduced blood volume and, often, by hyponatremia and hypokalaemia, which persist despite the activation of compensatory mechanisms [69]. In parallel, the hypothalamic–pituitary–adrenal (HPA) axis shows a complex response: although cortisol is often elevated during flight and upon re-entry, indicating a stress response and potentially contributing to protein and bone catabolism [69], other studies on missions such as D-2 have found that ACTH and cortisol levels may remain stable or adapt, suggesting that hypercortisolemia is not an inevitable consequence of microgravity but depends on the intensity of operational stressors [70,75]. Furthermore, the renin–angiotensin–aldosterone system (RAAS) shows dynamic fluctuations: after an initial suppression due to expansion, aldosterone and angiotensin I levels tend to increase to preserve electrolytes in the new reduced-volume state, although the renal response may be altered by changes in local blood flow [69,79]. The hydrosaline balance and stress response resulting from volemic alteration thus pass through different states of equilibrium during the mission, stabilizing on an altered situation after the first few days of the mission.

Microgravity induces an uncoupling in bone remodeling, with a net prevalence of resorption over formation, a process mediated by complex alterations of the calcium axis and thyroid function [80]. Recent studies and meta-analyses have highlighted that parathyroid hormone (PTH) secretion tends to decrease during exposure to microgravity, contributing to bone mass loss, only to show a rebound effect (compensatory increase) upon reentry to Earth [67]. This picture is further complicated by Vitamin D dynamics: while inactive metabolites remain stable, the active form (1α, 25-hydroxyvitamin D3) may increase early in flight, further stimulating calcium resorption from bone [69]. At a general metabolic level, a condition of "mild hypothyroidism" or subclinical hypothyroidism is frequently observed in astronauts and animal models, characterized by reduced T3 and T4 secretion and a slight compensatory increase in TSH [70,71]. The causes of this dysfunction are found at the cellular level: microgravity alters the thyrocyte cytoskeleton (particularly cytokeratin and vimentin filaments) and causes the detachment or "shedding" of the TSH receptor (TSHR) from the cell membrane, reducing the gland's sensitivity to pituitary stimulation [74].

However, the clinical manifestation of elevated TSH in astronauts was subsequently found to be largely an environmental artifact rather than a direct microgravity effect. Before 1997, the U.S. space program used pharmacological doses of iodine to purify spacecraft drinking water, inducing a transient hypothyroid state. Following the implementation of an iodine removal system, post-flight TSH elevations in astronauts were no longer observed [81]. Furthermore, specific loss of parafollicular cells (C cells) and a consequent reduction in calcitonin [67], a key hormone for protecting bone density, has been documented, further aggravating the osteopenic picture.

Exposure to microgravity has a profound and negative impact on male reproductive function, configuring a picture of reversible primary hypogonadism [70]. Studies conducted on astronauts have demonstrated a drastic reduction in testosterone levels in plasma, urine, and saliva during spaceflight, which recover rapidly upon return to Earth. It is interesting to note that, in some cases, this decline in androgens is accompanied by normal or even elevated luteinizing hormone (LH) levels, suggesting that the deficit is not of central origin (hypothalamic–pituitary) but due to direct testicular distress or local hemodynamic changes [75]. At the cellular level, it has indeed been observed, both in murine models and human samples, that microgravity and cosmic radiation induce oxidative stress and apoptosis in germ cells [82], compromising spermatogenesis and reducing sperm count and motility [83]. Studies conducted on the TCam-2 cell line, a model for human male germ cells, highlight that simulated microgravity induces a state of generalized oxidative stress, characterized by a significant increase in reactive oxygen

species (ROS) and superoxide anion levels, accompanied by metabolic alterations such as increased anaerobic metabolism in two-dimensional cultures [84,85]. It should be emphasized that in the female case, the Hypothalamic–Pituitary–Ovarian axis is even more susceptible: it has been observed that the ovarian follicle reserve is highly sensitive to space radiation and microgravity, leading to potential premature ovarian failure and interruption of the estrous cycle in rodents, mediated by an increase in gonadotropins (LH and FSH) due to the loss of ovarian negative feedback. These data indicate that the space environment acts as a powerful endocrine disruptor on fertility, activating programmed cell death pathways and altering steroidogenesis [86–89] (Figure 3).

