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Impact of spaceflight on endocrine, metabolic and kidney function: current evidence, open issues, and potential countermeasures

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Abstract

Changes in endocrine and kidney functions have been associated with spaceflight. Here, we discuss the most relevant evidence about the impact of spaceflight on the cardiometabolic system, the cardiorenal function and the reproductive/gonadal axis. Notably, these changes appear to be interrelated with other organ/system functions, suggesting the need of a systemic approach leading to a more comprehensive understanding of physiological and health-related impacts of the space environment. Therefore, this review will also focus on the need to move space endocrinological research to multi-omics approaches and the implementation of "machine learning" and "data mining" strategies.

Keywords Space exposome, Microgravity, Metabolic changes, Cardiorenal function, Reproduction, Oxidative stress

Introduction

Spaceflight-associated changes in human physiology have been observed and studied from the onset of space exploration in the middle of the last century. Human spaceflight-associated changes in endocrine and kidney functions have been addressed both during space missions and ground-based simulations. suggesting that they are interrelated with other organ/system functions, such as the alteration of bone and skeletal muscle homeostasis, as well as cardiac deconditioning [1, 2]. Indeed, endocrine, metabolic and kidney functions regulate body homeostasis in a very complex and interconnected way, with even the partial impairment in function of specific organs being associated with the onset and progression of a broader set of symptoms affecting multiple systems, spanning from reproductive alterations to metabolic diseases. Such observations suggest the need to consider specific physiological alterations using a broader systemic approach.

Despite the scientific attention given to space biomedicine and methodological advances over the years, it remains critically difficult to determine the molecular signatures of endocrine alterations associated with space exposome and to evaluate when hormonal changes represent a sign of harmless adaptation to changing environmental conditions or a significant health risk. It seems important to determine which are the parameters that

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distinguish reversible from non-reversible alterations, but the data so far available are not sufficient, and in many cases the scientific literature in this field is rather controversial.

Many of the well-known endocrine/metabolic diseases characterized at ground level under the influence of Earth's gravity may suggest useful approaches for the identification and management of spaceflight-associated dysfunctions. Reciprocally, the extreme conditions of the space environment may accelerate some pathological mechanisms and provide insights to speed-up the research on therapeutic approaches for the treatment of the corresponding diseases on Earth.

Recent literature has clearly depicted the five hazards that, taken together, represent the space exposome and include (1) space radiation, (2) confinement and isolation, (3) altered gravity, (4) hostile and confined environment and (5) distance from Earth. Herein, we collect and discuss the most relevant clinical and experimental evidence on the effect of space exposome on the following main topics: (A) endocrine and metabolic changes, including insulin resistance and dyslipidaemia; (B) cardiorenal function and salt-water balance; (C) bone, calcium/phosphate balance, kidney function, vitamin D, parathyroid hormone; (D) reproductive/gonadal axis as a health pillar (Fig. 1).

Endocrine and metabolic changes, including insulin resistance and dyslipidaemia

Prolonged spaceflight and related ground-based experiments, simulating microgravity or confinement, are associated with a relevant set of hormonal and metabolic changes, involving the neuroendocrine system and including circadian rhythmicity, function of the hypothalamus–pituitary–adrenal (HPA) axis and regulation of gluco-lipid metabolism [3].

Studies related to exposure to space radiation highlighted the possible role of chronic inflammation and increased oxidative stress in the aetiology of radiation-induced cardiovascular disease (CVD), suggesting to

