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Physiological Adaptations to Life in Space: An Update

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ABSTRACT

The historic flight of cosmonaut Yuri Alekeseyevich Gagarin, in 1961, established the need for research regarding the physiological adaptations of the human body when exposed to the space environment. Since then, several morpho-functional transformations – varying between normal and pathological – have been identified within the organisms of astronauts subjected to the extremely disparate environments of the cosmos, consequently, comprehension and preparation of these transformations becomes essential, considering the possibilities (1) of returning to the Moon and (2) of initiating the trip to Mars. Accordingly, the purpose of this article – conceived as a narrative literature review – is to present the main aspects of the physiological modifications within the human body due to the extraterrestrial environment, with emphasis on cardiovascular, renal, hydroelectrolytic, hematological, immunological, respiratory, neurological, psychological, sensory, gastrointestinal, endocrine, musculoskeletal, integumentary, and genetic adaptations.

Keywords: Aerospace medicine; Gravitational physiology; Space tourism; Space flight; Interplanetary flight.

INTRODUCTION

Space exploration began around the middle of the 20th century, initially by sending rockets into space. Then came the "race to the moon" – a consequence of the Cold War between the United States of America (USA) and the then Union of Soviet Socialist Republics (USSR) – which spurred intense technological development from the second half of the 1950s onwards. In fact, during this period, the Soviet Space Program was consolidated and the National Aeronautics and Space Administration (NASA) was founded by the USA in 1958. As a result, countless efforts went into scientific research in the quest for human conquest of extraterrestrial environments.

The first metazoan sent into space – to orbit the Earth – was the Soviet dog Laika, on November 3, 1957. Human beings were transported just over three years later, during a historic flight carried out by the Soviets on April 12, 1961, in which cosmonaut Yuri Alekeseyevich Gagarin

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became the first man to orbit the Earth aboard Vostok 1. Then, less than a month later – on May 5, 1961 – the US responded by sending astronaut Alan Bartlett Shepard Jr. into space aboard Freedom 7, but still on a suborbital flight. The first woman, also Russian, to make a space flight was Valentina Vladimirovna Tereshkova, on June 16, 1963. However, the crowning achievement in the endeavor to "conquer" the extraterrestrial environment was obtained by three American astronauts – Neil Armstrong, Edwin Aldrin and Michael Collins – who took part in the famous Apollo 11 mission, in the context of which, on July 20, 1969, the first human being, Neil Armstrong, set foot on the lunar soil.

Over the last 30 years, space has continued to be investigated, expanding the frontiers of humans on a grand scale. Recently, the company SpaceX announced a new phase of space travel, with the aim of making private flights possible – in the same vein as Jeff Bezos' first private trip in July 2021 – which marks the second phase of space tourism, the initial stage of which began in 2001 with the company Space Adventures. It is estimated that in the next two decades (2030-2050) space tourism will be a tangible reality, so that various aspects of these trips – such as the physiological changes of the human organism exposed to extraterrestrial environments, for example in microgravity – should be dealt with more comprehensively (Artemis 2022; Garrett-Bakelman *et al.* 2019).

Although various countermeasures have been implemented, there is still no effective and efficient protocol for protecting the human body from the intense accelerations and decelerations caused by take-off and re-entry, as well as the imponderability caused by the microgravity environment (Rocha 2018). In addition, there are additional factors that affect crew members, such as the artificial climate on board the spacecraft, radiation, social isolation, food, hydration and physical exercise (Kreykes 2020). Therefore, understanding the physiological adaptations that occur during gravitational changes is essential for establishing strategies to mitigate the effects of space travel on the human body (Rocha 2018), particularly when considering the prospect of a manned mission to Mars in the coming decades, whose estimated minimum duration would be two years.

Based on these considerations, the aim of this article is to review the main aspects of human adaptation, in physiological terms, to space travel, in view of the possibility of long-term interplanetary missions in the coming years.

METHODS

This is a narrative literature review, which aims to describe and discuss the "state of science of a specific theme or topic from a theoretical and contextual point of view" (Botelho *et al.* 2011, p. 125). To this end, a "critical analysis of the literature published in books and articles in electronic or paper-based journals" (Rother 2007, p. vii) was carried out, based on a non-systematic search of academic texts (Casarin *et al.* 2020), with a focus on gathering scientific data that would allow the main aspects of the human organism's adaptation to life in space to be updated.

Original articles – published in English, Portuguese or Spanish – that associated the spatial environment with human physiology were chosen as the preferred material for this review. The selected texts were read in full to extract relevant information. The systematized content resulting from this process was organized into the following sections, according to the body's adaptations: (i) cardiovascular; (ii) renal and hydroelectrolytic; (iii) hematological; (iv) immunological; (v) respiratory; (vi) neurological and psychic; (vii) sensory (relating to the sense organs); (viii) gastrointestinal; (ix) endocrine; (x) musculoskeletal; (xi) integumentary; and (xii) genetic.