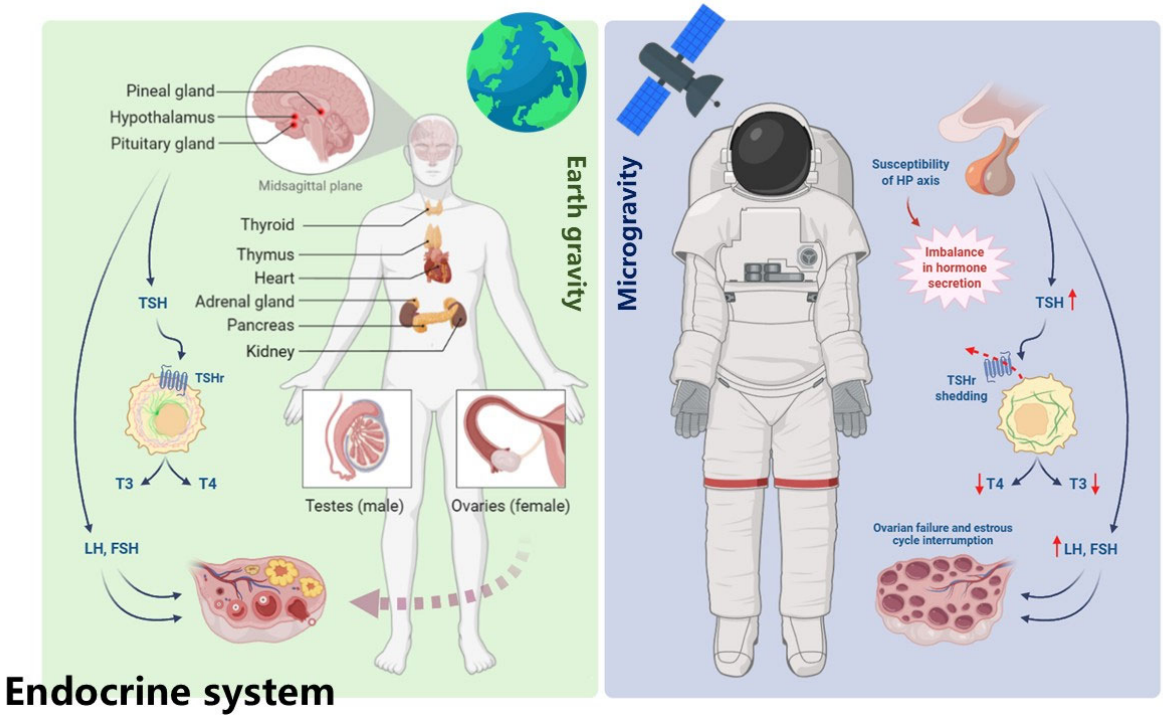


Figure 3. The space environment acts as a significant stressor that forces a drastic functional readaptation across major endocrine axes. Cephalic fluid shifts activate the hypothalamic–pituitary–adrenal (HPA) axis, leading to hormonal imbalances and an increased secretion of stress hormones. In thyrocyte models exposed to simulated and real microgravity, structural changes cause the shedding of thyroid-stimulating hormone (TSH) receptors from the cell membrane, reducing the sensitivity of the gland to pituitary stimulation. This in vitro mechanism should not be equated with the clinical picture: the post-flight TSH elevations recorded in astronauts before 1997 were largely attributable to the pharmacological doses of iodine used to purify spacecraft drinking water and were no longer observed once an iodine removal system had been introduced. Additionally, the space environment acts as a profound endocrine disruptor on the hypothalamic–pituitary–gonadal axis, altering steroidogenesis and leading to premature ovarian failure, estrous cycle interruption, and a corresponding increase in luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels. Effects shown derive from different experimental platforms and are not all documented in humans in flight: the cephalic fluid shift and activation of the HPA axis are established from human spaceflight; reduced plasma and salivary testosterone is documented in astronauts; TSH receptor shedding rests on simulated and real microgravity in thyrocyte models; premature ovarian failure and interruption of the estrous cycle rest on rodent studies.

9. Other Systems Affected by Microgravity: A Brief Overview

The four systems treated above are those in which mechanical unloading can be identified as the proximate cause of adaptation. Three further systems undergo

substantial change in weightlessness and are summarised here for completeness; each has been the subject of dedicated reviews, to which the reader is referred for a full treatment.

- Cardiovascular system. The loss of hydrostatic gradients removes the orthostatic load against which the heart works on Earth. Plasma volume falls within the first days of flight, stroke volume and left ventricular mass decrease, baroreflex sensitivity is blunted and orthostatic intolerance is common on return to 1g; increased arterial stiffness and in-flight insulin resistance have been reported after six-month missions, and cosmic radiation may act on the vascular endothelium in addition to the effects of unloading [90]. Multi-omic and physiological profiling of short-duration civilian crews has shown that most cardiovascular and fluid-regulatory markers return towards baseline within months of landing, whereas a subset of inflammatory and oxidative-stress signatures resolves more slowly [91,92]. As for the skeleton, the magnitude of the response scales with mission duration.
- Central nervous system. The headward fluid shift is accompanied by measurable structural change in the brain. Total ventricular volume increases after long-duration missions, with only partial recovery over the months following landing, and the spatiotemporal pattern of cerebrospinal fluid redistribution points to reduced resorption in weightlessness as the underlying mechanism [93]. The increase is observed after long-duration flights but not after short-duration flights, and correlates with mission duration [94]. A proportion of long-duration crew members develop spaceflight-associated neuro-ocular syndrome (SANS), a constellation of optic disc oedema, globe flattening, choroidal folds and hyperopic shift, for which no fully effective countermeasure has yet been identified and whose mechanism remains debated [95].
- Gastrointestinal tract and microbiome. Long-duration missions are associated with reproducible shifts in the composition of the intestinal microbiota: the microbial communities of crew members become more similar to one another in flight, largely through a fall in the abundance of a small number of taxa, some of which covary with dietary intake and with immune markers [96]. These observations connect directly to the immune findings discussed above, where intestinal dysbiosis correlates with circulating pro-inflammatory cytokines. The contribution of weightlessness itself, as distinct from the closed environment, the confined diet and the altered circadian regime of the International Space Station, has not been separated [96].

Taken together, these three systems reinforce the central argument of this review: the best characterised responses are those in which a gravity-dependent physical variable (hydrostatic pressure, mechanical loading, convective transport) can be identified, whereas changes mediated by the broader spaceflight environment remain difficult to attribute to weightlessness alone.

10. Countermeasures

In summary, to mitigate the physiological and cellular alterations induced by microgravity, currently developed countermeasures primarily focus on four main domains: physical exercise and resistive devices, nutritional and pharmacological interventions, artificial gravity, and environmental and technological modifications.

- Exercise and resistive devices. To counteract bone demineralization and the pronounced atrophy of antigravity musculature, physical activity performed before, during, and after spaceflight remains a fundamental, albeit currently incomplete, strategy. Specifically, the implementation of advanced resistive exercise devices, coupled with individualized training regimens and dietary support, has demonstrated promising efficacy in attenuating bone mineral density loss and

facilitating the recovery of muscle volume and strength. Furthermore, neurophysiological monitoring based on muscle synergy biomarkers has been proposed to guide and optimize post-flight rehabilitation protocols [41,42].

- Nutritional and immunomodulatory interventions. Regarding the immune system, exercise-induced immunomodulation and the strict management of nutritional balance represent the most relevant methodologies for curbing chronic low-grade inflammation. Specifically, to address the limitations of the standard International Space Station (ISS) diet—which is often meat-dense and lacks fresh fruits and vegetables due to storage constraints—the provision of higher portions of fresh plant-based foods constitutes a key approach to safeguarding immune function [66].
- Artificial gravity. Because weightlessness withdraws a load that acts on every system simultaneously, countermeasures that restore an inertial load have long been proposed as integrated rather than system-specific solutions: short-radius centrifugation and intermittent artificial gravity activate antigravity musculature, load the skeleton and the cardiovascular system, and provide otolith stimulation comparable to that experienced at 1g [97]. The 60-day AGBRESA campaign tested daily centrifugation in a head-down tilt bed rest analog and provides the most systematic human dataset on this approach [98]. A different route to the same end is self-generated artificial gravity through locomotion: in a terrestrial emulation of lunar gravity obtained by unloading 83% of body weight, participants were able to run horizontally along the inside of a cylinder of 4.7 m radius at 5.4–6.5 m/s, generating peak forces during foot contact of two to three times body weight in lunar conditions together with a substantial metabolic demand, and thereby loading muscle, bone, the cardiorespiratory system and neurovestibular control at the same time [99]. The concept was developed for the hypogravity of a lunar settlement rather than for orbital weightlessness, and it has not been validated in flight; it is nonetheless directly relevant to the problem addressed in this review, since in weightlessness the loading vector is absent altogether and must be supplied either by the crew member's own motion or by rotation of the vehicle.
- Environmental and technological measures. Finally, from an endocrine and environmental perspective, a notable technological success was the implementation of a filtration system to remove iodine from spacecraft drinking water. This environmental modification successfully eliminated the transient subclinical hypothyroidism previously induced by the pharmacological doses of iodine utilized for water purification [81].