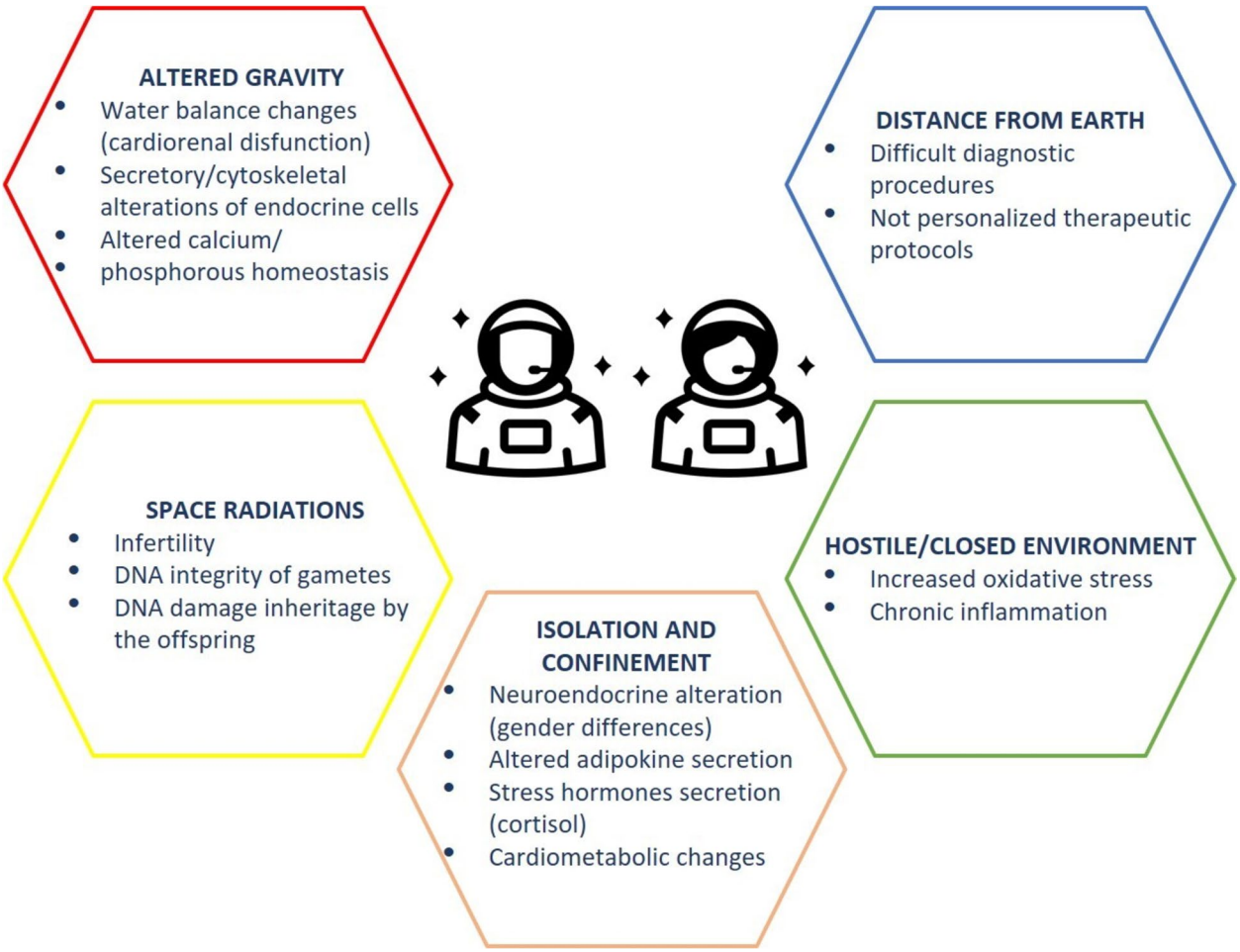

Fig. 1 Schematic representation of the effect of space exposome on endocrine, metabolic and kidney function

