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Fisiología humana en el espacio profundo: adaptación cardiovascular y metabólica durante vuelos espaciales de larga duración

Human Physiology in Deep Space: Cardiovascular and Metabolic Adaptation to Long-Duration Spaceflight

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RESUMEN

Los vuelos espaciales humanos de larga duración exponen al organismo a un ambiente caracterizado por microgravedad, modificación de la carga mecánica, redistribución cefálica de líquidos, exposición a radiación, confinamiento y otros factores capaces de alterar la homeostasis fisiológica. Esta revisión tuvo como objetivo analizar e integrar la evidencia actual sobre las adaptaciones cardiovasculares, metabólicas y sistémicas asociadas con misiones espaciales

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prolongadas, con énfasis en sus mecanismos, patrones de recuperación y relevancia para la futura exploración humana. Se realizó una revisión narrativa estructurada basada en el método científico mediante literatura internacional revisada por pares, priorizando estudios indexados en PubMed/MEDLINE y Scopus, así como evidencia procedente de vuelos espaciales humanos, investigaciones longitudinales, reportes clínicamente relevantes y estudios fisiológicos complementarios. La evidencia revisada identificó las respuestas cardiovasculares y hemodinámicas como el principal dominio de investigación, destacando la redistribución de líquidos, regulación del volumen plasmático, remodelado cardíaco y vascular, alteraciones de la circulación venosa, regulación de la presión arterial e intolerancia ortostática posterior al vuelo. Los hallazgos metabólicos y musculoesqueléticos incluyeron descarga mecánica, modificaciones del remodelado óseo y la regulación mineral, desacondicionamiento físico y alteraciones capaces de persistir después del retorno a la gravedad. Las respuestas renales, inmunológicas, moleculares, neurovasculares y neurooculares confirmaron el carácter multisistémico de la adaptación humana al vuelo espacial prolongado. La recuperación mostró diferencias entre los sistemas fisiológicos: la regulación del volumen de líquidos presentó una readaptación comparativamente rápida, mientras que la función cardiovascular, la estructura cardíaca y las respuestas inmunológicas o moleculares mostraron trayectorias variables, y algunas alteraciones esqueléticas y neurooculares presentaron una recuperación más lenta o incompleta. Estos hallazgos indican que los vuelos espaciales de larga duración deben comprenderse como un desafío fisiológico integrado que requiere vigilancia longitudinal e individualizada. Las futuras misiones lunares, marcianas y de espacio profundo requerirán contramedidas cardiovasculares, metabólicas, musculoesqueléticas y sistémicas combinadas, además de evaluación médica autónoma y una mayor colaboración internacional para preservar la reserva fisiológica y la capacidad operativa durante la exploración humana sostenida más allá de la Tierra.

PALABRAS CLAVE

medicina aeroespacial, vuelos espaciales de larga duración, microgravedad, adaptación cardiovascular, adaptación metabólica, desacondicionamiento cardiovascular, redistribución de líquidos, remodelado cardíaco, pérdida ósea, fisiología humana, exploración del espacio profundo

ABSTRACT

Long-duration human spaceflight exposes the organism to an environment characterized by microgravity, altered mechanical loading, cephalad fluid redistribution, radiation exposure, confinement, and other factors capable of modifying physiological homeostasis. This review aimed to analyze and integrate current evidence concerning cardiovascular, metabolic, and systemic adaptations associated with prolonged space missions, emphasizing their mechanisms, recovery patterns, and relevance to future human exploration. A structured narrative review based on the scientific method was conducted using international peer-reviewed literature, with priority given to studies indexed in PubMed/MEDLINE and Scopus and to evidence derived from human spaceflight, longitudinal observations, clinically relevant reports, and complementary physiological investigations. The reviewed evidence identified cardiovascular and hemodynamic responses as the predominant research domain, particularly fluid redistribution, plasma-volume regulation, cardiac and vascular remodeling, altered venous circulation, blood-pressure regulation, and postflight orthostatic intolerance. Metabolic and musculoskeletal findings included mechanical unloading, changes in bone remodeling and mineral regulation, physical deconditioning, and alterations that may persist after return to gravity. Renal, immune, molecular, neurovascular, and neuro-ocular responses further demonstrated the multisystem nature of human adaptation to prolonged spaceflight. Recovery was heterogeneous among physiological domains: fluid-volume regulation tended to readjust comparatively rapidly, whereas cardiovascular function, cardiac structure, and immune or molecular responses showed variable trajectories, and some skeletal and neuro-ocular alterations demonstrated slower or incomplete recovery. These findings indicate that long-duration spaceflight should be understood as an integrated physiological challenge requiring longitudinal and individualized monitoring. Future lunar, Martian, and deep-space missions will require combined cardiovascular, metabolic, musculoskeletal, and systemic countermeasures, together with autonomous medical assessment and broader international collaboration to preserve physiological reserve and operational capacity during sustained human exploration beyond Earth.

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IECCMEXICO Review

KEYWORDS

aerospace medicine, long-duration spaceflight, microgravity, cardiovascular adaptation, metabolic adaptation, cardiovascular deconditioning, fluid redistribution, cardiac remodeling, bone loss, human physiology, deep-space exploration

INTRODUCCIÓN

Human exploration beyond low-Earth orbit is entering a period in which the physiological limits of prolonged exposure to the space environment have become increasingly relevant to clinical medicine, aerospace medicine, and cardiovascular science. Unlike short-duration missions, extended stays in microgravity expose the human organism to a sustained combination of gravitational unloading, cephalad fluid redistribution, altered mechanical loading, radiation, confinement, circadian disruption, nutritional constraints, and operational stress. These conditions challenge physiological systems that evolved under a constant terrestrial gravitational field and require continuous adaptation to preserve cardiovascular stability, metabolic homeostasis, musculoskeletal integrity, and adequate organ function. Although many of these adaptations are initially compensatory, their persistence during long-duration missions may contribute to clinically relevant alterations during flight and particularly during the transition back to a gravitational environment (Hargens & Richardson, 2009; Norsk et al., 2015; Garrett-Bakelman et al., 2019).

Among these changes, cardiovascular adaptation represents one of the most important areas of concern because the cardiovascular system responds almost immediately to gravitational unloading. On Earth, gravity produces a hydrostatic pressure gradient that contributes to the distribution of blood and extracellular fluid toward the lower extremities while regulatory mechanisms maintain cerebral perfusion and arterial pressure. In microgravity, the disappearance of this gravitational gradient produces a rapid redistribution of fluid toward the thorax, neck, and head. The resulting central volume expansion initiates cardiovascular and neurohumoral responses that modify cardiac preload, vascular tone, plasma volume, renal handling of water and electrolytes, and autonomic regulation. With continued exposure, these early responses become part of a broader process of cardiovascular remodeling and deconditioning (Leach et al., 1996; Hargens & Richardson, 2009).

The reduction in circulating plasma volume observed during spaceflight is particularly important because it demonstrates that adaptation to microgravity cannot be understood simply as a positional redistribution of fluids. Neuroendocrine and renal mechanisms progressively establish a new equilibrium appropriate to the microgravity environment. Consequently, the cardiovascular system operates under physiological conditions substantially different from those encountered on Earth. Studies conducted during long-duration missions have reported changes in ambulatory blood pressure, vascular function, cardiac structure, venous hemodynamics, and responses to orthostatic stress, demonstrating that cardiovascular adaptation is a dynamic process involving multiple regulatory pathways rather than a single hemodynamic alteration (Norsk et al., 2015; Fu et al., 2019; Lee et al., 2020).

Cardiac remodeling constitutes another major component of this adaptation. The reduction in gravitational loading and changes in venous return modify the mechanical demands imposed on the myocardium. Earlier investigations demonstrated reductions in cardiac mass associated with prolonged unloading and spaceflight, supporting the concept that the heart itself undergoes structural adaptation when its usual workload is altered (Perhonen et al., 2001). More recent observations suggest that the magnitude and clinical relevance of cardiac remodeling depend on mission duration, exercise exposure, individual physiology, and the effectiveness of countermeasures. Comparisons between spaceflight and terrestrial conditions characterized by prolonged reductions in gravitational loading have further illustrated how cardiac morphology can respond to sustained changes in mechanical demand (MacNamara et al., 2021). These findings are particularly relevant as future missions may require astronauts to remain in altered gravitational environments for periods considerably longer than those typical of contemporary orbital missions.

A major clinical manifestation of cardiovascular deconditioning becomes apparent when astronauts return to gravity. Orthostatic intolerance may occur when the cardiovascular system, adapted to microgravity, is suddenly required to maintain cerebral perfusion against a restored gravitational gradient. Reduced plasma volume, altered autonomic responses, vascular adaptations, and changes in cardiac filling can collectively impair the capacity to maintain arterial pressure during standing. Historical research identified cardiovascular deconditioning and volume loss as important

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Edition 5, Year 3, Number 2, 2026
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IECCMEXICO Review

determinants of postflight orthostatic intolerance, leading to the development of fluid-loading strategies and other countermeasures (Bungo et al., 1985). Subsequent investigations have demonstrated that appropriate exercise and volume-replacement protocols can substantially improve orthostatic tolerance after prolonged spaceflight, emphasizing that physiological deconditioning can be modified through targeted preventive interventions (Fu et al., 2019).

At the same time, evidence obtained during recent missions has expanded cardiovascular risk assessment beyond traditional concepts of deconditioning. The identification of altered jugular venous flow and venous stasis during spaceflight has raised questions regarding cerebral and cervical venous hemodynamics under sustained microgravity. Marshall-Goebel et al. (2019) reported abnormalities in internal jugular venous flow during long-duration spaceflight, including stagnant or reversed flow in some observations, and documented an unexpected thrombotic event. A subsequent clinical report described venous thrombosis occurring during spaceflight, illustrating that thromboembolic disease must be considered within the spectrum of potential medical complications associated with prolonged missions (Auñón-Chancellor et al., 2020). More recent systematic evaluation of ultrasound-based venous assessment has reinforced the importance of developing reliable screening and monitoring strategies applicable to the operational limitations of spaceflight (Elias et al., 2024).