Finally, none of these measures can be optimised without individual monitoring. Biochemical markers of bone turnover and pre-flight bone metabolism have been shown to predict unloading-induced bone loss, and the neurophysiological biomarkers derived from muscle synergy analysis discussed above have been proposed as a basis for individualised prescription and for guiding post-flight rehabilitation [44,49].

11. Limitations, Conflicting Evidence and Knowledge Gaps

The evidence summarised in this review is heterogeneous in origin and uneven in strength, and several of its central findings remain contested. The principal open questions are set out below.

- Equivalence of platforms. Spaceflight and ground-based simulation are not interchangeable. Flight experiments expose cells to genuine free fall, but also to launch and re-entry accelerations, ionizing radiation and prolonged storage before analysis; ground-based devices remove those confounders but do not remove gravity, and introduce shear stress and convection of their own [12]. The symmetry-

breaking phenotype observed on the random positioning machine is a case in point, and requires confirmation in orbital flight before it can be attributed to weightlessness as such [18].

- Discordant endocrine findings. Cortisol is frequently reported as elevated in flight and at re-entry, yet data from missions such as D-2 indicate that ACTH and cortisol may remain stable, which suggests that hypercortisolism reflects the intensity of operational stressors rather than weightlessness as such [69,70,75]. Parathyroid hormone secretion is reported to fall during flight with a rebound after landing, but the direction and timing of the change are not consistent across studies [67]. The clearest case is thyroid function: a finding long attributed to microgravity proved to be an artefact of iodine-based water purification [81]. It stands as a caution against inferring in-flight endocrine mechanisms from in vitro cellular responses.
- Efficacy of countermeasures. Early reports found exercise largely ineffective against bone loss, whereas studies using advanced resistive devices combined with nutritional support report attenuation of bone mineral density loss [41–43]. The two bodies of evidence differ in hardware, protocol and mission duration, so the discrepancy is not resolved; what is established is that substantial loss persists despite near-daily exercise [44,45].
- Sample size and population. In-flight human studies are necessarily small: the muscle synergy data discussed above derive from five astronauts [47], and some of the classic bone datasets from two subjects [30]. Astronaut cohorts have also been predominantly male, and few datasets are disaggregated by sex. This is a particularly severe limitation for the reproductive and endocrine findings, where the female data derive largely from rodent experiments and from simulated microgravity in vitro [86,88].
- Exposure duration in vitro. Most immunological experiments expose cells to altered gravity for less than 72 h, which is shorter than the adaptation times observed in vivo, and the absence of standardised protocols makes results difficult to compare across laboratories [66].

Addressing these gaps requires a specific experimental agenda: paired flight and ground experiments on the same cell models and endpoints; in-flight sampling at multiple timepoints rather than pre- and post-flight only; sex-balanced crews and sex-disaggregated reporting; exposure durations that are in vitro matched to the physiological timescales of interest; and countermeasure trials designed with contemporaneous control conditions rather than historical comparisons.

12. Conclusions

Space exploration has shown that the human body is specifically designed for the terrestrial environment, meaning that the transition to microgravity is a biological shock that triggers a cascade of adaptations across every level of organization. While humans have shown a remarkable ability to adapt in the short term, the chronic changes afflicting astronauts remain the most difficult challenge for space biomedicine.

Through the disruption of mechanotransduction, cells lose their ability to convert physical gravitational loads into the biochemical signals necessary for healthy function.

Without the constant resistance of gravity, the skeleton enters a state of disuse-induced bone loss, in which resorption far outpaces formation; as set out above, this condition is not equivalent to terrestrial osteoporosis. Astronauts can lose bone mass at a staggering rate of 1–2% per month, particularly in weight-bearing regions like the legs and spine. Even with near-daily resistive exercise, this loss remains difficult to fully prevent.

The neurovestibular system is disturbed from the first days of flight: space motion sickness is reported in approximately 70% of astronauts and has been attributed either to the cephalad fluid shift or to a mismatch among visual, proprioceptive and vestibular inputs, the two explanations remaining open. The endocrine system is likewise reconfigured by the conditions of spaceflight. Across functions ranging from stress regulation by the HPA axis to hydrosaline balance, the body undergoes changes resembling accelerated aging, although these are largely reversible upon re-entry. The HPG axis is also particularly altered by microgravity and radiation: these combined conditions induce a state of reversible primary hypogonadism and significant drops in testosterone levels in men, while in women, a marked sensitivity of the ovarian follicle reserve is observed. Collectively, these effects qualify the space environment as an endocrine disruptor.

Looking toward the future, the success of missions to Mars or long-term lunar habitation will depend on the ability to transition from observing these effects to mitigating them. Current risk assessments for interplanetary travel are stark, with projections for crew survival and cancer risks suggesting that our current protective strategies are not yet sufficient for multi-year journeys.