In order to aid the understanding of gravitational actions on the human body, the standardized G-force nomenclature will be used: microG, hypoG (Mars and Moon) and hyperG (take-off and landing). In relation to the Cartesian axes, the vertical acceleration upwards generates the inertial force downwards, with the physiological effects - this is called Gz+ (in the downwards direction in the vertical direction); Gx+ has the transverse acceleration with the chest-to-back inertial force (in the front-to-back direction in the horizontal direction); Gy+ has the inertial force from right to left, in the lateral direction). It is worth noting that acceleration does not generate the physiological effects, which are a consequence of the inertial force (inertia).

RESULTS AND DISCUSSION

The articles selected for the review were related to human physiology and the space environment. Texts that did not describe some kind of adaptation of a human organ and/or system to the space environment, as well as incomplete texts and texts from dubious sources, were excluded.

Exposure to the microgravity space environment produces disparate changes in the human body, specifically physiological and morphological changes, at cellular and molecular levels, including changes in gene regulation, affecting cognitive, social and physical performance (Russomano and Castro 2020; Stella *et al.* 2021). This emphasizes the importance and need for research that describes, in detail, the changes in the human organism during and after a space mission, in order to enable preventive and therapeutic strategies for such changes (Krittanawong *et al.* 2023; Russomano and Castro 2020; Stella *et al.* 2021).

Cardiovascular adaptations

The cardiovascular system (CVS) undergoes significant changes during space flight, mainly triggered by (a) acceleration forces, (b) microgravity, (c) changes in the magnetic field and (d) hypobaric environments. Initially, in space travel, there is a simple linear acceleration – there may also be centrifugal acceleration (if there is a curved trajectory) – and at the end of the flight, a significant deceleration. Positive and negative linear accelerations are the most important gravitational forces in space travel. During launch, the spacecraft and passengers experience a force of up to +2-3Gx. Passengers need to be in a semi-recumbent position, transverse to the axis of acceleration (Ercan 2021; Kreykes 2019).

One notable effect comes from centrifugal acceleration, which impacts the circulatory system due to the fluidity of the blood. However, it's worth noting that centrifugal acceleration in space travel is less frequent and therefore less impactful when compared to airplane travel. In spacecraft, if the acceleration reaches +5Gz and the person is immobilized orthostatically, the venous pressure in the feet can reach 450 mmHg, well above its usual value. As the blood accumulates in the lower part of the body, due to the intense G-force on the Z+ axis, there is a decrease in cardiac output and an increase in heart rate. In addition, the systolic and diastolic arterial pressures, under the effect of an acceleration of approximately +3Gz, fall by around 22 mmHg, but there is a partial recovery of values due to baroreceptor reflexes. Due to the accumulation of blood in the lower body, if the centrifugal acceleration exceeds +4-6Gz, vision can go dark and if this intense gravitational force continues for a prolonged period of time, the astronaut will probably fall into a coma, with possible progression to death if exposure to this acceleration continues (Zhang and Hargens 2018).

Negative G-force in the Z-axis is less tolerated by humans because of the blood displacement in the cranial direction, generating eye redness, headache, eyelid edema and mental confusion (Kreykes 2020). The physiological compensation mechanisms are not efficient when cranial pooling occurs, so the tolerance level is only around -3G in the Z axis. The negative linear acceleration (deceleration) is equally considerable, with the spacecraft arriving at its destination – or even leaving orbit – needing thousands of kilometers to decelerate safely. Journeys with speeds of around Mach 100 (which would be used for interplanetary locomotion) would require at least 16,000 kilometers just to decelerate without causing damage to its passengers (Ercan 2021).

Microgravity alters some properties of the cardiovascular system. The environment with gravity close to 0G produces a deconditioning of the cardiovascular system, with atrophy of the heart muscle and a decrease in working capacity. Another significant and common change among astronauts is the so-called "puffy face, bird legs" syndrome, which refers to facial congestion caused by fluids from the lower limbs, displaced during the flight. After a week in an environment with gravity around 0G, cardiac output increases by 22% and peripheral resistance drops by 14% (Rocha 2018). After long flights, adaptations occur, such as hypovolemia and a decrease in peripheral vascular resistance. Cardiac output increased by 10% and a moderate decrease in systolic pressure was found (Garrett-Bakelman *et al.* 2019 and Guyton 2017).

Changes in the magnetic field can modify the cardiovascular system, which was documented in a study that analyzed the difference of the heart rate variability (HRV) of seven healthy astronauts on board the International Space Station (ISS) for 20 days and 138 days. It is worth noting that HRV is directly related to the risk of death. A recent study (Otsuka *et al.* 2019), based on data obtained from an animal model (Honda *et al.* 2012), identified an anti-aging effect after exposure to variations in the magnetic field that increased HRV indices, especially during the daytime. The possible anti-aging effects increased on days with higher magnetic activity, suggesting that astronauts may experience delayed aging in the space environment (Otsuka *et al.* 2019; 2021).