These cardiovascular phenomena are closely connected with changes occurring in other physiological systems. The metabolic consequences of microgravity include alterations in energy balance, muscle protein turnover, substrate utilization, endocrine signaling, oxidative processes, and body composition. Skeletal muscle unloading reduces the mechanical stimulus required to preserve muscle mass and functional capacity, while diminished skeletal loading promotes increased bone resorption. These processes are clinically relevant because the musculoskeletal system participates directly in glucose disposal, energy metabolism, locomotor capacity, and cardiovascular conditioning. Thus, deterioration in muscle and bone cannot be interpreted as an isolated consequence of weightlessness; rather, it forms part of an interconnected physiological response with implications for metabolic and cardiovascular health.

The skeletal system provides one of the clearest examples of incomplete physiological recovery following prolonged spaceflight. Long-duration exposure to microgravity can produce substantial deterioration in bone microarchitecture, particularly at weight-bearing skeletal sites. Importantly, recovery after return to Earth may be slower than the initial loss. Gabel et al. (2022) demonstrated that bone strength and trabecular microarchitecture at the distal tibia remained incompletely recovered one year after long-duration spaceflight. Such findings have implications beyond immediate mission performance, particularly as exploration programs consider repeated missions or prolonged stays in environments with reduced gravity. Bone loss also interacts with calcium metabolism and renal physiology, potentially contributing to increased urinary calcium excretion and renal stone risk, a complication previously identified as relevant during and after long-duration missions (Whitson et al., 2001).

Long-duration spaceflight also generates systemic molecular and metabolic changes that extend beyond conventional organ-based descriptions. The NASA Twins Study provided an unusually comprehensive examination of human adaptation during approximately one year in space, identifying changes across genomic, epigenetic, transcriptomic, proteomic, metabolomic, immune, microbiome, cardiovascular, and cognitive domains. Although many alterations returned toward baseline following the mission, others showed delayed or incomplete recovery, demonstrating that prolonged spaceflight produces an integrated biological response across multiple levels of organization (Garrett-Bakelman et al., 2019). These findings support a systems-medicine perspective in which cardiovascular and metabolic adaptation should be examined alongside immune regulation, oxidative stress, mitochondrial function, and other interconnected processes.

Immune dysregulation is particularly relevant within this framework. Spaceflight combines microgravity with psychological stress, altered sleep, radiation exposure, confinement, and other environmental factors capable of influencing immune function. Evidence has demonstrated changes in leukocyte distribution and function, inflammatory signaling, latent viral reactivation, and immune regulation during spaceflight. Such alterations may become increasingly important as missions extend beyond low-Earth orbit, where evacuation and access to terrestrial medical infrastructure would be severely limited. Crucian et al. (2018) emphasized that immune dysregulation represents a meaningful concern for deep-space exploration and that countermeasures will need to address both environmental and host-related determinants of immune function.

Edición 5, Año 3, Número 2, 2026
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Revista IECCMEXICO

The cephalad redistribution of fluids also has consequences for cerebral and ocular physiology. Prolonged spaceflight has been associated with neuro-ocular abnormalities collectively described as spaceflight-associated neuro-ocular syndrome (SANS). Reported manifestations include optic disc edema, globe flattening, choroidal and retinal changes, and hyperopic refractive shifts. Although its pathophysiology remains incompletely resolved, sustained alterations in cranial fluid dynamics and venous pressure have been proposed as important contributors (Lee et al., 2020; Martin Paez et al., 2020). Measurements suggesting changes in estimated intracranial pressure and cerebral blood velocity during long-duration spaceflight further demonstrate the complexity of cerebrovascular adaptation to microgravity (Iwasaki et al., 2021). Current models increasingly recognize that SANS may arise from interactions among venous congestion, cerebrospinal fluid dynamics, individual anatomical susceptibility, mission duration, and other physiological factors rather than from a single mechanism (Ong et al., 2023).

The importance of understanding these processes is amplified by the transition from orbital missions toward sustained human exploration of the Moon and Mars. A mission to Mars would expose crew members to prolonged microgravity during transit, altered gravity on the planetary surface, and another prolonged period of microgravity during return. The medical implications differ substantially from those of missions in low-Earth orbit, where emergency return can potentially occur within hours. During deep-space exploration, cardiovascular instability, metabolic deterioration, thrombotic events, renal complications, or progressive musculoskeletal loss would need to be identified and managed with limited diagnostic resources and delayed or unavailable terrestrial support. Consequently, preventive medicine, autonomous monitoring, individualized risk assessment, and effective countermeasures become essential components of mission architecture rather than supplementary clinical considerations.

The relevance of these investigations extends beyond astronaut health. Spaceflight can function as an extreme physiological model for studying mechanisms that are also encountered in terrestrial medicine, including physical inactivity, prolonged immobilization, cardiovascular deconditioning, muscle wasting, bone loss, vascular dysfunction, altered insulin sensitivity, and aging-related physiological decline. Cardiac changes associated with unloading, for example, may contribute to understanding myocardial plasticity during prolonged inactivity, whereas orthostatic intolerance research may inform the management of patients affected by extended bed rest or autonomic dysfunction. Similarly, accelerated bone and muscle loss during microgravity offers a distinctive model for examining mechanisms that develop more gradually in osteoporosis, sarcopenia, and chronic disease. The translational value of aerospace medicine therefore lies not only in protecting crews but also in using extreme environments to clarify fundamental mechanisms of human adaptation.

Despite major advances, several questions remain unresolved. The degree to which cardiovascular, metabolic, and systemic changes become clinically significant during missions lasting several years is not fully established. Interindividual variability remains considerable, and biological responses observed during six- or twelve-month orbital missions cannot automatically be extrapolated to multiyear exploration missions. The long-term consequences of repeated exposure, the interaction between microgravity and radiation, the reversibility of structural changes, the significance of venous abnormalities, and the optimal combination of exercise, nutritional, pharmacological, and technological countermeasures continue to require investigation. Furthermore, much of the available evidence originates from relatively small astronaut cohorts, an unavoidable limitation of human spaceflight research that makes integration of longitudinal studies, terrestrial analogues, mechanistic experiments, and multimodal physiological data particularly important.

Within the international context, these challenges also create opportunities for broader scientific cooperation. Human space exploration increasingly involves multinational agencies, academic institutions, biomedical researchers, commercial operators, and emerging space programs. Latin American countries possess growing capabilities in aerospace medicine, physiology, biomedical engineering, remote health, and space sciences that may contribute to future international research networks. Expanding participation from Latin America and other underrepresented regions could strengthen the external relevance of space-health research by incorporating broader scientific expertise and supporting the development of medical technologies with applications both in exploration missions and in terrestrial populations.

Against this background, the present review addresses the following central question: **How does prolonged exposure to the space environment modify cardiovascular, metabolic, and systemic human physiology, and which**

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IECCMEXICO Review

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Revista IECCMEXICO

adaptations are most relevant to health preservation during long-duration missions? The working premise is that prolonged spaceflight induces an interconnected adaptive response in which cardiovascular deconditioning, fluid redistribution, metabolic remodeling, musculoskeletal unloading, neurohumoral regulation, and other systemic alterations cannot be adequately understood in isolation. A second question concerns reversibility: **Which physiological changes normalize after return to gravity, and which may persist sufficiently to influence long-term health or operational performance?** Finally, the review examines how current evidence can inform preventive strategies and countermeasures for future exploration missions.

To address these questions, the study was structured as a narrative review of international biomedical literature, prioritizing peer-reviewed evidence relevant to human long-duration spaceflight and its principal physiological consequences. The literature base included studies indexed in major biomedical and multidisciplinary databases, with particular attention to investigations of astronauts, longitudinal spaceflight observations, physiological monitoring, clinically relevant reports, systematic reviews, and terrestrial analogues capable of clarifying mechanisms that cannot be investigated directly in large astronaut populations. Evidence was organized around cardiovascular adaptation, fluid regulation, vascular and thrombotic phenomena, metabolic and musculoskeletal changes, renal physiology, immune regulation, cerebral and neuro-ocular responses, recovery following return to gravity, and available countermeasures. This approach permits integration of organ-specific observations into a broader model of systemic adaptation while identifying areas in which current evidence remains insufficient.

Accordingly, the objective of this review is to critically integrate current knowledge regarding cardiovascular, metabolic, and physiological adaptations during long-duration space missions, emphasizing their mechanisms, clinical relevance, reversibility, interactions, and implications for future human exploration. By connecting cardiovascular medicine with systemic physiology and aerospace medicine, this review seeks to provide a clinically oriented framework for understanding how the human body adapts beyond Earth and which physiological vulnerabilities should receive priority as mission duration and distance from terrestrial medical support increase.

DESARROLLO

Long-duration spaceflight represents a complex physiological challenge because the human body must maintain homeostasis in an environment fundamentally different from terrestrial conditions. Microgravity modifies hydrostatic pressure gradients, reduces mechanical loading, alters fluid distribution, and changes the regulatory demands placed on cardiovascular, metabolic, musculoskeletal, renal, neurological, and immune systems. These effects become progressively more relevant as mission duration increases, particularly when adaptation must be maintained for months and followed by re-exposure to gravity during planetary landing or return to Earth.

One of the earliest physiological responses to microgravity is the cephalad redistribution of body fluids. In the absence of the terrestrial hydrostatic gradient, blood and interstitial fluid shift from the lower extremities toward the thorax, neck, and head. This produces an initial increase in central blood volume and cardiac filling, followed by compensatory renal and neuroendocrine responses that contribute to a reduction in plasma volume. Over time, the cardiovascular system adapts to a lower effective circulatory demand, which may promote cardiac remodeling, reduced orthostatic tolerance, and altered autonomic control (Leach et al., 1996; Hargens & Richardson, 2009; Norsk et al., 2015).

Cardiovascular adaptation is not limited to changes in volume regulation. Evidence from long-duration missions has demonstrated modifications in arterial structure, blood pressure behavior, cardiac loading, and venous circulation. Lee et al. (2020) described measurable changes in arterial structure and function during and after prolonged spaceflight, while Fu et al. (2019) showed that orthostatic tolerance after return to Earth depends strongly on the effectiveness of in-flight exercise and volume-replacement strategies. These findings indicate that cardiovascular deconditioning is partly preventable, but also highly influenced by mission duration, individual susceptibility, and the intensity of countermeasures.