take into consideration also this component, in combination with altered circulating lipid patterns (see below) when CVD risk of astronaut cohorts is assessed [3]. A long-term cohabitation under confinement may induce psychophysical stress and cause homeostatic changes within the neuroendocrine system (mainly in the HPA axis) and on adipokine secretion by the adipose tissue, which in turn may lead to insulin resistance [4]. In this context, the Mars-500 project was aimed at simulating crew's activities, workload and communication during a mission to Mars, evaluating the homeostatic adaptations to prolonged confinement and cohabitation. The 520-day experiment led to progressive reduction of body mass and lean mass, but not of fat mass, to moderate insulin resistance and earlier adiponectin reduction. As leptin levels did not vary, the leptin/adiponectin ratio tripled already after 60 days [5]. Unfortunately, no data are available so far regarding space flight-related changes in plasma ghrelin, another hormone that is very relevant for energy metabolism and fat-free mass [6]. A high salivary cortisol has also been reported in this study [7, 8]. These observations suggest that environmental stress has a strong impact upon both metabolic and stress response, which in turn affects body composition. Of note, the adipokines leptin and adiponectin are involved in the regulation of a wide variety of physiological processes including insulin responsiveness, glucose and lipid metabolism and low-grade chronic inflammation.

Distance from Earth may pose some relevant issues, broadly associated to all health aspects of the astronauts, and related to prevention and identification of health alterations and their specific countermeasures. Some examples may be an accurate evaluation of the individual CVD and metabolic risk in astronauts directed to the Moon and to Mars, including in-flight monitoring of biomarkers and arterial wall thickness and other biomedical parameters.

Actual (spaceflight) and simulated (head-down-tilt bed rest (HDTBR)) microgravity conditions have been the most commonly used experimental paradigms for evaluating endocrine and metabolic changes. The association of increased insulin resistance [9] and carotid artery distensibility coefficient and β-stiffness index was observed in astronauts of both sexes after a 6-month stay at the International Space Station. Spaceflight-by-sex interaction effects indicated greater changes in β-stiffness index in women, but greater changes in pulse wave transit time in men. The increase of insulin resistance was greater in men, while renin and aldosterone increases were greater in women [10]. Related to CVD risk assessment, the analysis of a dataset from 59 astronauts revealed higher levels of total cholesterol and low-density lipoprotein (LDL) cholesterol accompanied by decreased levels of high-density lipoprotein (HDL) cholesterol during spaceflight. These levels, generally associated with greater CVD risk, reverted to normal after returning to Earth [2]. Moreover, increased levels of the hepatokine fetuin-A and triglycerides were observed in a 60-day HDTBR study, along with greater insulin resistance, possibly with etiopathogenic involvement of the liver, rather than muscle and adipose tissue, and suggesting that fetuin-A released by the liver may be an important determinant of changes in whole body insulin resistance [11].

Hostile/confined environments may individually cause chronic stress, resulting in pathological changes like low-grade chronic inflammation and metabolic alterations, leading in the long term to permanent (metabolic, epigenetic, morphological, etc.) changes.

Cardiorenal function and salt/water homeostasis

An early microgravity-induced change in sodium/water homeostasis is represented by initial microgravity-induced changes like redistribution and centralization of body fluids from the lower peripheral body segments into central and upper body segments including the thorax and the head [12]. Due to this redistribution, plasma volume increases, leading to haemodilution. Secondary to centralization of body fluids and haemodilution is the activation of neuro-hormonal changes that stimulate kidney excretion of sodium and water, which leads to a reduction in their body content [13]. Overall, microgravity-induced changes in sodium/water homeostasis are not responsible for major dysfunctions during short-term missions, while they are associated with reduced mean, systolic and diastolic arterial pressure during long-term missions, leading in some cases to orthostatic hypotension and presyncope during flight, and contribute to orthostatic hypotension/incompetence and related alterations after returning to normal gravity [14].

Measurements of body fluids and/or of blood fluid to monitor changes in sodium/water homeostasis are only feasible by specialized laboratories on Earth. The measurement of blood or urine levels of sodium is of limited help due to the heavy confounding factor represented by dietary intake of sodium (salt) and water. Haemodilution can be disclosed by measurements of haematocrit [15] that require venipuncture. Micro-haematocrit could be a less invasive method requiring finger skin puncture only. Additional information can be obtained by bioimpedance measurements, a non-invasive method that is feasible also during the mission. Changes in sodium/water homeostasis are a direct consequence of altered gravity exposure and seem independent from other space-related hazards.