Gathering data on hypobaric effects on the cardiovascular system is important in the event of flight complications that can lead to a drop in cabin pressure. Decompression sickness occurs due to the transition from a higher to a lower barometric pressure environment, and is characterized by the formation of nitrogen bubbles in the blood vessels, with the production of occlusions and gas embolisms, reducing or interrupting blood perfusion and generating ischemia in different tissues and organs (Mitchell *et al.* 2022). Symptoms and signs of this clinical condition include dyspnea, tachypnea, retrosternal pain, hemoptysis, cough, cyanosis, neurological changes and possibly shock. If the embolus reaches the coronary arteries, for example, heart rhythm disturbances or acute myocardial infarction can occur (Rocha 2018). The main acute and chronic adaptations of the cardiovascular system are summarized below (Krittanawong *et al.* 2023; Russomano and Castro 2020; Stella *et al.* 2021).

Acute adaptations

- "Puffy face, bird legs", an alteration that refers to facial congestion and a reduction in the volume of the lower limbs due to the displacement of blood to the upper body (MicroG);
- Grey-out, Black-out and loss of consciousness (G-LOC) (HiperG - Gz+);
- Drop in systemic blood pressure as a result of body fluids and blood being dammed up in the lower body (HyperG - Gz+);
- Increased heart rate (HyperG - Gz+).

Chronic adaptations

- Deconditioning of the cardiovascular system, with atrophy of the heart muscle and a decrease in working capacity, especially worrying when returning to Earth, where there is a frequent occurrence of orthostatic intolerance (MicroG);
- Change in heart shape, becoming rounder (MicroG);
- Increased heart rate variability (HRV) indices (MicroG).

Renal and hydroelectrolytic adaptations

Astronauts have a reduced water intake on the ISS and are subjected to a low level of humidity. As a result, there is usually a decrease in urine volume over 24 hours and a drop in angiotensin levels. As a result of dehydration, there is a greater risk of developing kidney stones, which are more likely to occur in situations where there is a longer stay in space. It is worth noting that microgravity may have a significant impact on the propensity for nephrolithiasis. In fact, environments with gravity close to 0G – particularly when there is a lack of adequate physical exercise – can produce bone decalcification, further increasing the predisposition to kidney stone formation (Patel 2020).

The occurrence of urinary supersaturation does not differ significantly between men and women, so both groups are at increased risk of developing kidney stones after flight, which makes adequate hydration necessary (Smith *et al.* 2014).

The renal system participates in the homeostasis of magnesium, an essential nutrient for bone, cardiovascular and muscle health. Space flight increases the concentration of magnesium in the urine and blood, but it remains the same in the tissues, demonstrating an adapted protective homeostatic response, with no need for magnesium replacement during trips of four to six months (Smith and Zwart 2015). The main acute adaptations of the renal and hydroelectrolytic system are summarized below (Krittanawong *et al.* 2023; Russomano and Castro 2020; Stella *et al.* 2021).

Acute adaptations

- Decrease in urine volume and drop in angiotensin levels (MicroG);
- Increased propensity to develop kidney stones;
- Increased urinary calcium oxalate saturation (MicroG);
- Increased magnesium concentrations in urine and serum (MicroG).

Hematological adaptations

When astronauts remain in microgravity for a longer period of time, there is a reduction in the volume of blood plasma and the mass of red blood cells. In fact, in a study carried out on 14 astronauts aboard the ISS for six months, space flight caused increased levels of hemoglobin degradation. Anemia in astronauts in the first 10 days of space flight was described as a result of a drop of up to 12% in red blood cells, which occurred in response to microgravity. This reduces erythropoietin levels, alters hemoconcentration and modifies fluid hemodynamics in the cephalic region. Interestingly, the RBCs produced after 120 days (RBC lifespan) are considered "space-born RBCs", which, however, have also been hemolyzed – possibly more frequently – in the microgravity environment (Trudel *et al.* 2022).

Radiation is proving to be an important biological stressor for blood cells. Cytogenetic data shows that radiation in space causes significant damage to cells – particularly lymphocytes – but further studies are needed to determine the doses of radiation and the degree of impact of these variations (Maalouf *et al.* 2011; Russomano 2023).