Venous circulation has received increasing attention because of reports of abnormal jugular flow, venous stasis, and thrombosis during spaceflight. Marshall-Goebel et al. (2019) identified alterations in internal jugular venous hemodynamics during long-duration missions, including stagnant and reversed blood flow. The subsequent description

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IECCMEXICO Review

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Revista IECCMEXICO

of venous thrombosis during spaceflight reinforced the clinical relevance of this phenomenon and demonstrated that thromboembolic complications should be considered in future mission medical planning (Auñón-Chancellor et al., 2020). More recent evaluations have also supported ultrasound as an important tool for monitoring venous physiology in microgravity, particularly because it can be adapted for autonomous or remotely supervised use (Elias et al., 2024).

The metabolic response to prolonged microgravity is closely related to reduced mechanical activity and changes in body composition. Muscle unloading decreases contractile demand and contributes to progressive atrophy, especially in antigravity muscle groups. This reduction in active muscle mass can alter glucose utilization, protein turnover, and overall energy metabolism. At the same time, skeletal unloading accelerates bone resorption and reduces bone strength. Gabel et al. (2022) demonstrated that some alterations in trabecular microarchitecture and bone strength remained incompletely recovered even one year after long-duration spaceflight, suggesting that physiological recovery may extend considerably beyond mission completion.

Bone demineralization also has systemic consequences. Increased calcium release from bone may alter renal mineral handling and contribute to stone formation, particularly when combined with reduced fluid intake or changes in urine chemistry. Whitson et al. (2001) previously identified renal stone formation as an important risk during and after long-duration spaceflight. For this reason, metabolic, skeletal, and renal adaptations must be considered as interdependent components rather than isolated physiological effects.

Another important feature of prolonged spaceflight is the interaction between cardiovascular adaptation and cranial fluid dynamics. Cephalad fluid shifts may contribute to changes in cerebral venous drainage, intracranial pressure estimates, and ocular structure. Long-duration missions have been associated with spaceflight-associated neuro-ocular syndrome, characterized by findings such as optic disc edema, globe flattening, retinal and choroidal changes, and refractive alterations (Lee et al., 2020; Martin Paez et al., 2020). Iwasaki et al. (2021) also described changes in estimated intracranial pressure and cerebral blood velocity, reinforcing the hypothesis that prolonged microgravity affects both cardiovascular and neurovascular regulation.

At the systemic level, prolonged spaceflight also influences immune regulation, inflammatory activity, oxidative balance, and molecular signaling. The NASA Twins Study demonstrated that approximately one year of spaceflight was associated with changes across several biological domains, including transcriptomics, metabolomics, immune function, microbiome composition, cardiovascular physiology, and cognition (Garrett-Bakelman et al., 2019). Although many variables moved toward baseline after return to Earth, some showed delayed recovery, highlighting the need to study not only adaptation during flight but also the duration and completeness of postflight physiological restoration.

Immune dysregulation is particularly important because long missions combine microgravity with confinement, altered circadian rhythms, psychological stress, radiation exposure, and limited environmental variability. These conditions may affect leukocyte function, inflammatory signaling, and latent viral reactivation. Crucian et al. (2018) emphasized that immune alterations could become more relevant during deep-space missions, where medical evacuation is not immediately available and minor physiological disturbances may acquire greater operational importance.

The available evidence therefore supports the concept that human adaptation to long-duration spaceflight is a coordinated but potentially vulnerable process. Cardiovascular remodeling, fluid redistribution, metabolic changes, bone and muscle loss, venous alterations, immune dysregulation, and neuro-ocular effects occur simultaneously and may influence one another. This interaction becomes especially important when considering future missions to Mars, where prolonged transit, partial gravity, radiation exposure, delayed communication, and limited medical resources will create conditions substantially more demanding than current orbital missions.

From a clinical perspective, the central challenge is not simply to determine whether physiological changes occur, but to identify which changes represent effective adaptation and which may evolve into health risks. Some responses may be reversible and functionally appropriate in microgravity, whereas others may persist after return to gravity or reduce physiological reserve during emergency situations. Consequently, understanding the mechanisms, magnitude, duration, and reversibility of these adaptations is essential for the development of individualized countermeasures, improved monitoring strategies, and safer long-duration human exploration beyond Earth.

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IECCMEXICO Review

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Revista IECCMEXICO

Edition 5, Year 3, Number 2, 2026
E-ISSN: 3061-8045, P-ISSN: 3061-8517
IECCMEXICO Review

OBJETIVO GENERAL Y OBJETIVOS ESPECÍFICOS

General Objective

To **analyze and integrate** the available scientific evidence on cardiovascular, metabolic, and systemic physiological adaptations associated with long-duration space missions, identifying their principal mechanisms, clinical relevance, reversibility, and interactions in order to **evaluate** their implications for human health and the development of preventive and monitoring strategies for future space exploration.

Specific Objectives

Cognitive Domain

1. **Identify** the principal cardiovascular, metabolic, and systemic physiological adaptations associated with prolonged exposure to microgravity and the space environment.
2. **Analyze** the mechanisms involved in fluid redistribution, cardiovascular deconditioning, cardiac remodeling, vascular regulation, metabolic changes, and musculoskeletal deterioration during long-duration space missions.
3. **Compare** physiological responses occurring during spaceflight with those observed after return to a gravitational environment, emphasizing their reversibility and potential clinical relevance.
4. **Evaluate** current scientific evidence regarding cardiovascular, metabolic, renal, immune, musculoskeletal, and neurophysiological alterations to determine their implications for future long-duration human space exploration.

Psychomotor Domain

1. **Apply** physiological knowledge to the interpretation of cardiovascular, metabolic, and functional parameters used for monitoring human adaptation during long-duration space missions.
2. **Integrate** information obtained through clinical and physiological assessment tools, including cardiovascular measurements, ultrasound evaluation, body composition assessment, exercise testing, and biochemical monitoring.
3. **Develop** a structured framework for the assessment of physiological adaptations and potential health risks associated with prolonged exposure to microgravity.

Affective Domain

1. **Recognize** the importance of continuous health monitoring and preventive strategies for preserving astronaut health and functional capacity during long-duration missions.

2. **Value** interdisciplinary and international collaboration among aerospace medicine, internal medicine, cardiology, physiology, and related biomedical disciplines in addressing the health challenges of human space exploration.

3. **Promote** a preventive and evidence-based perspective toward the identification, monitoring, and management of physiological risks associated with future lunar, Martian, and deep-space missions.

OBJETO DE ESTUDIO

The object of study of this review is the **cardiovascular, metabolic, and systemic physiological adaptation of the human organism to long-duration space missions**, with particular emphasis on the biological responses associated with prolonged exposure to microgravity and other characteristics of the space environment.

The phenomenon under investigation comprises the physiological modifications that occur during extended spaceflight and the subsequent process of readaptation to gravitational conditions. Particular attention is given to cardiovascular responses, including cephalad fluid redistribution, plasma volume reduction, cardiac remodeling, vascular and autonomic regulation, venous hemodynamics, thrombotic risk, and orthostatic intolerance. These changes constitute a

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Revista IECCMEXICO

central component of space adaptation because they influence tissue perfusion, exercise capacity, functional performance, and the ability to tolerate gravitational transitions (Norsk et al., 2015; Fu et al., 2019; Marshall-Goebel et al., 2019).

The object of study also includes metabolic and musculoskeletal adaptations resulting from prolonged mechanical unloading. Changes in energy metabolism, muscle mass and function, bone remodeling, mineral balance, and renal physiology are considered because of their interaction with cardiovascular health and overall physiological reserve. Evidence showing incomplete recovery of bone strength following long-duration missions illustrates that some adaptations may persist beyond the period of exposure to microgravity (Gabel et al., 2022).

Additionally, immune, neurovascular, and neuro-ocular responses are incorporated when they contribute to understanding systemic adaptation. This includes immune dysregulation, altered cerebral and venous fluid dynamics, and spaceflight-associated neuro-ocular syndrome, recognizing that prolonged spaceflight generates interconnected responses rather than independent changes within isolated organs (Crucian et al., 2018; Garrett-Bakelman et al., 2019; Lee et al., 2020).

The population of interest consists primarily of **adult human spaceflight participants exposed to extended orbital missions**, complemented by evidence from terrestrial analogues and physiological models when necessary to clarify mechanisms or responses that cannot be studied extensively in astronaut populations. Particular relevance is assigned to findings applicable to future lunar, Martian, and deep-space missions.

Therefore, the object of study is defined as the **integrated human physiological response to prolonged spaceflight**, analyzed through cardiovascular, metabolic, and systemic dimensions and their implications for adaptation, recovery, functional capacity, and health preservation during future exploration beyond Earth.

METODOLOGÍA

This study was conducted as a **structured narrative review based on the scientific method**, designed to identify, analyze, and integrate international evidence concerning cardiovascular, metabolic, and physiological adaptations during long-duration space missions. The methodological process followed sequential stages of problem definition, formulation of research questions, systematic literature identification, evidence selection, thematic classification, critical analysis, and integrative synthesis.

Study Design

A narrative literature review with a structured search strategy was selected because the research question encompasses multiple physiological systems, heterogeneous study designs, human spaceflight observations, clinical reports, longitudinal investigations, and complementary physiological evidence. Rather than estimating a single intervention effect, the review sought to construct an integrated interpretation of human adaptation to prolonged spaceflight.

The scientific method provided the general methodological framework. The initial observation was that prolonged exposure to the space environment produces cardiovascular and systemic alterations whose interactions and long-term significance remain incompletely characterized. From this problem, research questions were formulated regarding the mechanisms, clinical relevance, reversibility, and potential prevention of these physiological changes.

Search Strategy

The literature search prioritized scientific publications indexed in **PubMed/MEDLINE and Scopus**, complemented by relevant peer-reviewed publications identified through reference tracking. Search terms were organized around four conceptual domains: space exposure, cardiovascular physiology, metabolic and systemic adaptation, and long-duration missions.

Edition 5, Year 3, Number 2, 2026
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IECCMEXICO Review

Edición 5, Año 3, Número 2, 2026
E-ISSN: 3061-8045, P-ISSN: 3061-8517
Revista IECCMEXICO

Search combinations included terms such as *spaceflight*, *long-duration spaceflight*, *microgravity*, *human physiology*, *cardiovascular adaptation*, *cardiovascular deconditioning*, *fluid shift*, *orthostatic intolerance*, *cardiac remodeling*, *vascular function*, *venous thrombosis*, *metabolism*, *bone loss*, *muscle atrophy*, *renal physiology*, *immune dysregulation*, and *spaceflight-associated neuro-ocular syndrome*. Boolean operators **AND** and **OR** were used to combine concepts and broaden or restrict retrieval according to each thematic domain.