Bone, calcium/phosphate balance, kidney function, vitamin D, parathyroid hormone

Hypercalciuria, that is the increase in urinary calcium, is a well-established feature of microgravity-induced changes. It can be mimicked on Earth by HDTBR or other conditions of prolonged immobilization [12], which have been conducted even up to 120 and 370 days [16]. For years, microgravity-induced hypercalciuria has been regarded because of the microgravity-induced loss of bone mass. Nevertheless, recent data suggest that hypercalciuria is a transient, self-limiting change [17, 18], although this observation remains controversial [19]. In contrast, bone mass loss continues over time [20], possibly due to the interplay of several factors.

A reduction in parathyroid gland secretion was consistently found in space missions and bed rest studies [17, 20]. A contributory role to microgravity-induced hypercalciuria could be played by suppressed parathyroid hormone (PTH) levels given that PTH reduces urinary calcium by activation its reabsorption at the kidney tubule. Consistently with the reports of lower PTH levels and with PTH effects on phosphorus homeostasis, microgravity associates also with higher extracellular phosphorus, a change that can be detected in serum or saliva [16, 17]. Theoretically, suppressed PTH could have a role also in bone mass loss as proved by the efficacy of PTH analogues in the treatment of osteoporosis [20]. The causes of suppressed parathyroid gland secretion in microgravity are not well clarified yet.

Regarding the monitoring of the changes in calcium/phosphorus homeostasis, the measurement of these minerals in the urine would be of limited help because of the confounding effects of their dietary intake. Measurement in blood would necessarily require venipuncture. Data collected in two astronauts during a 6-month mission suggests that non-invasive methods for saliva measurement could be reliable for monitoring the changes in phosphorus homeostasis and, perhaps, also as a proxy of PTH changes [17]. Changes in calcium/phosphorus homeostasis are a direct consequence of microgravity exposure, but theoretically they could also be affected by exposure to space radiation, since UV are well-known activators of endogenous generation of 25-hydroxy-vitamin D that suppresses PTH secretion [21]. Perspectives and challenges in future space missions could include investigations on determinants of PTH suppression and on efficacy of PTH analogues against bone mass loss.

It should be mentioned that a decrease of plasma levels of 25-hydroxy-vitamin D has been observed over time in astronauts during spaceflight. For this reason, astronauts actually require an adequate oral intake of vitamin D to minimize this negative balance, and this countermeasure is currently recommended for space flights of up to 1 year duration [22, 23]. Being the kidney responsible for 25-hydroxy-vitamin D metabolism via the expression of CYP27B1, CYP3A5 and CYP24A1 enzymes, its role been proposed in the alteration of 25-hydroxy-vitamin D availability. However, recent data obtained on a human kidney microphysiological system cultured on board the ISS indicates that space environment did not appear to affect the metabolism of 25(OH)D3 via CYP27B1, CYP3A5 or CYP24A1 [24, 25].

Notably, observations on astronauts and a mouse animal model on board the ISS indicate that spaceflight induces increased risk of nephrolithiasis, remodelling of the nephron with expansion of distal convoluted tubule size and loss of overall tubule density, and renal damage and dysfunction, when exposed to a Mars roundtrip dose-equivalent of simulated galactic cosmic radiation (GCR) [26]. Noteworthy the formation of nephrolithiasis seems to be a direct consequence of space environment exposure, and just partly due to the spaceflight-associated bone loss and consequent hypercalcemia. Overall, it should be highlighted that kidney complications may potentially endanger long/very-long final frontier exploration [27].