Venous thromboembolism (VTE) is a relevant disorder whose causative factors include changes in blood flow (stasis), damage to the vascular endothelium and changes in blood constituents (inherited or acquired hypercoagulable state) (Limper *et al.* 2021; Marshall-Goebel *et al.* 2019). Stressors such as accentuated acceleration, microgravity, radiation, dietary changes, hypobaric environment and low humidity can generate endothelial damage, a relevant risk factor for this morbid condition. As previously described, changes in the concentration of red blood cells on space flights can contribute to greater chances of VTE due to the increase in factors belonging to Virchow's triad (Mitchell *et al.* 2022). There is a description of the occurrence of jugular vein thrombosis in an astronaut in space (Marshall-Goebel *et al.* 2019). There are specific adaptations to the hematological system, as can be seen below (Krittanawong *et al.* 2023; Russomano and Castro 2020; Stella *et al.* 2021):

Acute adaptations

- Reduction in plasma volume and erythrocyte mass (MicroG);
- Increased levels of hemoglobin degradation (MicroG);
- Hemolysis anemia, as an adaptation to acute exposure to space (MicroG).

Chronic adaptations

- Anemia

Immune adaptations

Changes in the expression of genes related to the immune system after long periods in a space environment have been revealed in studies of monozygotic twins (Garrett-Bakelman *et al.* 2019). An increase in pro-inflammatory fatty acid levels and a decrease in anti-inflammatory fatty acids were identified in the test twin, suggesting an increased state of inflammatory response. Regarding the effects of microgravity, there is a greater susceptibility to infections and a greater propensity to increase the inflammatory response, through the impact on *natural killer* cells (cT NK), cytokine production, humoral immunity and signaling pathways (Rocha 2018). In addition, microgravity has caused immunosuppression in some individuals and hyper-stimulation of the immune system in others, causing allergies and the emergence of autoimmune diseases. An increase in components such as nitric oxide and interleukins 6 and 8 (the latter being pro-inflammatory cytokines) has been documented, due to leukocyte dysfunction. These changes are associated with a greater risk of infections, secondary immunodeficiency, reactivation of latent viruses, allergic reactions, impaired healing, among other alterations. Hypergravity, which occurs at launch, has caused an increase in the immune response (Rocha 2018).

Moser *et al.* (2019) carried out a study to evaluate the effects of oscillating G-forces in parabolic flight on cells of the immune system, specifically on the adhesion of blood mononuclear cells (PBMC) to adhesion molecules. Parabolic flights are the most reliable way of reproducing a microgravity environment on Earth, through an ascent of the plane followed by a free fall, creating the shape of a parabola. At the top of the parabola, the crew and researchers feel the absence of gravity for a few moments, around 20 seconds. The authors found that there was a decrease in PBMC adhesiveness and that the monocytes were in a "prepared" state with antigen-inducing potential, specific for generating proinflammatory responses. This analysis also revealed an increase in the concentration of anti-inflammatory cytokines, so there is a state of equilibrium between immunostimulation and immunosuppression in parabolic flights. The main acute and chronic adaptations of the immune system according to Russomano and Castro (2020), Stella *et al.* (2021) and Krittanawong *et al.* (2023) are cited bellow.

Acute adaptations

- Increased levels of pro-inflammatory fatty acids and a drop in anti-inflammatory fatty acids, suggesting an increased state of inflammatory response (MicroG);
- Immunosuppression in some individuals and hyperstimulation of the immune system in others (the latter as a cause of allergies and autoimmune diseases) (MicroG);
- Increase in products such as nitric oxide and interleukins 6 and 8 (pro-inflammatory), due to leukocyte dysfunction (MicroG);
- Decreased adhesiveness of peripheral blood mononuclear cells (PBMC) (MicroG).

Chronic adaptations

- Immunosuppression in some individuals and hyperstimulation of the immune system in others (the latter as a cause of allergies and autoimmune diseases) (MicroG).

Respiratory adaptations

Achieving a habitable environment on board the spacecraft depends on producing an artificial atmosphere composed of oxygen, nitrogen and no carbon dioxide. If there aren't adequate levels of O_2, passengers can become hypoxemic, a situation that can lead to death in extreme cases. Nitrogen makes up the artificial breathing air to avoid higher concentrations of oxygen, reducing the chance of fires and explosions, and also to minimize the risk of pulmonary atelectasis (Russomano *et al.* 2022).

G-force usually increases the weight of the ribs, intercostal muscles and diaphragm, which can result in dyspnea and fatigue. This alters respiratory dynamics and the possibility of adequate blood oxygenation (Kreykes 2019). The main physiological adaptations of this system can be seen below (Krittanawong *et al.* 2023; Russomano and Castro 2020; Stella *et al.* 2021).

Acute adaptations

- Reduction of thoracic blood pressure (MicroG);
- Decreased lung volumes and capacities (MicroG);
- Almost homogeneous ventilation and pulmonary perfusion distribution from the base to the apex of the lungs (MicroG);
- Increased rib weight (over +2-3Gx) of the intercostal muscles and diaphragm, resulting in dyspnea and fatigue (HyperG - Gx+);
- Inspiratory difficulty (due to increased chest weight) (HyperG - Gx+).

Chronic adaptations

- Increased rib weight (over +2-3Gx) of the intercostal muscles and diaphragm, resulting in dyspnea and fatigue (HyperG - Gx+);
- Inspiratory difficulty (due to increased chest weight) (HyperG - Gx+).