Eligibility Criteria

Studies were considered eligible when they addressed physiological adaptations associated with human spaceflight, particularly prolonged exposure to microgravity; evaluated cardiovascular, metabolic, musculoskeletal, renal, immune, neurovascular, or related systemic responses; or provided clinically relevant information regarding recovery and countermeasures.

Priority was given to peer-reviewed original investigations, longitudinal studies, systematic reviews, major narrative reviews, and clinically relevant reports. Human evidence was prioritized, while terrestrial analogues and mechanistic studies were considered when they contributed directly to explaining physiological mechanisms that are difficult to investigate during actual missions.

Publications without a clear relationship to human physiological adaptation, non-scientific sources, duplicated records, and documents lacking sufficient methodological or clinical relevance were excluded from the principal synthesis.

Evidence Selection and Organization

Following identification, publications were evaluated according to their relevance to the objectives of the review. The selected literature was organized into thematic categories: cardiovascular adaptation and fluid redistribution; cardiac and vascular remodeling; orthostatic intolerance; venous circulation and thrombotic risk; metabolic adaptation; musculoskeletal changes; renal and mineral regulation; immune responses; cerebral and neuro-ocular physiology; postflight recovery; and preventive countermeasures.

A core set of **20 scientific references** was used to support the integrative analysis. Emphasis was placed on evidence derived from astronaut observations and international research collaborations, while findings from complementary models were used to contextualize mechanisms and address areas where direct human spaceflight evidence remains limited.

Data Analysis and Synthesis

The selected evidence was analyzed qualitatively. Findings were compared according to the physiological system evaluated, duration of exposure, direction of physiological change, recovery after return to gravity, and potential clinical or operational relevance. Particular attention was given to findings reproduced across different investigations and to areas where evidence remains inconsistent or limited.

The final synthesis integrated cardiovascular, metabolic, musculoskeletal, renal, immune, and neurovascular findings within a systemic framework. This approach allowed the review to examine how adaptations interact during prolonged spaceflight and to identify physiological vulnerabilities relevant to future lunar, Martian, and deep-space missions.

Reproducibility

To facilitate replication, the methodological sequence was defined as follows: formulation of the research question, database selection, application of predefined search concepts and Boolean combinations, eligibility assessment, thematic classification, critical comparison of findings, and integrative synthesis. Researchers applying the same databases, conceptual search strategy, eligibility criteria, and thematic categories should be able to reproduce the general evidence-identification process and update the review as new spaceflight research becomes available.

FASES DEL DESARROLLO

Edition 5, Year 3, Number 2, 2026
E-ISSN: 3061-8045, P-ISSN: 3061-8517
IECCMEXICO Review

Edición 5, Año 3, Número 2, 2026
E-ISSN: 3061-8045, P-ISSN: 3061-8517
Revista IECCMEXICO

Phase 1. Identification and Delimitation of the Research Problem

The first phase consisted of defining the central problem: prolonged exposure to the space environment produces physiological adaptations that involve several interconnected systems and may influence health, functional capacity, and postflight recovery. The topic was delimited to cardiovascular, metabolic, and systemic responses associated primarily with long-duration human spaceflight, emphasizing changes with potential clinical and operational relevance.

This delimitation established the cardiovascular system as a principal analytical axis while incorporating metabolic, musculoskeletal, renal, immune, neurovascular, and neuro-ocular responses necessary to understand adaptation as a systemic process.

Phase 2. Formulation of the Research Questions

Based on the identified problem, the review was structured around questions concerning **which physiological adaptations occur during prolonged spaceflight, how these responses interact, what mechanisms explain them, and to what extent they are reversible after return to gravity**.

A further question addressed which physiological changes may transition from adaptive responses to potential health risks during longer missions. This distinction was considered particularly relevant to future lunar and Martian exploration, where prolonged exposure and limited access to terrestrial medical support may increase the consequences of physiological deterioration.

Phase 3. Identification of Scientific Evidence

A structured search of the biomedical literature was conducted using PubMed/MEDLINE and Scopus as the principal databases. Keywords and Boolean combinations related to *microgravity*, *long-duration spaceflight*, *cardiovascular adaptation*, *fluid shifts*, *cardiac remodeling*, *orthostatic intolerance*, *venous thrombosis*, *metabolic adaptation*, *bone loss*, *muscle atrophy*, *immune dysregulation*, and *neuro-ocular alterations* were used to identify relevant publications.

The search emphasized peer-reviewed international literature and evidence derived from human spaceflight. Complementary physiological studies and terrestrial analogues were considered when they contributed to the interpretation of mechanisms that cannot be extensively investigated in astronaut populations.

Phase 4. Selection and Critical Assessment

The identified publications were screened according to their relationship with the objectives and object of study. Priority was assigned to original investigations, longitudinal astronaut studies, systematic reviews, clinically relevant reports, and major physiological analyses.

Studies were assessed according to population, exposure characteristics, physiological variables, methodological relevance, and contribution to understanding long-duration adaptation. Particular attention was given to the limitations associated with small astronaut cohorts, differences in mission duration, individual variability, and the influence of countermeasures.

Phase 5. Thematic Classification of Findings

The selected evidence was organized into major analytical domains: **cardiovascular and hemodynamic adaptation; metabolic and musculoskeletal responses; renal and mineral regulation; immune alterations; neurovascular and neuro-ocular changes; postflight recovery; and preventive countermeasures**.

This classification facilitated comparison among studies while preserving the relationships between systems. For example, fluid redistribution was analyzed not only as a cardiovascular response but also in relation to renal regulation, cerebral circulation, venous hemodynamics, and neuro-ocular alterations.

Phase 6. Integration and Interpretation of Evidence

Edition 5, Year 3, Number 2, 2026
E-ISSN: 3061-8045, P-ISSN: 3061-8517
IECCMEXICO Review

Edición 5, Año 3, Número 2, 2026
E-ISSN: 3061-8045, P-ISSN: 3061-8517
Revista IECCMEXICO

Edition 5, Year 3, Number 2, 2026
E-ISSN: 3061-8045, P-ISSN: 3061-8517
IECCMEXICO Review

The findings were subsequently integrated to identify common physiological patterns, differences between studies, potential mechanisms, and areas of uncertainty. Evidence concerning cardiovascular deconditioning, plasma volume reduction, vascular adaptation, bone and muscle deterioration, venous abnormalities, and systemic regulation was interpreted collectively.

This phase allowed physiological responses to be differentiated according to whether they represented expected adaptation to microgravity, potentially adverse alterations, or changes whose long-term significance remains uncertain. Evidence regarding recovery after return to gravity was also considered to determine which effects appear rapidly reversible and which may persist beyond mission completion.

Phase 7. Synthesis and Clinical-Physiological Application

The final phase consisted of synthesizing the evidence within a framework applicable to aerospace and clinical medicine. The integrated findings were used to characterize the principal physiological vulnerabilities associated with prolonged missions and the role of exercise, nutritional strategies, fluid management, physiological monitoring, ultrasound assessment, and other countermeasures.

The resulting synthesis provides a basis for understanding human adaptation beyond Earth as a dynamic and multisystem process. It also supports the identification of knowledge gaps relevant to future research, particularly regarding multiyear missions, individual susceptibility, long-term recovery, and the development of autonomous medical strategies for exploration beyond low-Earth orbit.

RESULTADOS Y DISCUSIÓN

Figure 1.

Distribution of the reviewed evidence according to the principal physiological domain

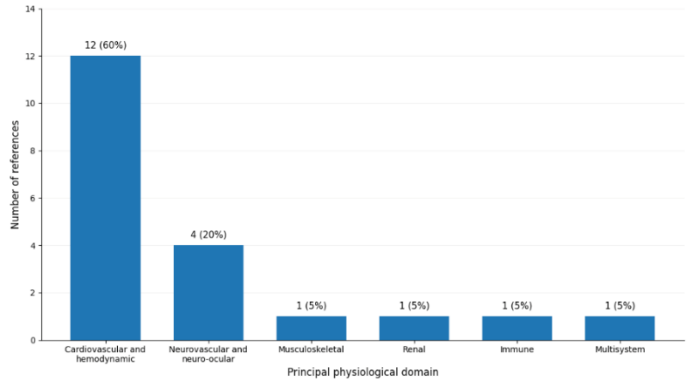

Figure 1 shows the distribution of the 20 core publications included in the review according to the principal physiological domain addressed by each study. Cardiovascular and hemodynamic research represented the largest category, accounting for 12 of the 20 references (60%). Neurovascular and neuro-ocular research represented four publications (20%), while musculoskeletal, renal, immune, and multisystem research each accounted for one publication (5%). The classification reflects the primary analytical focus assigned to each reference; therefore, studies addressing secondary physiological outcomes were retained within their predominant domain to avoid duplicate counting.

The predominance of cardiovascular and hemodynamic evidence was consistent with the central role of circulatory adaptation during exposure to microgravity. Several investigations focused on fluid redistribution and the reduction of circulating volume that occurs as the organism adjusts to the absence of the terrestrial hydrostatic gradient. Early observations demonstrated that spaceflight modifies body-fluid compartments and promotes regulatory responses

Edición 5, Año 3, Número 2, 2026
E-ISSN: 3061-8045, P-ISSN: 3061-8517
Revista IECCMEXICO

involving cardiovascular and renal mechanisms, providing an important basis for subsequent studies of long-duration adaptation (Leach et al., 1996). Hargens and Richardson (2009) similarly described fluid shifts as a major component of cardiovascular adaptation, linking gravitational unloading with changes in central blood volume, vascular regulation, and cardiovascular deconditioning.

Within this cardiovascular group, the reviewed evidence also addressed blood-pressure regulation and orthostatic tolerance. Norsk et al. (2015) reported changes involving fluid shifts, vasodilation, and ambulatory blood pressure during long-duration spaceflight, whereas Fu et al. (2019) evaluated orthostatic tolerance and blood-pressure profiles following prolonged missions. These studies contributed to the characterization of the transition between adaptation to microgravity and cardiovascular readaptation after return to Earth. Historical evidence concerning cardiovascular deconditioning and the use of saline loading as a countermeasure further demonstrated that postflight orthostatic responses have been recognized as an important physiological consequence of spaceflight for several decades (Bungo et al., 1985).