In conclusion, microgravity research provides a new perspective to rethink the relationship between physics and biology. If the aim is to become a multi-planetary species, we must bridge the gap between our past on Earth and our evolution in space, developing the tools to maintain our health in environments we were never designed to inhabit. [2,100]

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References

1. Bizzarri, M.; Cucina, A.; Palombo, A.; Masiello, M.G. Gravity sensing by cells: Mechanisms and theoretical grounds. *Rend. Lincei* **2014**, *25*, 29–38. https://doi.org/10.1007/s12210-013-0281-x.
2. Bizzarri, M.; Masiello, M.G.; Guzzi, R.; Cucina, A. Journey to Mars: A Biomedical Challenge. Perspective on future human space flight. *Org. J. Biol. Sci.* **2017**, *1*, 15–26. https://doi.org/10.13133/2532-5876/14197.
3. Morey-Holton, E. 9 The impact of gravity on life. In *Evolution on Planet Earth*; Academic Press: Cambridge, MA, USA, 2003. https://doi.org/10.1016/B978-012598655-7/50036-7.
4. Crawford-Young, S.J. Effects of microgravity on cell cytoskeleton and embryogenesis. *Int. J. Dev. Biol.* **2006**, *50*, 183–191. https://doi.org/10.1387/ijdb.052077sc.
5. Wuest, S.L.; Richard, S.; Kopp, S.; Grimm, D.; Egli, M. Simulated Microgravity: Critical Review on the Use of Random Positioning Machines for Mammalian Cell Culture. *BioMed Res. Int.* **2015**, *2015*, 971474. https://doi.org/10.1155/2015/971474.
6. Ferranti, F.; Del Bianco, M.; Pacelli, C. Advantages and Limitations of Current Microgravity Platforms for Space Biology Research. *Appl. Sci.* **2020**, *11*, 68. https://doi.org/10.3390/app11010068.

7. Thorne, S. Modeling the role of gravitation in metabolic processes. *Commun. Integr. Biol.* **2021**, *14*, 115–135. https://doi.org/10.1080/19420889.2021.1914913.
8. Todd, P. Gravity-dependent phenomena at the scale of the single cell. *ASGSB Bull. Publ. Am. Soc. Gravitational Space Biol.* **1989**, *2*, 95–113.
9. Kondrachuk, A.V.; Sirenko, S.P. The theoretical consideration of microgravity effects on a cell. *Adv. Space Res. Off. J. Comm. Space Res.* **1996**, *17*, 165–168. https://doi.org/10.1016/0273-1177(95)00630-w.
10. Corydon, T.; Schulz, H.; Richter, P.; Strauch, S.; Böhmer, M.; Ricciardi, D.; Wehland, M.; Krüger, M.; Erzinger, G.; Lebert, M.; et al. Current Knowledge about the Impact of Microgravity on Gene Regulation. *Cells* **2023**, *12*, 1043. https://doi.org/10.3390/cells12071043.
11. Garzón, N.A.L.; Pinzón-Fernández, M.V.; Saavedra, T.J.S.; Nati-Castillo, H.A.; Arias-Intriago, M.; Salazar-Santoliva, C.; Izquierdo-Condoy, J.S. Microgravity and Cellular Biology: Insights into Cellular Responses and Implications for Human Health. *Int. J. Mol. Sci.* **2025**, *26*, 3058. https://doi.org/10.3390/ijms26073058.
12. Herranz, R.; Anken, R.; Boonstra, J.; Braun, M.; Christianen, P.C.M.; De Geest, M.; Hauslage, J.; Hilbig, R.; Hill, R.J.A.; Lebert, M.; et al. Ground-Based Facilities for Simulation of Microgravity: Organism-Specific Recommendations for Their Use, and Recommended Terminology. *Astrobiology* **2013**, *13*, 1–17. https://doi.org/10.1089/ast.2012.0876.
13. Testa, F.; Palombo, A.; Dinicola, S.; D'Anselmi, F.; Proietti, S.; Pasqualato, A.; Masiello, M.G.; Coluccia, P.; Cucina, A.; Bizzarri, M. Fractal analysis of shape changes in murine osteoblasts cultured under simulated microgravity. *Rend. Lincei* **2014**, *25*, 39–47. https://doi.org/10.1007/s12210-014-0291-3.
14. Masiello, M.G.; Cucina, A.; Proietti, S.; Palombo, A.; Coluccia, P.; D'Anselmi, F.; Dinicola, S.; Pasqualato, A.; Morini, V.; Bizzarri, M. Phenotypic Switch Induced by Simulated Microgravity on MDA-MB-231 Breast Cancer Cells. *BioMed Res. Int.* **2014**, *2014*, 652434. https://doi.org/10.1155/2014/652434.
15. Nikitiuk, A.S.; Bayandin, Y.V.; Naimark, O.B. Cell Mechanobiology in Microgravity Conditions. *Microgravity Sci. Technol.* **2025**, *37*, 34. https://doi.org/10.1007/s12217-025-10186-4.
16. Bizzarri, M.; Fedeli, V.; Piombarolo, A.; Angeloni, A. Space Biomedicine: A Unique Opportunity to Rethink the Relationships between Physics and Biology. *Biomedicines* **2022**, *10*, 2633. https://doi.org/10.3390/biomedicines10102633.
17. Longo, G.; Montévil, M.R.; Pocheville, A. From Bottom-Up Approaches to Levels of Organization and Extended Critical Transitions. *Front. Physiol.* **2012**, *3*, 232. https://doi.org/10.3389/fphys.2012.00232.
18. Wadhwa, A.; Bruun, L.; Petersen, J.C.G.; Petersen, L.G. Guidelines for use of the random positioning machine as a reduced-gravity analog. *Sci. Rep.* **2026**, *16*, 10012. https://doi.org/10.1038/s41598-026-39316-7.
19. Kondepudi, D.K.; Prigogine, I. Sensitivity of nonequilibrium systems. *Phys. Stat. Mech. Its Appl.* **1981**, *107*, 1–24. https://doi.org/10.1016/0378-4371(81)90021-2.
20. Masiello, M.G.; Verna, R.; Cucina, A.; Bizzarri, M. Physical constraints in cell fate specification. A case in point: Microgravity and phenotypes differentiation. *Prog. Biophys. Mol. Biol.* **2018**, *134*, 55–67. https://doi.org/10.1016/j.pbiomolbio.2018.01.001.
21. Nikitiuk, A.S.; Koshkina, A.A.; Bayandin, Y.V.; Naimark, O.B. On thermodynamics and relaxation properties of eukaryotic cells. *Int. J. Non-Linear Mech.* **2023**, *157*, 104532. https://doi.org/10.1016/j.ijnonlinmec.2023.104532.
22. Vorselen, D.; Roos, W.; Mackintosh, F.; Wuite, G.; Loon, J. The role of the cytoskeleton in sensing changes in gravity by nonspecialized cells. *FASEB J. Off. Publ. Fed. Am. Soc. Exp. Biol.* **2013**, *28*, 536–547. https://doi.org/10.1096/fj.13-236356.
23. Antonsen, E.L.; Myers, J.G.; Boley, L.; Arellano, J.; Kerstman, E.; Kadwa, B.; Buckland, D.M.; Van Baalen, M. Estimating medical risk in human spaceflight. *Npj Microgravity* **2022**, *8*, 8. https://doi.org/10.1038/s41526-022-00193-9.
24. Krittanawong, C.; Singh, N.K.; Scheuring, R.A.; Urquieta, E.; Bershad, E.M.; Macaulay, T.R.; Kaplin, S.; Dunn, C.; Kry, S.F.; Russomano, T.; et al. Human Health during Space Travel: State-of-the-Art Review. *Cells* **2023**, *12*, 40. https://doi.org/10.3390/cells12010040.
25. Kenkre, J.S.; Bassett, J. The bone remodelling cycle. *Ann. Clin. Biochem.* **2018**, *55*, 308–327. https://doi.org/10.1177/0004563218759371.
26. Man, J.; Graham, T.; Squires-Donelly, G.; Laslett, A.L. The effects of microgravity on bone structure and function. *Npj Microgravity* **2022**, *8*, 9. https://doi.org/10.1038/s41526-022-00194-8.
27. Tosi, D.D.; Tiberio, F.; Di Pietro, L.; Polito, L.; Parolini, O.; Minotti, A.; Arcovito, A.; Lattanzi, W. Effects of microgravity mechanotransduction in bone tissue and cells: Systematic review on primary cilium-dependent mechanisms. *Npj Microgravity* **2026**, *12*, 12. https://doi.org/10.1038/s41526-025-00556-y.
28. Caillot-Augusseau, A.; Lafage-Proust, M.H.; Soler, C.; Pernod, J.; Dubois, F.; Alexandre, C. Bone formation and resorption biological markers in cosmonauts during and after a 180-day space flight (Euromir 95). *Clin. Chem.* **1998**, *44*, 578–585.