Neurological and psychological adaptations

Cognitive alterations related to long stays in space have been consistently investigated in view of the possibility of long-duration flights – e.g. to Mars – and even the colonization of other celestial bodies. This situation is manifested by unconsciousness, known as "G-LOC" or "induced lack of consciousness", which may or may not be preceded by visual symptoms. There is often a period of mental confusion and amnesia before complete recovery of consciousness, a process that occurs slowly. In microgravity, there is a redistribution of cerebrospinal fluid, producing greater intracranial pressure (Zhang and Hargens 2018), among other factors still under study.

The neuro-ophthalmological symptoms and signs associated with extraterrestrial flight make up an important syndromic diagnosis, Spaceflight-Associated Neuro-ocular Syndrome (SANS). Cerebral perfusion is reduced during initial exposure to microgravity, due to changes in the balance between intracranial pressure and mean arterial blood pressure, but circulation usually remains normal (Mader 2011; Zhang and Hargens 2018).

Adequate sleep can be a genuine challenge for life in a space environment. In fact, when considering the ISS – where sunset occurs every 90 minutes – the difficulties in maintaining the circadian rhythm and sleep-wake pattern – regulated by the hypothalamus and synchronized with the solar clock in a terrestrial environment – are often significant. In fact, the alteration of the "solar clock" in space generates significant sleep disturbances – from insomnia (the most common) to excessive sleepiness – which result in reduced cognitive capacity during wakefulness, as well as endocrine and neurological changes (Vernikos and Russomano 2022). These and other changes can be seen below (Krittanawong *et al.* 2023; Russomano and Castro 2020; Stella *et al.* 2021):

Acute adaptations

- Headache and mental confusion (MicroG);
- Increased intracranial pressure. Spaceflight-Associated Neuro-Ocular Syndrome (SANS) (MicroG);
- Sleep disturbances and impaired cognition during wakefulness (MicroG).

Chronic adaptations

- Increased intracranial pressure. Spaceflight-Associated Neuro-Ocular Syndrome (SANS) (MicroG);
- Sleep disturbances and impaired cognition during wakefulness (MicroG).

Adaptations of the sense organs

Human senses have evolved over thousands of years adapted to terrestrial life (Buzsáki and Llinás 2017; Helayel *et al.* 2015). Thus, in the context of life in space, these structures are sensitive to changes in gravity, temperature, atmosphere and other environmental factors. A number of hypotheses have been proposed to explain these findings, most notably the increase in pressure in the internal jugular vein – and the consequent congestion of the retinal vasculature – during flight. If there is a drop in O_2 in the spacecraft environment, there is a risk that travelers will develop hypoxemia, a situation in which the reduced blood supply to the retina can affect the passenger's field of vision, even producing the condition known as "tunnel vision". Hypoxia also makes it difficult to differentiate colors (color vision). This function is also impaired in the situation known as "gray-out" and "black-out", in which travelers suffer loss of color vision, followed by complete loss of vision, during high angle acceleration (Rickards and Newman 2005).

Reports of "eye flashes" have been documented by several astronauts, from the Apollo team onwards. These flashes – described as sensations of light rays appearing in the visual field – are probably a consequence of the exposure to radiation in space. The frequency of visual alteration was highest over the South Atlantic Anomaly, a region in which the inner part of the Van A llen Belt is closest to the Earth and in which there is a significant flow of protons and electrons (Avdeev *et al.* 2002; Budinger *et al.* 1997). The occurrence of cataracts seems to be a consequence of excessive radiation (Händel *et al.* 2021; Maalouf *et al.* 2011). However, it cannot be said at the moment that this condition is related to flashes of light.

The vestibular system – located in the inner ear and responsible for orienting the head and body in relation to the Earth's gravity – is also affected in space flights. This system detects linear acceleration through the otolith organs and angular acceleration through the semicircular canals. The macula contains hair cells which, when tilted to one side or the other, generate electrical impulses which are transmitted to the brain, indicating the direction of movement. Angular acceleration is identified by the semicircular canals of the inner ear, which are oriented in three different planes in space. The dissonance of sensory perception involving vision, hearing/balance and proprioception can lead to "space motion sickness" (SMS), which can be explained by two probable mechanisms. In the first hypothesis, authors believe that this syndrome occurs due to circulatory changes, causing engorgement of vessels in the endolymphatic duct, possibly altering the responses of vestibular receptors. The second model includes the sensory conflict theory, which states that the stimuli provided by the organs and systems (muscles, joints, eyes and others) are altered in space, due to the Earth's lack of gravity, and these changes generate sensory conflicts. Typical SMS symptoms include nausea, vomiting, headache, sweating, disorientation and pallor (Russomano *et al.* 2019). Below is a short summary of these acute adaptations, according to Russomano and Castro (2020), Stella *et al.* (2021) and Krittanawong *et al.* (2023).