Cardiac and arterial remodeling constituted another component of the cardiovascular evidence represented in the figure. Perhonen et al. (2001) reported cardiac atrophy following prolonged unloading associated with bed rest and spaceflight, supporting the presence of structural cardiac adaptation when gravitational and mechanical demands are reduced. More recent work has expanded this perspective by examining cardiac responses under prolonged weightlessness and other extreme unloading conditions (MacNamara et al., 2021). At the vascular level, Lee et al. (2020) documented changes in arterial structure and function during and after long-duration spaceflight, demonstrating that adaptation extends beyond cardiac performance and circulating volume to the vascular system itself.

Venous hemodynamics also contributed substantially to the cardiovascular category. Arbeille et al. (2015) evaluated changes in the cross-sectional area of major veins during long-duration spaceflight, providing evidence of altered venous blood distribution. Marshall-Goebel et al. (2019) subsequently reported internal jugular venous flow abnormalities, including venous stasis and altered flow patterns. The clinical relevance of these observations was reinforced by the report of venous thrombosis during spaceflight by Auñón-Chancellor et al. (2020). The systematic assessment conducted by Elias et al. (2024) further consolidated ultrasound-based venous evaluation as a relevant component of contemporary spaceflight research.

The second largest category corresponded to neurovascular and neuro-ocular physiology, representing 20% of the selected literature. This evidence primarily addressed alterations associated with cephalad fluid redistribution and its relationship with cerebral circulation and ocular structures. Iwasaki et al. (2021) identified changes in estimated intracranial pressure and cerebral blood velocity during long-duration spaceflight, providing physiological evidence that microgravity affects cranial hemodynamics in addition to systemic circulation.

The remaining neuro-ocular publications concentrated on spaceflight-associated neuro-ocular syndrome. Reviews by Lee et al. (2020) and Martin Paez et al. (2020) described ocular findings associated with prolonged spaceflight and examined proposed mechanisms involving altered cranial fluid dynamics. Ong et al. (2023) subsequently reviewed emerging pathophysiological explanations and mitigation strategies, reflecting the continued development of this research area. Collectively, these studies accounted for the second major concentration of evidence in the reviewed literature.

Musculoskeletal evidence represented 5% of the core references. Gabel et al. (2022) examined bone strength and trabecular microarchitecture after long-duration spaceflight and reported incomplete recovery at the distal tibia one year after return. Although represented by a smaller number of publications within the selected core literature, this study provided longitudinal evidence relevant to the persistence of skeletal alterations after prolonged gravitational unloading.

The renal category also represented 5% of the references. Whitson et al. (2001) evaluated renal stone formation during and after long-duration spaceflight, addressing an important interaction among skeletal demineralization, calcium handling, hydration, urinary composition, and renal physiology. Renal findings therefore appeared in the evidence base both as a specific physiological domain and as part of the mechanisms associated with fluid and mineral regulation.

Edition 5, Year 3, Number 2, 2026
E-ISSN: 3061-8045, P-ISSN: 3061-8517
IECCMEXICO Review

Edición 5, Año 3, Número 2, 2026
E-ISSN: 3061-8045, P-ISSN: 3061-8517
Revista IECCMEXICO

Edition 5, Year 3, Number 2, 2026
E-ISSN: 3061-8045, P-ISSN: 3061-8517
IECCMEXICO Review

Immune physiology accounted for another 5%. Crucian et al. (2018) reviewed immune-system dysregulation during spaceflight and potential countermeasures for deep-space exploration, describing changes in immune regulation that occur within the combined context of microgravity and other mission-related stressors. This evidence expanded the results beyond cardiovascular and mechanical adaptations by incorporating systemic biological responses relevant to prolonged exposure.

Finally, 5% of the selected evidence was classified as multisystem. The NASA Twins Study by Garrett-Bakelman et al. (2019) integrated molecular, cardiovascular, metabolic, immune, microbiome, cognitive, and other biological measurements during approximately one year of human spaceflight. Its inclusion as a multisystem investigation reflects the breadth of variables evaluated rather than assignment to a single organ system. The study also provided longitudinal observations spanning preflight, inflight, and postflight periods, allowing multiple dimensions of physiological adaptation and recovery to be examined within the same research framework.

Figure 2.

Cardiovascular and hemodynamic adaptations identified during long-duration spaceflight

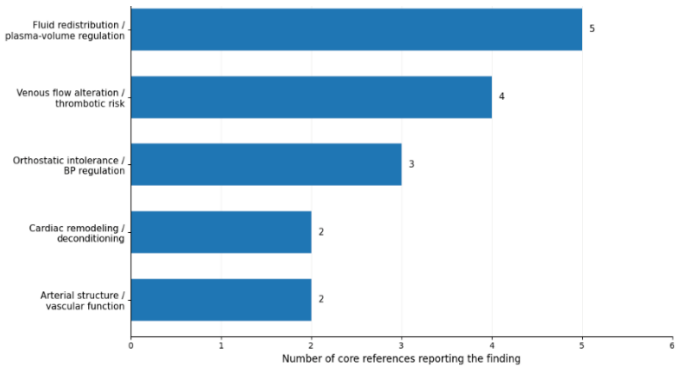

Figure 2 summarizes the principal cardiovascular and hemodynamic findings identified within the core literature, expressed as the number of selected references addressing each major adaptation. Fluid redistribution and plasma-volume regulation constituted the most frequently represented finding, appearing in five core publications. Alterations in venous flow and thrombotic risk were identified in four, orthostatic intolerance and blood-pressure regulation in three, and cardiac remodeling/deconditioning and arterial structure/vascular function in two publications each. Because individual studies could contribute evidence to more than one cardiovascular category, these frequencies represent thematic occurrence rather than mutually exclusive groups.

The predominance of fluid redistribution and plasma-volume regulation reflects one of the earliest and most reproducible physiological responses to gravitational unloading. Under terrestrial conditions, gravity generates hydrostatic gradients that favor blood pooling in dependent regions. During microgravity exposure, this gradient is markedly reduced, producing redistribution of blood and extracellular fluid toward the central and cephalic compartments. Leach et al. (1996) documented changes in body-fluid compartments during spaceflight, while Hargens and Richardson (2009) described the relationship between these fluid shifts and cardiovascular adaptation. Rather than remaining as a transient redistribution phenomenon, central fluid displacement is followed by renal, hormonal, and circulatory adjustments that establish a different volume-regulatory state during continued exposure.

Norsk et al. (2015) further demonstrated that long-duration spaceflight involves changes in fluid distribution together with vasodilation and alterations in ambulatory blood pressure. The evidence therefore showed that volume regulation is closely associated with vascular behavior and arterial-pressure control. These findings were also relevant to postflight physiology because a cardiovascular system adapted to microgravity must rapidly re-establish effective circulatory regulation when gravitational hydrostatic gradients return.

Edición 5, Año 3, Número 2, 2026
E-ISSN: 3061-8045, P-ISSN: 3061-8517
Revista IECCMEXICO

Edition 5, Year 3, Number 2, 2026
E-ISSN: 3061-8045, P-ISSN: 3061-8517
IECCMEXICO Review

The second most frequently represented finding involved **venous flow alteration and thrombotic risk**. Arbeille et al. (2015) demonstrated changes in the dimensions of major venous vessels during long-duration spaceflight, supporting substantial redistribution within the venous circulation. More specifically, Marshall-Goebel et al. (2019) documented abnormal internal jugular venous hemodynamics during spaceflight, including stagnant and reversed flow patterns. These observations provided direct evidence that cephalad fluid redistribution can alter venous circulation in ways that extend beyond conventional descriptions of central volume expansion.

The identification of venous thrombosis during spaceflight further expanded the cardiovascular findings. Auñón-Chancellor et al. (2020) reported a thrombotic event occurring during a mission, while subsequent literature has examined the role of ultrasound in assessing venous flow and identifying thrombosis under spaceflight conditions. Elias et al. (2024) reviewed ultrasound-based approaches for venous assessment and thrombosis screening, demonstrating the increasing attention given to this component of cardiovascular monitoring. Within the reviewed evidence, venous hemodynamics therefore represented a distinct and repeatedly investigated aspect of adaptation.

Orthostatic intolerance and blood-pressure regulation formed the third major cardiovascular category. These findings primarily concerned the transition from microgravity back to terrestrial gravity. Cardiovascular adaptation during flight reduces the need to continuously compensate for gravitational pooling in the lower extremities. When gravity is restored, reduced circulating volume and altered cardiovascular regulation may limit the capacity to maintain arterial pressure and cerebral perfusion during upright posture.

Bungo et al. (1985) described cardiovascular deconditioning and investigated saline administration as a countermeasure for orthostatic intolerance, demonstrating that the phenomenon was already identifiable during earlier stages of human spaceflight research. More recent evidence has provided a more detailed assessment of this response. Fu et al. (2019) evaluated orthostatic tolerance and blood-pressure profiles following prolonged missions and showed that appropriate countermeasures could influence the magnitude of postflight impairment. Norsk et al. (2015) similarly documented blood-pressure adaptations during long-duration exposure, supporting the presence of regulatory changes across both inflight and postflight periods.

Cardiac remodeling and deconditioning were represented by two core studies. Perhonen et al. (2001) reported cardiac atrophy following prolonged bed rest and spaceflight, demonstrating that sustained reductions in mechanical and circulatory loading can produce measurable structural cardiac changes. The heart, like skeletal muscle, adapts to the mechanical demands imposed upon it; consequently, prolonged reduction in loading provides a physiological stimulus for remodeling.

MacNamara et al. (2021) subsequently examined cardiac responses to extreme-duration unloading conditions and compared these findings with spaceflight-associated changes. Together, these studies supported the presence of cardiac structural adaptation during prolonged reductions in gravitational demand. The evidence also demonstrated that cardiac response is not uniform and may be influenced by exercise exposure, mission characteristics, and individual physiological conditions.

Finally, arterial structure and vascular function were represented in two core publications. Lee et al. (2020) evaluated arterial structure and function during and after long-duration spaceflight, identifying vascular changes across the mission and recovery periods. These observations complemented findings concerning blood pressure and cardiac remodeling by showing that adaptation involves the arterial circulation itself. Hargens and Richardson (2009) also described vascular responses as part of the broader cardiovascular adaptation to altered gravitational loading.