29. Nagaraja, M.P.; Risin, D. The current state of bone loss research: Data from spaceflight and microgravity simulators. *J. Cell. Biochem.* **2013**, *114*, 1001–1008. https://doi.org/10.1002/jcb.24454.
30. Collet, P.; Uebelhart, D.; Vico, L.; Moro, L.; Hartmann, D.; Roth, M.; Alexandre, C. Effects of 1- and 6-month spaceflight on bone mass and biochemistry in two humans. *Bone* **1997**, *20*, 547–551. https://doi.org/10.1016/s8756-3282(97)00052-5.
31. Pandiarajan, M.; Hargens, A.R. Ground-Based Analogs for Human Spaceflight. *Front. Physiol.* **2020**, *11*, 716. https://doi.org/10.3389/fphys.2020.00716.
32. Tomilovskaya, E.; Shigueva, T.; Sayenko, D.; Rukavishnikov, I.; Kozlovskaya, I. Dry Immersion as a Ground-Based Model of Microgravity Physiological Effects. *Front. Physiol.* **2019**, *10*, 284. https://doi.org/10.3389/fphys.2019.00284.
33. Rittweger, J.; Simunic, B.; Bilancio, G.; Gaspare De Santo, N.; Cirillo, M.; Biolo, G.; Pisot, R.; Eiken, O.; Mekjavic, I.B.; Narici, M. Bone loss in the lower leg during 35 days of bed rest is predominantly from the cortical compartment. *Bone* **2009**, *44*, 612–618. https://doi.org/10.1016/j.bone.2009.01.001.
34. Rittweger, J.; Frost, H.M.; Schiessl, H.; Ohshima, H.; Alkner, B.; Tesch, P.; Felsenberg, D. Muscle atrophy and bone loss after 90 days' bed rest and the effects of flywheel resistive exercise and pamidronate: Results from the LTBR study. *Bone* **2005**, *36*, 1019–1029. https://doi.org/10.1016/j.bone.2004.11.014.
35. Smith, S.M.; Heer, M.; Shackelford, L.C.; Sibonga, J.D.; Spatz, J.; Pietrzyk, R.A.; Hudson, E.K.; Zwart, S.R. Bone metabolism and renal stone risk during International Space Station missions. *Bone* **2015**, *81*, 712–720. https://doi.org/10.1016/j.bone.2015.10.002.
36. Nakagaki, R.; Mukaibo, T.; Monir, A.; Gao, X.; Munemasa, T.; Nodai, T.; Tamura, A.; Obikane, Y.H.; Kondo, Y.; Masaki, C.; et al. Simulated microgravity environment inhibits matrix mineralization during the osteoblast to osteocyte differentiation. *Biochem. Biophys. Res. Commun.* **2024**, *739*, 150963. https://doi.org/10.1016/j.bbrc.2024.150963.
37. Compston, J.E.; McClung, M.R.; Leslie, W.D. Osteoporosis. *Lancet* **2019**, *393*, 364–376. https://doi.org/10.1016/S0140-6736(18)32112-3.
38. Orwoll, E.S.; Adler, R.A.; Amin, S.; Binkley, N.; Lewiecki, E.M.; Petak, S.M.; Shapses, S.A.; Sinaki, M.; Watts, N.B.; Sibonga, J.D. Skeletal health in long-duration astronauts: Nature, assessment, and management recommendations from the NASA bone summit. *J. Bone Miner. Res.* **2013**, *28*, 1243–1255. https://doi.org/10.1002/jbmr.1948.
39. Sibonga, J.D. Spaceflight-induced Bone Loss: Is there an Osteoporosis Risk? *Curr. Osteoporos. Rep.* **2013**, *11*, 92–98. https://doi.org/10.1007/s11914-013-0136-5.
40. Vico, L.; Hargens, A. Skeletal changes during and after spaceflight. *Nat. Rev. Rheumatol.* **2018**, *14*, 229–245. https://doi.org/10.1038/nrrheum.2018.37.
41. Cavanagh, P.R.; Licata, A.A.; Rice, A.J. Exercise and pharmacological countermeasures for bone loss during long-duration space flight. *Gravitational Space Biol. Bull. Publ. Am. Soc. Gravitational Space Biol.* **2005**, *18*, 39–58.
42. Hawkey, A. The importance of exercising in space. *Interdiscip. Sci. Rev.* **2003**, *28*, 130–138. https://doi.org/10.1179/030801803225010377.
43. Smith, S.M.; Heer, M.A.; Shackelford, L.C.; Sibonga, J.D.; Ploutz-Snyder, L.; Zwart, S.R. Benefits for bone from resistance exercise and nutrition in long-duration spaceflight: Evidence from biochemistry and densitometry. *J. Bone Miner. Res.* **2012**, *27*, 1896–1906. https://doi.org/10.1002/jbmr.1647.
44. Gabel, L.; Liphardt, A.-M.; Hulme, P.A.; Heer, M.; Zwart, S.R.; Sibonga, J.D.; Smith, S.M.; Boyd, S.K. Pre-flight exercise and bone metabolism predict unloading-induced bone loss due to spaceflight. *Br. J. Sports Med.* **2022**, *56*, 196–203. https://doi.org/10.1136/bjsports-2020-103602.
45. Sibonga, J.D.; Evans, H.J.; Sung, H.G.; Spector, E.R.; Lang, T.F.; Oganov, V.S.; Bakulin, A.V.; Shackelford, L.C.; LeBlanc, A.D. Recovery of spaceflight-induced bone loss: Bone mineral density after long-duration missions as fitted with an exponential function. *Bone* **2007**, *41*, 973–978. https://doi.org/10.1016/j.bone.2007.08.022.
46. Fitts, R.H.; Riley, D.R.; Widrick, J.J. Physiology of a microgravity environment invited review: Microgravity and skeletal muscle. *J. Appl. Physiol.* **2000**, *89*, 823–839. https://doi.org/10.1152/jappl.2000.89.2.823.
47. Hagio, S.; Ishihara, A.; Terada, M.; Tanabe, H.; Kibushi, B.; Higashibata, A.; Yamada, S.; Furukawa, S.; Mukai, C.; Ishioka, N.; et al. Muscle synergies of multidirectional postural control in astronauts on Earth after a long-term stay in space. *J. Neurophysiol.* **2022**, *127*, 1230–1239. https://doi.org/10.1152/jn.00232.2021.
48. White, R.J.; Averner, M. Humans in space. *Nature* **2001**, *409*, 1115–1118. https://doi.org/10.1038/35059243.
49. Lacquaniti, F.; Ivanenko, Y.P.; Sylos-Labini, F.; La Scaleia, V.; La Scaleia, B.; Willems, P.A.; Zago, M. Human Locomotion in Hypogravity: From Basic Research to Clinical Applications. *Front. Physiol.* **2017**, *8*, 893. https://doi.org/10.3389/fphys.2017.00893.
50. Russomano, T.; da Rosa, M.; dos Santos, M.A. Space motion sickness: A common neurovestibular dysfunction in microgravity. *Neurol. India* **2019**, *67*, S214–S218. https://doi.org/10.4103/0028-3886.259127.