Acute adaptations

- Spatial kinetosis, which presents with nausea, vomiting, headache, sweating, disorientation and pallor (MicroG).

Digestive adaptations

The digestive microbiota is also modified in the context of space travel. In fact, a study carried out on twins concluded that the sibling who spent 12 months in space showed changes in the microbial community of the gastrointestinal tract (GIT), probably due to changes in eating habits (Siddiqui *et al.* 2021).

The environment on board the spacecraft is a confined space, with no exposure to colonies of intensely diverse microorganisms like on Earth. Therefore, astronauts tend to develop similar microbiotas throughout their journey. Authors suggest that the use of antibiotics should be indicated with caution, since these drugs can produce a major disturbance in the astronauts' microbiota. Other factors implicated in microbiota changes include stress, food sterilization and level of fibre intake (Al *et al.* 2022; Takahashi *et al.* 2002).

Another point worth highlighting in relation to the microbiome is the damaging effect of cosmic radiation on the microbial populations that populate the human body. Some species of bacteria can become more virulent, such as *Escherichia coli*, which exhibits greater adherence to enterocytes, and *Salmonella typhimurium*, which showed higher values of resistance to macrophages (Barrila *et al.* 2022; Takahashi *et al.* 2002). Some studies have raised the possibility of autologous fecal microbiota transplantation (aFMT), to reconstitute the diversity of intestinal species if necessary, for example, in cases of antibiotic therapy on board and in view of the possibility of a future trip to Mars (Al *et al.* 2022; Lapelusa *et al.* 2021; Kuehnast 2022).

Nutrition needs to be meticulously planned for astronauts, given that macronutrients and micronutrients are indispensable for the cosmonaut's health and the fact that every 0.45 kg on board the spacecraft generates a cost of approximately 10,000 euros.

A common problem in spaceflight is the loss of body mass among astronauts, a finding that is linked to a decrease in calorie consumption, especially in the first few days of flight (Chaloulakou *et al.* 2022; Matsumoto *et al.* 2011). If this context persists, it can predispose to immunosuppression, reduced wound healing, mood swings and reduced ability to carry out the mission. For anabolism to occur on board, even with rigorous and constant physical exercise training, it is necessary to have a healthy intestinal microbiota, given the participation of bacteria in the digestive tract in the absorption of nutrients (Bergouignan *et al.* 2016). These main acute changes can be seen below (Krittanawong *et al.* 2023; Russomano and Castro 2020; Stella *et al.* 2021):

Acute adaptations

- Modifications to the microbiome of the gastrointestinal tract (MicroG);
- Increased virulence in some species of bacteria (e.g. *Escherichia coli* and *Salmonella typhimurium*) (MicroG).

Endocrine adaptations

Microgravity causes numerous organic changes, including disturbances in glucose and lipid metabolism, increased production of pro-inflammatory cytokines and increased oxidative stress. Studies show that space travel can trigger peripheral insulin resistance. Insulin resistance is a characteristic of metabolic syndrome, which increases the risk of cardiovascular morbidity and mortality. People with insulin resistance may have type 2 diabetes mellitus, paradoxical postprandial hypoglycemia, *acanthosis nigricans* and increased androgen hormones in females (Lee *et al.* 2022; Strollo 2022). Other factors that cause an insulin response are changes in the microbiota and constant exposure to artificial light (which can lead to vitamin D3 deficiencies). Stressors such as isolation, noise exposure and exhaustion have led to increased levels of cortisol and catecholamines, the stress hormones assessed in astronauts (Russomano and Castro 2020). Below are the main physiological adaptations related to the endocrine and metabolic system (Krittanawong *et al.* 2023; Russomano and Castro 2020; Stella *et al.* 2021).

Acute adaptations

- Increased osteoclast activity and increased bone resorption (MicroG);
- Modifications to protein synthesis metabolic pathways (MicroG);
- Disorders of glucose and lipid metabolism, increased production of pro-inflammatory cytokines, and increased oxidative stress (MicroG);
- Peripheral insulin resistance (MicroG);
- Increased levels of cortisol and catecholamines (MicroG).

Chronic adaptations

- Acute changes tend to cease to exist when gravity returns.

Musculoskeletal adaptations

The actions of gravity have a significant impact on the human musculoskeletal system in the space environment. Being in space for just 24 hours results in a loss of calcium from the body – via urine –, the reduction of which usually reaches its highest point after around five weeks. It is estimated that in one month each astronaut can lose approximately 150mg of calcium per day, due to the reduced load on the bones. Bone metabolism changes after exposure to microgravity, so that osteoclasts tend to be more active than usual, increasing bone resorption. This process takes place over several months while crew members remain in the extraterrestrial environment (Smith *et al.* 2014 and Guyton 2017).