Taken together, the findings displayed in Figure 2 demonstrate that the cardiovascular response to long-duration spaceflight involves several simultaneous components. Fluid redistribution and plasma-volume regulation were the most frequently represented phenomena, followed by venous hemodynamic alterations, orthostatic and blood-pressure responses, cardiac remodeling, and arterial adaptation. The reviewed evidence therefore characterized cardiovascular adaptation as a multidimensional process involving circulating volume, cardiac structure, arterial regulation, venous flow, and gravitational tolerance rather than a single isolated physiological change (Hargens & Richardson, 2009; Fu et al., 2019; Marshall-Goebel et al., 2019; Lee et al., 2020).

Edición 5, Año 3, Número 2, 2026
E-ISSN: 3061-8045, P-ISSN: 3061-8517
Revista IECCMEXICO

Edition 5, Year 3, Number 2, 2026
E-ISSN: 3061-8045, P-ISSN: 3061-8517
IECCMEXICO Review

Figure 3.

Metabolic and musculoskeletal alterations associated with long-duration spaceflight

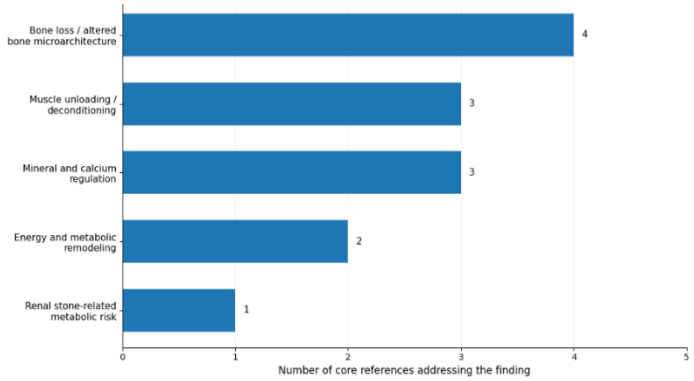

Figure 3 summarizes the principal metabolic and musculoskeletal alterations identified in the core literature. Bone loss and alterations in bone microarchitecture constituted the most frequently represented finding, appearing across four references. Muscle unloading and physical deconditioning, together with alterations in mineral and calcium regulation, were each represented in three publications. Energy and metabolic remodeling appeared in two, while renal stone-related metabolic risk was specifically addressed in one core study. As in the previous figure, categories were not considered mutually exclusive because individual investigations could contribute evidence to more than one physiological process.

The predominance of skeletal alterations is consistent with the substantial reduction in mechanical loading experienced during microgravity. Under terrestrial conditions, weight-bearing bones are continuously exposed to gravitational and muscular forces that contribute to the maintenance of bone remodeling. During spaceflight, this mechanical stimulus is markedly reduced, modifying the balance between bone formation and resorption. The resulting deterioration is particularly relevant in skeletal regions normally subjected to weight-bearing loads.

Gabel et al. (2022) provided important longitudinal evidence by evaluating bone strength, density, and microarchitecture following long-duration spaceflight. Their findings showed that recovery was not uniform after return to Earth and that aspects of distal tibial bone strength and trabecular microarchitecture remained incompletely restored one year after the mission. The results therefore demonstrated that skeletal alterations can extend beyond the period of direct microgravity exposure and that recovery trajectories differ among bone characteristics.

Muscle unloading and deconditioning represented another prominent component of the evidence. In microgravity, muscles responsible for maintaining posture and locomotion against gravity experience substantially reduced mechanical demand. This condition changes the physiological stimulus required to preserve muscle mass and functional capacity. Although the reviewed literature focused primarily on cardiovascular and systemic adaptations, evidence concerning prolonged unloading demonstrated that changes in muscular demand occur alongside cardiovascular deconditioning and influence the overall physiological response to long-duration missions (Hargens & Richardson, 2009; Garrett-Bakelman et al., 2019).

The interaction between muscular and cardiovascular deconditioning was also apparent in studies examining exercise and postflight functional responses. Fu et al. (2019) demonstrated the relevance of exercise-based countermeasures for maintaining cardiovascular function and improving orthostatic tolerance following prolonged missions. Although orthostatic tolerance is principally cardiovascular, the effectiveness of exercise countermeasures illustrates the close relationship between maintenance of physical conditioning and preservation of physiological capacity during spaceflight.

Mineral and calcium regulation constituted a third major category. Reduced skeletal loading alters bone turnover and can increase the mobilization of minerals from skeletal tissue. This connects musculoskeletal adaptation with renal physiology because changes in calcium balance can influence urinary mineral excretion. Whitson et al. (2001)

Edición 5, Año 3, Número 2, 2026
E-ISSN: 3061-8045, P-ISSN: 3061-8517
Revista IECCMEXICO

Edition 5, Year 3, Number 2, 2026
E-ISSN: 3061-8045, P-ISSN: 3061-8517
IECCMEXICO Review

examined the risk of renal stone formation during and after long-duration spaceflight and identified urinary and physiological conditions relevant to stone development. Thus, alterations originating in the skeletal system may be reflected in renal and metabolic variables during prolonged missions.

Fluid balance further interacts with these processes. Changes in body-fluid compartments occur early during spaceflight, followed by physiological adjustments in renal handling and circulating volume (Leach et al., 1996). Consequently, renal stone-related risk cannot be interpreted solely through changes in bone metabolism; hydration, urinary volume, mineral excretion, and the broader adaptation of fluid regulation also contribute to the physiological environment in which stone formation may occur.

Energy and metabolic remodeling appeared in two core references and represented a broader level of physiological adaptation. Garrett-Bakelman et al. (2019), through the NASA Twins Study, identified changes across multiple molecular and metabolic pathways during approximately one year of spaceflight. Metabolomic, transcriptomic, immune, microbiome, cardiovascular, and other biological findings demonstrated that prolonged exposure was associated with systemic changes extending beyond the effects of mechanical unloading alone.

The same investigation showed that physiological recovery after return was heterogeneous. Numerous variables approached preflight conditions during the postflight period, whereas others demonstrated slower or incomplete normalization (Garrett-Bakelman et al., 2019). This temporal variation parallels the skeletal findings reported by Gabel et al. (2022), in which some bone characteristics remained altered after a prolonged recovery interval.

The renal stone-related metabolic category was represented specifically by Whitson et al. (2001). Although numerically smaller within the selected literature, this finding connected several physiological processes represented elsewhere in the figure: bone mineral mobilization, urinary calcium handling, hydration status, and renal adaptation. It therefore illustrates how a finding represented by a single specialized study may intersect with broader metabolic and musculoskeletal changes documented across multiple investigations.

Figure 4.

Systemic physiological responses identified during long-duration spaceflight

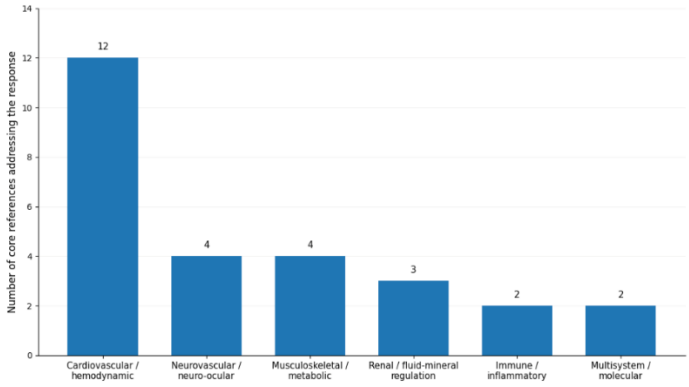

Figure 4 presents the distribution of the principal systemic physiological responses identified across the core literature. Cardiovascular and hemodynamic responses were addressed in 12 publications, followed by neurovascular/neuro-ocular and musculoskeletal/metabolic alterations, each represented in four. Renal and fluid-mineral regulation appeared in three publications, while immune/inflammatory and multisystem/molecular responses were each represented in two. The categories overlap because individual studies could provide evidence for more than one physiological system.

The cardiovascular and hemodynamic domain showed the greatest representation. This concentration reflects the immediate influence of microgravity on hydrostatic gradients, fluid distribution, venous return, cardiac loading, arterial

Edición 5, Año 3, Número 2, 2026
E-ISSN: 3061-8045, P-ISSN: 3061-8517
Revista IECCMEXICO

regulation, and orthostatic responses. Fluid shifts occur early after gravitational unloading and are followed by changes in circulating volume and cardiovascular regulation (Leach et al., 1996; Hargens & Richardson, 2009). During longer exposure, these responses coexist with modifications in ambulatory blood pressure, cardiac structure, vascular function, and the capacity to tolerate gravitational loading after return (Norsk et al., 2015; Fu et al., 2019; Lee et al., 2020).

The cardiovascular evidence also incorporated the venous circulation. Changes in venous dimensions during long-duration spaceflight have been documented through ultrasound assessment (Arbeille et al., 2015). More recent observations identified internal jugular venous stasis and altered flow patterns, while a thrombotic event documented during spaceflight demonstrated that venous abnormalities are measurable components of the physiological response to microgravity (Marshall-Goebel et al., 2019; Auñón-Chancellor et al., 2020). Ultrasound assessment has consequently become an important component of research examining venous circulation during missions (Elias et al., 2024).

Neurovascular and neuro-ocular alterations represented another recurrent systemic response. Cephalad fluid redistribution affects not only cardiovascular compartments but also the circulation of the head and neck. Iwasaki et al. (2021) reported alterations in estimated intracranial pressure and cerebral blood velocity during long-duration spaceflight, demonstrating measurable changes in cerebral hemodynamics under microgravity conditions.

Neuro-ocular findings were predominantly represented by investigations of spaceflight-associated neuro-ocular syndrome. Reported abnormalities include optic disc edema, globe flattening, choroidal and retinal changes, and refractive alterations. Reviews of the available evidence have emphasized the relationship between prolonged spaceflight and changes in ocular structures while recognizing that the underlying mechanisms remain multifactorial (Lee et al., 2020; Martin Paez et al., 2020; Ong et al., 2023). Within the reviewed literature, these findings linked cardiovascular fluid redistribution with cranial and ocular physiology.