51. Lackner, J.R.; Graybiel, A. Etiological factors in space motion sickness. *Aviat. Space Environ. Med.* **1983**, *54*, 675–681.
52. Reschke, M.F.; Bloomberg, J.J.; Harm, D.L.; Paloski, W.H.; Layne, C.; McDonald, V. Posture, locomotion, spatial orientation, and motion sickness as a function of space flight. *Brain Res. Brain Res. Rev.* **1998**, *28*, 102–117. https://doi.org/10.1016/s0165-0173(98)00031-9.
53. Awasthi, S.K.; Rajguru, R. Space Motion Sickness—An Overview. *Indian J. Aerosp. Med.* **2012**, *56*, 44–49.
54. Najrana, T.; Sanchez-Esteban, J. Mechanotransduction as an Adaptation to Gravity. *Front. Pediatr.* **2016**, *4*, 140. https://doi.org/10.3389/fped.2016.00140.
55. Ismail, A.; Elmoselhi, A.B.; Nada, L.A.; Rahman, B.; Badran, Z.; Verron, E. Immune and inflammatory responses in microgravity: Implications and therapeutic approaches. *Drug Discov. Today* **2025**, *30*, 104503. https://doi.org/10.1016/j.drudis.2025.104503.
56. Telomere Length Dynamics and DNA Damage Responses Associated with Long-Duration Spaceflight: Cell Reports Available online: https://www.cell.com/cell-reports/fulltext/S2211-1247(20)31446-7?_returnURL=https%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS2211124720314467%3Fshowall%3Dtrue (accessed on 18 January 2026).
57. Canaday, D.H.; Parker, K.E.; Aung, H.; Chen, H.E.; Nunez-Medina, D.; Burant, C.J. Age-dependent changes in the expression of regulatory cell surface ligands in activated human T-cells. *BMC Immunol.* **2013**, *14*, 45. https://doi.org/10.1186/1471-2172-14-45.
58. Pradhan, K.; Yi, Z.; Geng, S.; Li, L. Development of Exhausted Memory Monocytes and Underlying Mechanisms. *Front. Immunol.* **2021**, *12*, 778830. https://doi.org/10.3389/fimmu.2021.778830.
59. Linton, P.-J.; Thoman, M.L. Immunosenescence in monocytes, macrophages, and dendritic cells: Lessons learned from the lung and heart. *Immunol. Lett.* **2014**, *162*, 290–297. https://doi.org/10.1016/j.imlet.2014.06.017.
60. Zhang, J.; He, T.; Xue, L.; Guo, H. Senescent T cells: A potential biomarker and target for cancer therapy. *eBioMedicine* **2021**, *68*, 103409. https://doi.org/10.1016/j.ebiom.2021.103409.
61. Zhao, Y.; Shao, Q.; Peng, G. Exhaustion and senescence: Two crucial dysfunctional states of T cells in the tumor microenvironment. *Cell. Mol. Immunol.* **2020**, *17*, 27–35. https://doi.org/10.1038/s41423-019-0344-8.
62. Blank, C.U.; Haining, W.N.; Held, W.; Hogan, P.G.; Kallies, A.; Lugli, E.; Lynn, R.C.; Philip, M.; Rao, A.; Restifo, N.P.; et al. Defining 'T cell exhaustion.' *Nat. Rev. Immunol.* **2019**, *19*, 665–674. https://doi.org/10.1038/s41577-019-0221-9.
63. Franceschi, C.; Garagnani, P.; Parini, P.; Giuliani, C.; Santoro, A. Inflammaging: A new immune–metabolic viewpoint for age-related diseases. *Nat. Rev. Endocrinol.* **2018**, *14*, 576–590. https://doi.org/10.1038/s41574-018-0059-4.
64. Fitzgerald, W.; Chen, S.; Walz, C.; Zimmerberg, J.; Margolis, L.; Grivel, J.-C. Immune suppression of human lymphoid tissues and cells in rotating suspension culture and onboard the International Space Station. *Vitro Cell. Dev. Biol.–Anim.* **2009**, *45*, 622–632. https://doi.org/10.1007/s11626-009-9225-2.
65. Winer, D.A.; Du, H.; Kim, J.; Chang, V.; Burke, M.; Winer, S.; Costes, S.V.; Frippiat, J.-P.; Sams, C.; Paul, A.M.; et al. Astroimmunology: The effects of spaceflight and its associated stressors on the immune system. *Nat. Rev. Immunol.* **2026**, *26*, 189–212. https://doi.org/10.1038/s41577-025-01226-6.
66. Klos, B.; Kaul, A.; Straube, E.; Steinhauser, V.; Gödel, C.; Schäfer, F.; Lambert, C.; Enck, P.; Mack, I. Effects of isolated, confined and extreme environments on parameters of the immune system—A systematic review. *Front. Immunol.* **2025**, *16*, 1532103. https://doi.org/10.3389/fimmu.2025.1532103.
67. Blue, B.S. The effect of microgravity on parathyroid hormone secretion: A meta-analysis. *J. Endocrinol. Metab.* **2023**, *13*, 1–12.
68. Zhu, H.; Zhang, L.; Qian, M.; Shi, T.; Fan, F.; Li, W.; Zhu, S.; Xie, M. Microgravity versus Microgravity and Irradiation: Investigating the Change of Neuroendocrine-Immune System and the Antagonistic Effect of Traditional Chinese Medicine Formula. *BioMed Res. Int.* **2020**, *2020*, 2641324. https://doi.org/10.1155/2020/2641324.
69. Leach, C.; Johnson, P.; Cintron, N. The endocrine system in space flight. *Acta Astronaut.* **1988**, *17*, 161–166.
70. Strollo, F. Adaptation of the human endocrine system to microgravity in the context of integrative physiology and ageing. *Pflüg. Arch.* **2000**, *441*, R85–R90.
71. Biolo, G.; Heer, M.; Narici, M.; Strollo, F. Microgravity as a model of ageing. *Curr. Opin. Clin. Nutr. Metab. Care* **2003**, *6*, 31–40.
72. Macho, L.; Koška, J.; Kšinantová, L.; Pacak, K.; Hoff, T.; Noskov, V.; Grigoriev, A.; Vigaš, M.; Kvetňanský, R. The response of endocrine system to stress loads during space flight in human subject. *Adv. Space Res.* **2003**, *31*, 1605–1610.
73. Jokšienė, J.; Sahana, J.; Wehland, M.; Schulz, H.; Cortés-Sánchez, J.; Prat-Duran, J.; Grimm, D.; Simonsen, U. Effects of High Glucose on Human Endothelial Cells Exposed to Simulated Microgravity. *Biomolecules* **2023**, *13*, 189. https://doi.org/10.3390/biom13020189.