In fact, vertebral fractures can occur when there are strong acceleration forces in minimal time, specifically at high G-force levels. Exposure to microgravity also increases the risk of fractures as a result of the loss of bone mass (around 1-2% per month), which is more pronounced when there is a long stay in space. Astronauts can lose around 30% of their bone density during a mission. In addition, weightlessness can weaken bone adhesion to ligaments and tendons (Russomano and Castro 2020). It is also worth noting that in prolonged conditions of microgravity, astronauts can increase their height by 3-6 cm. The almost complete decrease in weight on the spine reduces the cushioning function of the intervertebral discs. In fact, low back pain is a common complaint of astronauts, caused by the stretching of the paravertebral muscles due to microgravity.

In space, the metabolism of the muscles decreases due to their atrophy and, consequently, there is less energy consumption. In addition, in space, the antigravity muscles are not used, so these muscles atrophy. The exercise programs implemented (2.5 hours a day, six times a week) are crucial countermeasures to slow down the damage to the musculoskeletal system caused by space travel. Some exercise devices perform vibrations to prevent the loss of bone and muscle mass, as it is believed that muscles produce similar vibrations on the skeleton in a terrestrial environment (Kreykes 2020).

Another study revealed that the change in bone mineral density was the same for men and women, and that there was no drop in bone mineral density in either sex who practiced the Advanced Resistive Exercise Device (ARED), unlike that observed in individuals using other exercise devices. Astronauts who used ARED and 800 IU of vitamin D daily preserved more bone mass (Smith *et al.* 2014).

Exposure to artificial gravity, by centrifugal acceleration of +2-3Gz, for just one hour a day, can help prepare for landings after long-duration journeys, such as the possible journey planned for the 2030s, to Mars. Among the various changes that the musculoskeletal system undergoes, the main adaptations of this system to the space environment are explained below (Krittanawong *et al.* 2023; Russomano and Castro 2020; Stella *et al.* 2021).

Acute adaptations

- Loss of approximately 2% of bone mass per month in lower body bones (MicroG);
- Decreased adhesion between bones, ligaments and tendons (MicroG);
- 3-6 cm increase in height (due to greater spacing between the intervertebral discs and stretching of soft tissues around the spine) (MicroG).

Chronic adaptations

- Reduction in height (due to flattening of the space between the intervertebral discs) (HyperG);
- Impairment of the cushioning function of the intervertebral discs (MicroG);
- Low back pain due to paravertebral muscle strain (MicroG);
- Significant loss of muscular endurance (MicroG).

Skin adaptations

Some studies have identified a drop in extracellular matrix production capacity and collagen concentration, along with limited angiogenesis and decreased keratinocyte migration, when analyzing skin changes in space. Loss of epidermal thickness and elasticity has also been identified in situations of continuous exposure to microgravity. Dry skin is common in astronauts and is related to a decrease in the *turnover of* epidermal cells and causes thinning of the skin layer. It should also be noted that the concentration of collagen in the dermis showed an increase of 143% in astronauts who underwent a six-month mission. This showed a compromised healing process in space environments. Salt accumulation has occurred in the skin of astronauts in its inactive form, but there are still no conclusive studies on the causal factor of this event (Á Farkas and G Farkas 2021).

Dermatological conditions have also been described in astronauts, such as atopic dermatitis, due to the cold and low humidity in the spacecraft and possibly due to immunosuppression. In addition, contact dermatitis – an inflammatory and itchy condition capable of producing serious consequences – can be caused by clothing, electrodes, gloves, masks, headphones, among others.

Skin infections seem to be more frequent in the space environment. Furthermore, data shows that there is an increased risk of direct transmission in flight because it is a confined space. For example, the transmission of *Staphylococcus aureus* between crew members has been described (Pierson *et al.* 1996). Dry hair and incomplete rinsing of areas of the body during sanitization also facilitate the proliferation of pathogens on the skin. With immunosuppression present, increased virulence and antibiotic resistance become more relevant to finding protective measures against infectious changes. Other lesions also identified include acne vulgaris, cellulitis, dermatophytosis, reactivation of the herpes virus, psoriasis, skin cancer and urticaria (Dunn *et al.* 2018 and Caswell 2022).

Acne vulgaris has been documented in cosmonauts and should be treated mainly with oral antibiotics and retinoids (Dunn *et al.* 2018). Another possible manifestation is cellulitis, which appears as an erythematous plaque, usually after trauma. The common etiological agents are bacteria of the *Staphylococcus* and *Streptococcus* genera (Siqueira-Batista and Gomes 2021), which have been found to colonize ISS (Tozzo *et al.* 2022). Fungi can also generate lesions in these scenarios, as in the case of dermatophytosis, which appears in damp places. Crew members have shown reactivation of the herpes virus, particularly in the first few weeks of flight, and there is a need for vaccination against the varicella zoster virus. Due to ionizing radiation, astronauts have an increased chance of developing skin cancer, as the spacecraft passes through the Earth's magnetosphere, which offers protection against cosmic radiation. Hypersensitivity reactions – urticaria and angioedema – have also been described. It is thought that urticaria may be a consequence of decompression syndrome, due to the accumulation of nitrogen bubbles in the tissues (Dunn *et al.* 2018). The main adaptations to the skin system are described below (Krittanawong *et al.* 2023; Russomano and Castro 2020; Stella *et al.* 2021).