Reproductive/gonadal axis as a health pillar

The reproductive system of both sexes is at the crossroad of endocrine and immune systems, being dependent on the hypothalamus-pituitary–gonadal (HPG) axis [28, 29], and sensitive to stress signals derived from the HPA axis and the immune system (i.e. pro-inflammatory cytokines) [30]. Notably, being gonads themselves endocrine organs, their proper function is requested for the homeostatic regulation of other tissues such as bone and muscle as well as for central nervous system proper functionality [31–33]. Moreover, sex hormones also regulate endocrine functions via positive and negative feedback [30]. Based on this evidence, altered functionality of the reproductive system has a negative impact not only on reproductive performance, but also on systemic physiology, in addition to having detrimental effects on the quality of gametes and therefore the health of future generations. The hazards related to spaceflights and space exploration [1] may negatively influence the reproductive system in a direct and indirect way [34–36], as discussed below. Sleep loss is one of the hazards associated with spaceflight and threatens reproductive function since disruption of circadian rhythmicity, including that of glucocorticoid and melatonin release, affects fertility [37]. Prolonged confinement and work overload associated with spaceflight are stressful conditions that could negatively influence reproductive function and fertility. Cortisol modulation due to stressful environments is often associated

with testosterone decrease in astronauts during or after (real or simulated) space travels [34]. However, it should be highlighted that our knowledge on the effects of prolonged confinement on reproductive function and behaviour is still limited. Increased core body temperature has been observed in astronauts in long-duration space missions [38]. Heat stress represents a relevant threat to reproductive function especially for male germ cell development [39], but it is worth mentioning that systematic studies on this spaceflight-related threat are lacking. Gravity force changes some features of space missions and directly influences the reproductive system. The direct effect of microgravity on gonadal function has been studied thanks to experimental models. Testicular alterations have been reported by several studies, being both seminiferous epithelium and endocrine Leydig cells affected by the change of gravitational force. In female animal models, the microgravity-dependent disruption of ovarian secondary follicle development and the decrease of plasma estradiol concentrations have been reported, albeit very few studies are available in the scientific literature on this subject [34]. Space radiations represent a serious threat for long-term space missions for their deleterious effect on DNA integrity. In the reproductive system, this is of particular interest since damaged DNA of gametes is inherited by the offspring [40].

Although no systematic studies are available in humans regarding reproductive function changes during spaceflight, some information from short (up to 15–22 days) unmanned missions with experimental animal models (COSMOS-1514, NIH.R1, NIH.R2 and NIH.R3) shows that short-term exposure to low Earth orbit during mid to late gestation does not cause major disruptions in foetal development or parturition, nor relevant changes in male reproductive parameters [34, 41]. On the other hand, it should be noted that a systematic study of the health of post-flight offspring has never been addressed.

Further studies, especially related to long-term associated exposure to space radiation (as occurring during longer missions), are necessary: experimental in vivo studies demonstrate that exposure to high charge and energy (HZE) particles and neutrons induces oxidative damage, double strand DNA breaks and apoptosis in oocytes and granulosa cells of ovarian follicles in various stages of development. This results in dose-dependent depletion of the ovarian reserve and increased incidence of ovarian tumours, as well as spermatogenic cell alterations [34]. Currently, female astronauts often suppress their ovarian cycles during spaceflight, particularly during longer missions, using combined oral contraceptives, although such approach appears insufficient, as it does not represent a protective countermeasure against radiation and other hazards [42].

Finally, it should be highlighted that the reproductive system is particularly sensitive to environmental alterations and therefore the control of the derangement of reproductive hormones could be considered as a useful, sensitive and early marker of the effect of space exposome on human physiology.