74. Albi, E.; Krüger, M.; Hemmersbach, R.; Lazzarini, A.; Cataldi, S.; Codini, M.; Beccari, T.; Ambesi-Impiombato, F.; Curcio, F. Impact of Gravity on Thyroid Cells. *Int. J. Mol. Sci.* **2017**, *18*, 972. https://doi.org/10.3390/ijms18050972.
75. Strollo, F.; Riondino, G.; Harris, B.; Strollo, G.; Casarosa, E.; Mangrossa, N.; Ferretti, C.; Luisi, M. The effect of microgravity on testicular androgen secretion. *Aviat. Space Environ. Med.* **1998**, *69*, 133–136.
76. Po, A.; Giuliani, A.; Masiello, M.G.; Cucina, A.; Catizone, A.; Ricci, G.; Chiacchiarini, M.; Tafani, M.; Ferretti, E.; Bizzarri, M. Phenotypic transitions enacted by simulated microgravity do not alter coherence in gene transcription profile. *Npj Microgravity* **2019**, *5*, 27. https://doi.org/10.1038/s41526-019-0088-x.
77. Miglietta, S.; Cristiano, L.; Espinola, M.; Masiello, M.; Micara, G.; Battaglione, E.; Linari, A.; Palmerini, M.; Familiari, G.; Aragona, C.; et al. Effects of Simulated Microgravity In Vitro on Human Metaphase II Oocytes: An Electron Microscopy-Based Study. *Cells* **2023**, *12*, 1346. https://doi.org/10.3390/cells12101346.
78. Bradbury, P.; Wu, H.; Choi, J.; Rowan, A.; Zhang, H.; Poole, K.; Lauko, J.; Chou, J. Modeling the Impact of Microgravity at the Cellular Level: Implications for Human Disease. *Front. Cell Dev. Biol.* **2020**, *8*, 96. https://doi.org/10.3389/fcell.2020.00096.
79. Ksinantova, L.; Koska, J.; Kvetnansky, R.; Marko, M.; Hamar, D.; Vigas, M. Effect of Simulated Microgravity on Endocrine Response to Insulin-Induced Hypoglycemia in Physically Fit Men. *Horm. Metab. Res.* **2002**, *34*, 155–159. https://doi.org/10.1055/s-2002-23200.
80. Zayzafoon, M.; Meyers, V.E.; McDonald, J.M. Microgravity: The immune response and bone. *Immunol. Rev.* **2005**, *208*, 267–280.
81. Smith, S.M.; Zwart, S.R.; McMonigal, K.A.; Huntoon, C.L. Thyroid Status of Space Shuttle Crewmembers: Effects of Iodine Removal. *Aviat. Space Environ. Med.* **2011**, *82*, 49–51. https://doi.org/10.3357/ASEM.2926.2011.
82. Mishra, B.; Luderer, U. Reproductive hazards of space travel in women and men. *Nat. Rev. Endocrinol.* **2019**, *15*, 713–730. https://doi.org/10.1038/s41574-019-0267-6.
83. Amann, R.P.; Deaver, D.R.; Zirkin, B.R.; Grills, G.S.; Sapp, W.J.; Veeramachaneni, D.N.; Clemens, J.W.; Banerjee, S.D.; Folmer, J.; Gruppi, C.M.; et al. Effects of microgravity or simulated launch on testicular function in rats. *J. Appl. Physiol.* **1992**, *73*, S174–S185. https://doi.org/10.1152/jappl.1992.73.2.S174.
84. Berardini, M.; Gesualdi, L.; Morabito, C.; Ferranti, F.; Reale, A.; Zampieri, M.; Karpach, K.; Tinari, A.; Bertuccini, L.; Guarnieri, S.; et al. Simulated Microgravity Exposure Induces Antioxidant Barrier Deregulation and Mitochondria Enlargement in TCam-2 Cell Spheroids. *Cells* **2023**, *12*, 2106. https://doi.org/10.3390/cells12162106.
85. Morabito, C.; Guarnieri, S.; Berardini, M.; Gesualdi, L.; Ferranti, F.; Reale, A.; Ricci, G.; Catizone, A.; Mariggiò, M. Microgravity-Induced Metabolic Response in 2D and 3D TCam-2 Cell Cultures. *Biol. Life Sci. Forum* **2023**, *21*, 7. https://doi.org/10.3390/blsf2023021007.
86. Cutigni, M.; Cucina, G.; Galante, E.; Cerri, M.; Bizzarri, M. Microgravity impairs endocrine signaling and reproductive health of women. A narrative review. *Front. Physiol.* **2025**, *16*, 1558711. https://doi.org/10.3389/fphys.2025.1558711.
87. Arnold, C.; Casaletto, J.; Heller, P. Spaceflight Disrupts Gene Expression of Estrogen Signaling in Rodent Mammary Tissue. *Med. Res. Arch.* **2024**, *12(3)*. https://doi.org/10.18103/mra.v12i3.5220.
88. Mathyk, B.; Imudia, A.N.; Quaas, A.M.; Halicigil, C.; Karouia, F.; Avci, P.; Nelson, N.G.; Guzeloglu-Kayisli, O.; Denbo, M.; Sanders, L.M.; et al. Understanding how space travel affects the female reproductive system to the Moon and beyond. *Npj Womens Health* **2024**, *2*, 20. https://doi.org/10.1038/s44294-024-00009-z.
89. Bizzarri, M.; Gaudenzi, P.; Angeloni, A. The biomedical challenge associated with the Artemis space program. *Acta Astronaut.* **2023**, *212*, 14–28. https://doi.org/10.1016/j.actaastro.2023.07.021.
90. Hughson, R.L.; Helm, A.; Durante, M. Heart in space: Effect of the extraterrestrial environment on the cardiovascular system. *Nat. Rev. Cardiol.* **2018**, *15*, 167–180. https://doi.org/10.1038/nrcardio.2017.157.
91. Overbey, E.G.; Kim, J.; Tierney, B.T.; Park, J.; Houerbi, N.; Lucaci, A.G.; Garcia Medina, S.; Damle, N.; Najjar, D.; Grigorev, K. The Space Omics and Medical Atlas (SOMA) and international astronaut biobank. *Nature* **2024**, *632*, 1145–1154. https://doi.org/10.1038/s41586-024-07639-y.
92. Jones, C.W.; Overbey, E.G.; Lacombe, J.; Ecker, A.J.; Meydan, C.; Ryon, K.; Tierney, B.; Damle, N.; MacKay, M.; Afshin, E.E. Molecular and physiological changes in the SpaceX Inspiration4 civilian crew. *Nature* **2024**, *632*, 1155–1164. https://doi.org/10.1038/s41586-024-07648-x.
93. Van Ombergen, A.; Jillings, S.; Jeurissen, B.; Tomilovskaya, E.; Rumshiskaya, A.; Litvinova, L.; Nosikova, I.; Pechenkova, E.; Rukavishnikov, I.; Manko, O.; et al. Brain ventricular volume changes induced by long-duration spaceflight. *Proc. Natl. Acad. Sci. USA* **2019**, *116*, 10531–10536. https://doi.org/10.1073/pnas.1820354116.