Acute adaptations

- Decrease in extracellular matrix production capacity and collagen concentration;
- Limited angiogenesis;
- Decreased migration of keratinocytes;
- Impairment of the healing process;
- Loss of thickness and elasticity of the epidermis;
- Skin dryness;
- Increased propensity to develop atopic dermatitis, acne vulgaris, psoriasis, skin cancer and urticaria;
- Increased occurrence of skin infections (e.g. cellulitis, dermatophytosis and reactivation of herpes virus).

Chronic adaptations

- Loss of thickness and elasticity of the epidermis;
- Increased propensity to develop atopic dermatitis, acne vulgaris, psoriasis, skin cancer and urticaria.

Genetic adaptations

Telomeres make up the ends of chromosomes and prevent degradation and physical damage to DNA. In addition, these structures shorten as a result of cell multiplication (thus, with age), stress and other aggressors, such as radiation, and this is directly correlated with shorter longevity. There was an increase in the translocation of genes, specifically related to DNA damage response pathways, probably due to ionizing radiation. The expression of genes associated with the immune system was altered, including genes from the adaptive and innate immune system, and from immunity mediated by natural killer cells (Garrett-Bakelman *et al.* 2019).

Astronauts have also shown changes in plasma-derived extracellular vesicles (EVs) microRNA (microRNA is transported by EVs and can alter gene expression in the target cell), due to environmental stressors in space. A study that collected data from 14 astronauts on various missions in low-Earth orbit noted an increase in the production of the microRNA "hsa-miR-4732-3p", which is involved in the deregulation of cardiovascular hemodynamics (as in atherosclerosis), cancer, the regulation of cellular homeostasis and insulin signaling pathways, among others (Goukassian *et al.* 2022). The main acute genetic adaptations involved can then be visualized (Krittanawong *et al.* 2023; Russomano and Castro 2020; Stella *et al.* 2021;).

Acute adaptations

- Increased telomere length (MicroG);
- Increased translocation of genes, specifically related to DNA damage response pathways (MicroG);
- Changes in microRNA of extracellular vesicles (MicroG).

FINAL CONSIDERATIONS

There is a considerable interest in how the human body adapts to extraterrestrial environments. This narrative review of the literature on the organic modifications of *Homo sapiens* in space contexts was carried out with the aim of helping to understand the risks involved and how they can affect the health of astronauts and the mission of all crew members. This analysis identified that the main systems affected include the cardiovascular, neuropsychic, musculoskeletal and immune systems.

The most effective prevention strategies are essential if humans are to conquer outer space. In fact, new research into minimizing harmful physiological changes needs to be undertaken. Examples include adequate sleep time, a healthy diet, protection of the spacecraft from ionizing radiation, physical training (using ARED) and the adoption of simple procedures, such as establishing a "floor" on board (space reference) – carried out by experienced astronauts – which prevents nausea, dizziness and disorientation in space.

Among the main challenges for the solid scientific study of physiological changes in the space environment is the restricted access to data, due to the distance, the complexity of space missions and the limitations concerning the population being investigated (there are few astronauts, most of them male and, as a rule, recruited in full health). This scenario has changed with the incorporation of private enterprise into space tourism, which opens up countless perspectives for understanding human life in space, as well as bringing more challenges to space medicine and physiology.

The commitment to ensure that the research carried out in space missions continues to reflect a close relationship with good science seems to be the *sine qua non* condition for maintaining the health of cosmic travelers, so that the undertakings that are now being announced - whether the return to the Moon or the first manned flight to Mars - can have a "*long and prosperous life*".

CONFLICT OF INTEREST

Nothing to declare.

DATA AVAILABILITY STATEMENT

All dataset were generated or analyzed in the current study.

AUTHORS CONTRIBUTIONS

Conceptualization: Siqueira-Batista R; Geller M and Silva IC; **Data curation:** Ferreira RA and Siqueira-Batista R; **Formal analysis:** Ferreira RA and Silva IC; **Methodology:** Siqueira-Batista R; **Project administration:** Siqueira-Batista R and Russomano T; **Supervision:** Cima OMD; Cupertino MC and Alcântra FA; **Validation:** Cima OMD; Cupertino MC and Alcântra FA; **Writing - Preparation of original draft:** Silva IC and Siqueira-Batista R; **Writing - Proofreading and editing:** Siqueira-Batista R and Russomano T.

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