Musculoskeletal and metabolic responses showed an equivalent representation in the evidence synthesis. Mechanical unloading substantially changes the demands placed on skeletal muscle and bone. The reduction in weight-bearing activity affects muscle conditioning and skeletal remodeling, while prolonged exposure can produce changes that remain detectable after return to Earth. Gabel et al. (2022) demonstrated incomplete recovery of distal tibial bone strength and trabecular microarchitecture one year after long-duration spaceflight, documenting persistent skeletal alterations during the recovery period.

Metabolic adaptation extended beyond bone and muscle. Garrett-Bakelman et al. (2019) identified metabolic and molecular alterations during approximately one year of spaceflight as part of a comprehensive longitudinal assessment. Changes were detected across metabolomic, transcriptomic, cardiovascular, immune, microbiome, and other biological domains. The simultaneous presence of these responses demonstrated that physiological adaptation was detectable across several levels of biological organization.

Renal and fluid-mineral regulation represented three publications. Renal physiology is closely associated with the redistribution of body fluids and the regulation of circulating volume. Leach et al. (1996) described modifications in body-fluid compartments during spaceflight, providing evidence for renal and systemic adjustment to the altered distribution of fluids. Mineral metabolism also connects renal physiology with skeletal adaptation because changes in bone remodeling modify calcium handling.

Whitson et al. (2001) examined renal stone formation during and after long-duration spaceflight, identifying changes relevant to urinary mineral balance and stone risk. These findings positioned renal adaptation at the intersection of fluid regulation, skeletal demineralization, hydration, and mineral metabolism. Consequently, the renal category displayed in Figure 4 represents both direct renal responses and interactions with physiological processes occurring elsewhere in the body.

Immune and inflammatory alterations were less frequently represented but remained identifiable within the selected evidence. Crucian et al. (2018) described immune dysregulation during spaceflight, including changes in cellular immune function and latent viral reactivation, and examined potential countermeasures relevant to deep-space

Edition 5, Year 3, Number 2, 2026
E-ISSN: 3061-8045, P-ISSN: 3061-8517
IECCMEXICO Review

Edición 5, Año 3, Número 2, 2026
E-ISSN: 3061-8045, P-ISSN: 3061-8517
Revista IECCMEXICO

Edition 5, Year 3, Number 2, 2026
E-ISSN: 3061-8045, P-ISSN: 3061-8517
IECCMEXICO Review

exploration. Garrett-Bakelman et al. (2019) also reported immune-related molecular and cellular changes during prolonged exposure.

Finally, multisystem and molecular responses represented evidence in which several physiological domains were evaluated simultaneously rather than independently. The NASA Twins Study was particularly relevant because it integrated genomic, epigenetic, transcriptomic, proteomic, metabolomic, immune, microbiome, cardiovascular, and cognitive measurements across an extended mission and recovery period (Garrett-Bakelman et al., 2019). This type of evidence provided a broader characterization of physiological changes than studies focused on a single organ system.

Figure 5.

Recovery patterns of physiological alterations after long-duration spaceflight

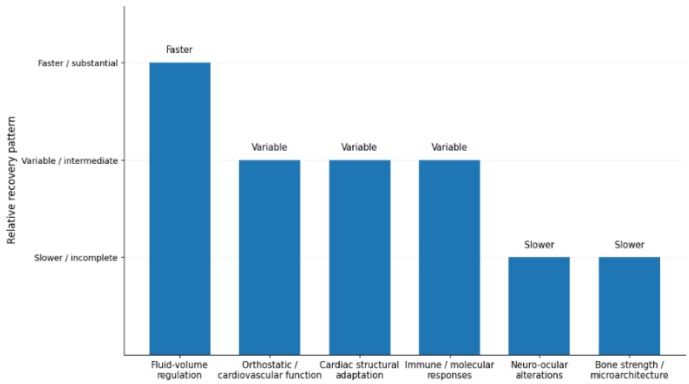

Figure 5 summarizes the recovery patterns identified across the reviewed literature following prolonged exposure to microgravity. Unlike the previous figures, the categories represent a **qualitative synthesis of recovery tendency rather than numerical clinical measurements**. Fluid-volume regulation showed a comparatively faster or more substantial recovery pattern, whereas orthostatic and cardiovascular function, cardiac structural adaptation, and immune or molecular responses displayed variable or intermediate recovery. Neuro-ocular alterations and changes in bone strength and microarchitecture showed comparatively slower or potentially incomplete recovery within the follow-up periods reported in the selected studies.

Fluid-volume regulation demonstrated the most rapid recovery tendency among the evaluated domains. During microgravity exposure, cephalad fluid redistribution and subsequent volume-regulatory responses modify circulating plasma volume and fluid compartments. Once terrestrial gravity is restored, hydrostatic gradients return and initiate another period of cardiovascular and renal adjustment. Leach et al. (1996) documented substantial changes in body-fluid compartments associated with spaceflight, while Norsk et al. (2015) demonstrated that fluid shifts occur together with vascular and blood-pressure adaptations. The reviewed evidence indicates that fluid regulation begins to readjust relatively early after return, although normalization of volume does not necessarily imply simultaneous recovery of every cardiovascular variable.

Orthostatic and cardiovascular function displayed a more variable recovery profile. After return to Earth, the cardiovascular system must again maintain arterial pressure and cerebral perfusion while blood is displaced toward dependent regions. Reduced plasma volume, altered vascular responses, cardiovascular deconditioning, and changes in autonomic regulation can contribute to postflight orthostatic intolerance. Earlier observations demonstrated this phenomenon and evaluated volume expansion as a countermeasure (Bungo et al., 1985). Fu et al. (2019) subsequently showed that astronauts receiving appropriate exercise and volume-replacement countermeasures could maintain or improve orthostatic tolerance after long-duration missions.

Edición 5, Año 3, Número 2, 2026
E-ISSN: 3061-8045, P-ISSN: 3061-8517
Revista IECCMEXICO

The variability observed in cardiovascular recovery is therefore consistent with differences in countermeasure exposure and individual physiological response. Some components may improve rapidly following restoration of gravitational loading, whereas functional cardiovascular responses can require additional readaptation. Changes in arterial structure and function observed across inflight and postflight periods also demonstrate that vascular recovery follows its own temporal trajectory (Lee et al., 2020).

Cardiac structural adaptation was similarly classified as variable or intermediate. Perhonen et al. (2001) documented cardiac atrophy following prolonged unloading associated with bed rest and spaceflight, demonstrating the capacity of cardiac morphology to respond to reduced mechanical demand. The available evidence indicates that restoration of gravitational loading and exercise provides renewed physiological stimulation after flight, but the rate of structural recovery depends on the magnitude and duration of unloading as well as subsequent physical conditioning.

MacNamara et al. (2021) further demonstrated that cardiac remodeling during prolonged weightlessness or analogous unloading conditions is influenced by the balance between reduced gravitational demand and exercise-related loading. These observations explain why structural cardiac adaptation cannot be represented as a uniform process with a single recovery trajectory.

Immune and molecular responses also demonstrated heterogeneous recovery. The NASA Twins Study provided extensive longitudinal evidence showing that many biological variables altered during approximately one year of spaceflight moved toward baseline after return, while some molecular changes persisted or recovered more gradually (Garrett-Bakelman et al., 2019). This heterogeneity was observed across several biological levels and indicates that postflight recovery does not occur simultaneously throughout the organism.

Crucian et al. (2018) similarly documented immune dysregulation associated with spaceflight and highlighted changes involving cellular immune function, inflammatory signaling, and latent viral reactivation. The immune system therefore demonstrated a dynamic response influenced by multiple aspects of the spaceflight environment rather than a single effect attributable exclusively to microgravity.

Neuro-ocular alterations were positioned among the slower recovery patterns. Spaceflight-associated neuro-ocular syndrome includes structural ocular findings that may persist after return and whose resolution varies among affected individuals and manifestations. Reviews by Lee et al. (2020) and Martin Paez et al. (2020) documented the range of ocular abnormalities associated with prolonged spaceflight and the persistence of some findings during postflight assessment. Ong et al. (2023) further described current evidence concerning SANS pathophysiology and mitigation, emphasizing the continued presence of uncertainties regarding its development and recovery.

Changes in cranial hemodynamics provide additional context for these observations. Iwasaki et al. (2021) reported alterations in estimated intracranial pressure and cerebral blood velocity during long-duration missions. Together with evidence of abnormal jugular venous flow during spaceflight (Marshall-Goebel et al., 2019), these findings show that the cranial and ocular environment is exposed to altered fluid and hemodynamic conditions for prolonged periods.

Bone strength and microarchitecture showed one of the clearest patterns of delayed recovery in the reviewed evidence. Gabel et al. (2022) reported incomplete recovery of distal tibial bone strength and trabecular microarchitecture one year after return from long-duration spaceflight. Importantly, recovery differed according to skeletal characteristics and the degree of loss experienced during the mission, demonstrating that restoration of terrestrial mechanical loading does not immediately reverse all skeletal changes.

This slower skeletal recovery contrasts with the comparatively rapid readjustment of fluid-volume regulation and illustrates the different temporal scales of physiological adaptation. Fluid compartments can respond over relatively short periods, whereas restoration of bone structure requires remodeling processes occurring over months and potentially longer intervals. Consequently, the postflight period is characterized by simultaneous recovery processes progressing at different rates.

Edition 5, Year 3, Number 2, 2026
E-ISSN: 3061-8045, P-ISSN: 3061-8517
IECCMEXICO Review

DISCUSIÓN

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Revista IECCMEXICO

The findings of this review indicate that prolonged spaceflight produces a coordinated physiological response involving cardiovascular regulation, metabolism, musculoskeletal integrity, renal function, immune activity, and neurovascular physiology. The predominance of cardiovascular and hemodynamic evidence is consistent with the immediate effects of gravitational unloading on fluid distribution and circulatory regulation. However, the results also demonstrate that the physiological consequences of long-duration missions cannot be adequately interpreted through a cardiovascular model alone. Instead, the available evidence supports a multisystem framework in which adaptation in one physiological domain may influence responses occurring in others.