Increased oxidative stress, spaceflight and endocrine health impact

Increased oxidative stress during prolonged spaceflight represents a common feature of all space-related hazards. In detail, GCR and solar particle events (SPEs) generate ROS by directly interacting with biomolecules at the cellular level [41]. The biological mechanisms underlying microgravity-induced ROS production are still only roughly understood being mitochondria alteration and the impairment of antioxidant barrier enzymes at least partly responsible for this phenomenon [43–45]. Since excessive levels of reactive oxygen radicals (ROS) are implicated in macromolecule damage (such as lipids, proteins and nucleic acids) and in the pathophysiology of several diseases [46, 47], such activation of ROS generation is considered responsible, at least in part, of the main spaceflight-related systemic changes and potential morbidities, especially including the endocrine and cardiometabolic impairments. For this reason, antioxidant supplements have been proposed as protective countermeasures to reduce the impact of pace environment on human physiology with variable results whose causes remain unexplored [48, 49]. Indeed, experimental studies clearly show the negative impact of increased ROS generation by simulated microgravity in different cell-based models. Although some ROS generation is physiological, since ROS are signalling molecules necessary for the maintenance of physiological functions [50], they may become toxic when they are produced in excess. Thus, a hormetic/biphasic role of ROS molecules may be hypothesized during spaceflight: the initial ROS increase can indeed have a role in the perception and adaptation to the space exposome [51], albeit chronically high levels of ROS would negatively impact on human physiology. The currently available data on ROS production during actual and simulated spaceflight in humans are quite scarce and further investigations would be helpful to collect a full knowledge for setting-up the appropriate countermeasures and mitigation strategies to protect human physiology. Moreover, genetic features related to the endogenous antioxidant capability of astronauts should be assessed, in order to provide more personalized strategies to counteract space-related hazards.

Knowledge gap and limitations of space biomedical research

The current knowledge about the impact of the space exposome on the endocrine and renal systems is still fragmented and shows several gaps, although the evidence depicted above reports specific and systemic aspects of reproductive system changes, cardiometabolic alterations and salt/fluids and calcium metabolism regulation. Other endocrine and metabolic changes may be rather subtle or individually present, suggesting the need for an in-depth and personalized evaluation.

Among the limitation of available studies, it should be highlighted that:

- There is a lack of data on sex-specific changes. Indeed, the Mars-500 project and many other studies evaluated only male subjects. The effects of space exposome on women is still poorly understood because of the relatively small number of female astronauts.
- The access to space missions-related data is limited, and this negatively influences the statistical significance of some studies.
- Given the different age, sex and in-flight activities, as well as different exposure time to the space exposome, observations on astronauts' health cannot be easily standardized. This severely biased some of the results obtained in-flight on astronauts' health.
- There are serious constraints to the in-flight clinical and analytical assessment of astronaut's health; novel and more effective approaches are urgently needed in this area.

Open questions

Based on what the here reported discussion, there are still several unresolved open questions that arise and need to be solved to allow a safe space exploration by humans:

- How does the cumulative "spaceflight exposome" (and its different hazards alone) impacts on endocrine-metabolic functions?
- Is it possible to assess endocrine physiological adaptations to the space exposome, i.e. the "normal" (reversible/not harmful) hormonal levels in space-adapted physiology as well as the markers of endocrine health in space?
- Is there a sex/gender-specific endocrine and metabolic response to spaceflight-related hazards?
- Which specific pathophysiological mechanisms and related countermeasures may be related to (A) repro-