94. Roberts, D.R.; Brown, T.R.; Nietert, P.J.; Eckert, M.A.; Inglesby, D.C.; Bloomberg, J.J.; George, M.S.; Asemani, D. Prolonged Microgravity Affects Human Brain Structure and Function. *Am. J. Neuroradiol.* **2019**, *40*, 1878–1885. https://doi.org/10.3174/ajnr.A6249.
95. Lee, A.G.; Mader, T.H.; Gibson, C.R.; Tarver, W.; Rabiei, P.; Riascos, R.F.; Galdamez, L.A.; Brunstetter, T. Spaceflight associated neuro-ocular syndrome (SANS) and the neuro-ophthalmologic effects of microgravity: A review and an update. *Npj Microgravity* **2020**, *6*, 7. https://doi.org/10.1038/s41526-020-0097-9.
96. Voorhies, A.A.; Ott, C.M.; Mehta, S.; Pierson, D.L.; Crucian, B.E.; Feiveson, A.; Oubre, C.M.; Torralba, M.; Moncera, K.; Zhang, Y.; et al. Study of the impact of long-duration space missions at the International Space Station on the astronaut microbiome. *Sci. Rep.* **2019**, *9*, 9911. https://doi.org/10.1038/s41598-019-46303-8.
97. Clément, G.R.; Bukley, A.P.; Paloski, W.H. Artificial gravity as a countermeasure for mitigating physiological deconditioning during long-duration space missions. *Front. Syst. Neurosci.* **2015**, *9*, 92. https://doi.org/10.3389/fnsys.2015.00092.
98. Clément, G.; Rittweger, J.; Nitsche, A.; Doering, W.; Frings-Meuthen, P.; Hand, O.; Frett, T.; Noppe, A.; Paulke, F.; Lecheler, L.; et al. Assessing the effects of artificial gravity in an analog of long-duration spaceflight: The protocol and implementation of the AGBRESA bed rest study. *Front. Physiol.* **2022**, *13*, 976926. https://doi.org/10.3389/fphys.2022.976926.
99. Minetti, A.E.; Luciano, F.; Natalucci, V.; Pavei, G. Horizontal running inside circular walls of Moon settlements: A comprehensive countermeasure for low-gravity deconditioning? *R. Soc. Open Sci.* **2024**, *11*, 231906. https://doi.org/10.1098/rsos.231906.
100. Szocik, K.; Braddock, M. Why Human Enhancement is Necessary for Successful Human Deep-space Missions. *New Bioeth.* **2019**, *25*, 295–317. https://doi.org/10.1080/20502877.2019.1667559.

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