Cephalad fluid redistribution represents one of the central mechanisms connecting several of the findings identified in this review. The loss of the terrestrial hydrostatic gradient initially increases central fluid distribution, followed by adjustments in circulating volume, renal regulation, vascular tone, and blood-pressure control (Leach et al., 1996; Hargens & Richardson, 2009). During prolonged exposure, these responses establish a physiological state adapted to microgravity but less prepared for the sudden restoration of gravitational loading. This mechanism helps explain why orthostatic intolerance becomes particularly evident after return rather than necessarily during orbital flight.

The findings of Norsk et al. (2015) and Fu et al. (2019) reinforce this interpretation by demonstrating that long-duration missions alter cardiovascular regulation while the severity of postflight orthostatic impairment can be influenced by countermeasures. This distinction is important because cardiovascular deconditioning should not be regarded as an unavoidable fixed consequence of spaceflight. Exercise, maintenance of physical conditioning, and appropriate volume management can modify functional outcomes, suggesting that the magnitude of adaptation depends partly on the balance between environmental exposure and physiological countermeasures.

Cardiac remodeling adds another dimension to this process. The evidence reported by Perhonen et al. (2001) demonstrated cardiac atrophy following prolonged unloading, while subsequent observations have shown that cardiac morphology responds dynamically to the mechanical demands imposed during prolonged weightlessness (MacNamara et al., 2021). The heart therefore appears to behave as a plastic organ whose structure adapts to reduced loading. For future exploration missions, the relevant issue is whether this remodeling remains physiologically appropriate under microgravity or reduces cardiovascular reserve when astronauts encounter partial or terrestrial gravity.

The findings related to venous circulation are particularly important because they expand the traditional model of spaceflight cardiovascular adaptation. Abnormal internal jugular venous flow and venous stasis reported by Marshall-Goebel et al. (2019), together with the thrombotic event described by Auñón-Chancellor et al. (2020), demonstrate that cephalad fluid redistribution may create hemodynamic conditions that were not considered prominent clinical concerns during earlier periods of human spaceflight. Ultrasound-based monitoring may consequently acquire increasing importance during extended missions, both for evaluating venous physiology and for identifying abnormalities when access to advanced diagnostic infrastructure is unavailable (Elias et al., 2024).

The relationship between venous circulation and neuro-ocular physiology also illustrates the need for multisystem interpretation. SANS has been associated with prolonged spaceflight and includes structural ocular changes that may persist following return. Although its pathophysiology remains unresolved, evidence involving altered cerebral blood velocity, estimated intracranial pressure, jugular venous flow, and cephalad fluid redistribution supports the hypothesis that cranial hemodynamics contribute to its development (Marshall-Goebel et al., 2019; Lee et al., 2020; Iwasaki et al., 2021; Ong et al., 2023). Nevertheless, the available evidence does not support reduction of SANS to a single mechanism. Anatomical susceptibility, venous drainage, cerebrospinal fluid dynamics, mission duration, and individual biological characteristics may interact in determining its expression.

Musculoskeletal findings demonstrated a different temporal pattern. Unlike fluid-volume responses, which begin to readjust relatively rapidly after gravitational loading is restored, skeletal recovery can remain incomplete for considerably longer periods. Gabel et al. (2022) demonstrated incomplete recovery of distal tibial bone strength and trabecular microarchitecture one year after long-duration spaceflight. This finding is relevant because future exploration missions may involve repeated transitions between microgravity and partial gravity, potentially before complete musculoskeletal recovery has occurred.

Edition 5, Year 3, Number 2, 2026
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IECCMEXICO Review

Edición 5, Año 3, Número 2, 2026
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Revista IECCMEXICO

Bone deterioration also illustrates the connection between mechanical, metabolic, and renal physiology. Increased bone resorption modifies mineral availability and urinary calcium handling, while spaceflight simultaneously alters hydration and fluid regulation. The renal stone risk described by Whitson et al. (2001) can therefore be understood as a consequence of interacting skeletal, renal, nutritional, and fluid-regulatory processes rather than an isolated urinary abnormality. This interdependence supports the use of combined countermeasures addressing exercise, nutrition, hydration, and metabolic monitoring.

At the molecular and immune levels, the results similarly demonstrate substantial biological complexity. Crucian et al. (2018) described immune dysregulation during spaceflight, while the NASA Twins Study identified changes across genomic, epigenetic, transcriptomic, metabolomic, immune, microbiome, cardiovascular, and cognitive domains during approximately one year in space (Garrett-Bakelman et al., 2019). Importantly, recovery was heterogeneous: many variables approached baseline following return, while others required longer periods or remained altered during follow-up. These observations are consistent with the recovery pattern identified in the present review, in which physiological systems did not return to terrestrial conditions at the same rate.

This heterogeneity has direct relevance to long-duration exploration. A crew member may demonstrate recovery or adequate adaptation in one physiological system while simultaneously presenting persistent changes in another. Consequently, reliance on isolated indicators of health may provide an incomplete assessment of physiological readiness. Integrated monitoring incorporating cardiovascular function, exercise capacity, body composition, bone health, metabolic markers, venous assessment, and other relevant parameters may provide a more representative evaluation during extended missions.

The reviewed evidence also highlights an important distinction between **adaptation and pathology**. A physiological change occurring in microgravity is not necessarily harmful. Reduced cardiac loading, altered circulating volume, and changes in vascular regulation may represent appropriate responses to an environment in which the gravitational demands of terrestrial circulation no longer exist. Clinical relevance emerges when an adaptation reduces functional reserve, contributes to secondary abnormalities, persists beyond exposure, or becomes disadvantageous during transitions between gravitational environments. Future research should therefore focus not only on identifying changes but also on determining thresholds at which adaptive responses become clinically or operationally significant.

Several limitations of the current evidence should be considered. Human spaceflight research necessarily involves small populations, heterogeneous mission durations, highly selected and medically screened participants, and continuously evolving countermeasure protocols. These characteristics limit conventional statistical comparisons and complicate extrapolation to larger or more diverse populations. Furthermore, findings from contemporary low-Earth-orbit missions cannot be directly assumed to predict responses during multiyear deep-space missions, where radiation exposure, isolation, communication delays, altered gravity, and limited medical support will introduce additional variables.

The international nature of future exploration also provides an opportunity to broaden the geographical diversity of aerospace biomedical research. Much of the current human evidence has been generated through established space agencies and institutions in North America, Europe, Russia, and Asia. Greater scientific participation from Latin America could contribute expertise in cardiovascular medicine, internal medicine, physiology, biomedical engineering, remote medicine, and population health. Such collaboration would also strengthen the translation of technologies developed for spaceflight—including remote monitoring, portable ultrasound, exercise countermeasures, and autonomous clinical assessment—to terrestrial environments with limited access to specialized medical infrastructure.

From a translational perspective, spaceflight physiology has implications beyond aerospace medicine. Prolonged unloading reproduces or accelerates several processes observed in terrestrial clinical conditions, including physical deconditioning, muscle loss, bone deterioration, cardiovascular remodeling, orthostatic dysfunction, and metabolic changes. The extreme environmental conditions of spaceflight therefore provide a model for investigating mechanisms relevant to immobilization, aging, rehabilitation, osteoporosis, sarcopenia, and cardiovascular deconditioning.

CONCLUSIÓN

Edition 5, Year 3, Number 2, 2026
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IECCMEXICO Review

Edición 5, Año 3, Número 2, 2026
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Revista IECCMEXICO

Edition 5, Year 3, Number 2, 2026
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IECCMEXICO Review

Long-duration spaceflight produces a complex process of human physiological adaptation that extends well beyond the effects of microgravity on a single organ system. The evidence reviewed demonstrates that cardiovascular, metabolic, musculoskeletal, renal, immune, neurovascular, and neuro-ocular responses occur simultaneously and interact throughout exposure and subsequent recovery. Among these responses, cardiovascular and hemodynamic alterations constitute a central component, particularly through cephalad fluid redistribution, plasma-volume regulation, cardiac and vascular remodeling, altered venous circulation, and changes in orthostatic tolerance.

The available evidence also shows that physiological adaptation does not necessarily represent pathological deterioration. Many changes reflect the capacity of the human organism to establish a functional state under reduced gravitational loading. Their clinical relevance becomes greater when these adaptations reduce physiological reserve, contribute to secondary complications, persist after return, or interfere with the ability to tolerate transitions between gravitational environments. Reports of abnormal jugular venous flow and thrombosis illustrate how previously recognized adaptive mechanisms may coexist with emerging medical risks during prolonged missions (Marshall-Goebel et al., 2019; Auñón-Chancellor et al., 2020).

Metabolic and musculoskeletal findings further demonstrate that prolonged unloading can produce changes whose recovery extends beyond mission completion. Persistent alterations in bone strength and microarchitecture highlight the comparatively slow restoration of some physiological systems (Gabel et al., 2022). Similarly, renal mineral regulation, immune function, and molecular responses demonstrate that adaptation occurs at multiple biological levels and follows heterogeneous temporal trajectories (Crucian et al., 2018; Garrett-Bakelman et al., 2019).

The reviewed evidence therefore supports the need for integrated health surveillance during future long-duration missions. Cardiovascular assessment, exercise conditioning, metabolic and nutritional monitoring, musculoskeletal protection, fluid management, and portable diagnostic strategies should be considered complementary components of health preservation. The effectiveness of exercise and volume-related countermeasures in limiting postflight cardiovascular dysfunction demonstrates that at least part of the physiological impact of prolonged spaceflight can be modified through targeted interventions (Fu et al., 2019).

Future lunar and Martian missions will require a more individualized understanding of physiological adaptation because mission duration, radiation exposure, partial gravity, delayed communication, and limited medical support will differ substantially from current orbital operations. Longitudinal research should therefore prioritize individual susceptibility, interactions between physiological systems, persistent postflight alterations, and the development of autonomous monitoring and countermeasure strategies. Broader international collaboration, including greater scientific participation from Latin America, could contribute additional clinical, physiological, and technological perspectives to this field.

In conclusion, maintaining human health beyond Earth will depend not only on the capacity to survive microgravity but on preserving sufficient physiological reserve to function across changing gravitational environments. Long-duration spaceflight provides both a major challenge for aerospace medicine and a unique model for understanding cardiovascular deconditioning, metabolic adaptation, musculoskeletal loss, and systemic human plasticity. Integrating these findings will be essential for supporting safe and sustainable human exploration of the Moon, Mars, and future destinations beyond low-Earth orbit.

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IECCMEXICO Review

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IECCMEXICO Review