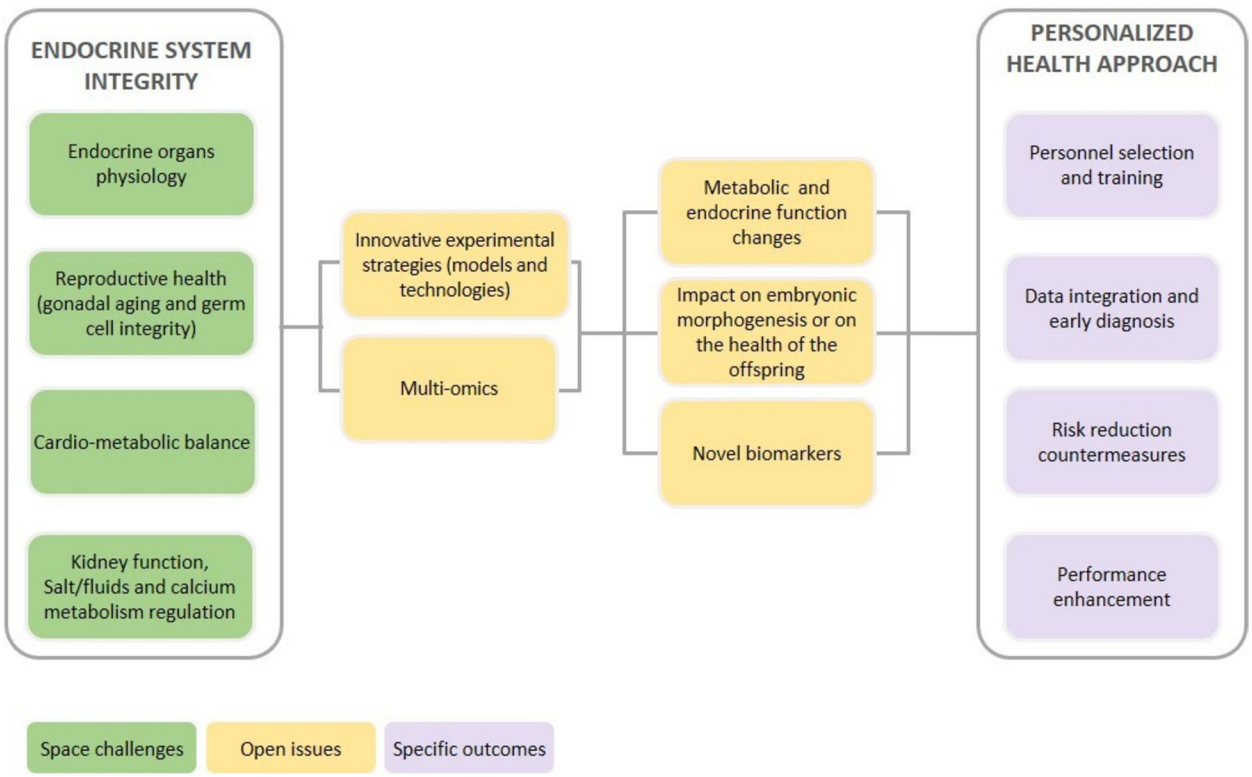

Fig. 2 Graphical representation of the main challenges for space endocrinological research

ductive function; (B) insulin resistance and cardiometabolic aspects? (C) salt/water and calcium/phosphorus balance?

– At the practical level, what biological matrices and biomarkers/methodologies are better suited for assessing specific molecular mechanisms/countermeasure targets? In this regard, it should be highlighted that specific exercise programs [52] and nutrition (including antioxidants and anti-inflammatory supplements) countermeasures proved only partly effective [22] since they do not fully counterbalance the physiological alterations related to the space exposome.

Perspectives and challenges

In light of the above-mentioned limitations of space biomedical research, an expansion in the use of ground-based microgravity simulation systems as well as confinement/isolation paradigms using experimental models as well studying human volunteers (i.e. HDTBR and submarine missions) is strongly recommended. These studies are needed to assess the effects of cumulative/selected hazards on human male and female biology and potentially accelerated ageing and to assess the specific effects of spaceflight biohazards on embryogenesis and morphogenesis, starting from animal models.

The expansion of ground-based simulation of space exposome would help in the identification of the molecular mechanisms promoting cardiometabolic changes during (simulated) spaceflight as well as the accurate assessment of salt/fluids and calcium metabolism regulation during (simulated) spaceflight. This would also help identifying novel and more effective biomarkers/methodologies for detecting these changes, as the current methods are not entirely satisfactory.

In this regard, it is worth noting that the development of new bio-engineering technologies (such as wearable sensors) needs to be implemented to enable in-flight collection of relevant data. Moreover, implementation of multi-omics approaches and data analysis by artificial intelligence/machine learning may result crucial. This approach may support the development of appropriate "integrated countermeasures" aimed at preserving not only the endocrine, metabolic, reproductive and renal health of space mission participants, but also the homeostasis of other physiological systems and, likely, also the health of their offspring. Precision and personalized space medicine should be the final challenge of space-related research that needs to be addressed (Fig. 2).

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Authors' contributions
All authors have contributed to the original writing draft. Conceptualization of the main flow stream was performed by PM, GR and FF. All authors read and approved the final version.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Competing interests
The authors declare no competing interests.

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