



Research Article

Geriatric Space Travel[©]Gabrielle M Caswell^{©*}

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The world community continues to move towards exploring the solar system, with exploration of our immediate solar system aimed at establishing intra-planetary colonies, first perhaps on our nearest Earth neighbour Mars. Long haul and intergenerational space flight, with intra- and perhaps extra-planetary colonisation, at the current level of technology, will probably create the need for geriatric space travel.

Humans are uniquely adapted to a live, survive and thrive in Earth gravity (1g) of approximately 9.8m². When humans move beyond this gravity and the Earth's protective gravitational field, human growth, development and physiology is impacted. This brings to the forefront two main areas of consideration: multi-morbidity and increasingly complex care needs of an active geriatric crew, whose skills, academia and practical knowledge may be required for longer, and more enduring working lives, and the physiological hostility of altered gravity environments.

Whilst aging on Earth is a complex topic; altered gravity environments will bring even greater challenges. Bodily systems known to be affected by altered gravity environments include the immune, cardio-vascular and muscular-skeletal systems. Gross effects on these systems have been catalogued over the years; the most notable being rapid onset of osteopenia and osteoporosis, even after relatively short exposure to altered gravity environments of two weeks. Newer areas of study of the effects of altered gravity have broadened to include infection susceptibility and disruptions to the gastrointestinal-pulmonary and gastrointestinal-skin axes. Nutritional changes caused by gastrointestinal microbiome imbalances can affect both the uptake of nutrients as well as medications, with possible impacts on cellular operations and perhaps cognition.

In the altered gravity environment those individuals genetically predisposed to certain diseases may be at risk of accelerated onset of cognitive decline, immunological and physiological changes. This paper explores some of the known physiological stresses caused by altered gravity environments, highlighting the possibly of disease and aging insults that may be experienced by the geriatric astronaut.

Keywords: Geriatric, microgravity, altered gravity environments, long haul space flight, intergenerational space flight, intra-planetary colonisation

Introduction

Human or Earth orientated beings struggle in altered- or micro-gravity (*ug*) [1-3]. It is apparent that human cells are uniquely bound to the Earth gravity of 9.8 m² (1g) [4-6]. When humans are removed from 1g experience shows that almost all physiological systems are affected. Such data that has been collected over the years from various space programs: The Russian Soyuz and MIR missions, The International Space Station (ISS), Skylab and from relatively short haul shuttle resupply and satellite launch missions [7]. Mission data confirms that even minute changes in gravity

can have significant effects on human health. To appreciate these concepts, ISS gravity is 89% of 1g but effective gravity is 0, hence even short trips of 2 weeks create appreciable measurable bony changes on the osteoporotic continuum in astronauts [8,9]. These altered gravity impacts have been described affecting the musculoskeletal, cardiovascular and immunological systems and are hypothesized to be the expression of cellular change [10-13]. If short exposure to altered gravity creates physiological changes, it can be assumed that biological protection will be needed for humans in this hostile environment, with particular consideration given to longer journeys or colonisation [14,15].

Missions to the ISS for example, are mere 'hops', with respect to distance and time, when compared to journeys to the outer planets of our solar system or beyond. These journeys require

long haul/inter-generational space flight based on current rocket propellant technology. Problems caused by the altered gravity environment and its influence on the human body will not abate with colonisation of the Earth's Moon or our nearest planet Mars [16,17]. Appreciating the gravity of the Moon is approximately 0.017% of 1g and Mars 0.028%-0.038% of 1g, the gravitational influence on human living systems and the evolution of their molecules on Earth, it is reasonable to predict that any colonisation outside of 1g will be extremely challenging for the human species survive and thrive [18-20].

Aging on Earth, as a testament to ongoing medical science, has seen healthcare dominated by individuals with multiple comorbidities and complex care needs, resulting in significant challenges for practitioners and the community overall [21]. Mental and behavioural conditions (including anxiety, depression and mood disorders), musculoskeletal (including arthritis), respiratory (including asthma) and endocrine and metabolic conditions (including diabetes) were the most common health concerns managed by general practitioners in Australia in 2021, consistent with most developed Western countries [22, 23] It would be expected that the same conditions, especially those which are innate to the aging human, would be encountered with long haul and intergenerational space flights.

Adding complexity is the growing knowledge of the human skin- and gut- microbiomes and the various axes the gastrointestinal tract contributes. The gastrointestinal-skin axis plays an important role in immune and cognitive health; whilst the gastrointestinal-pulmonary axis sees mutual support of both systems for healthy nutritional and immunological states [24-29]. There is increasing evidence that gut microbiome is both genetically and environmentally determined, as changes to an individual's gut microbiome has been observed in a confined habitats, becoming 'generic' in nature across all inhabitants [30-32]. This can contribute to mitochondrial dysfunction and an independent effect on the human immune system, with downstream effects on nutrition and medicine uptake, as well as impacting on overall healing capacity [30-32].

The Earth's gravitational field protects humans and mammals from the radiation innate in space. There are arguments for and against the current level of space travel affecting or inducing cancer, with some researchers advocating the use of alternative medicines so that space travelers may 'grow' future treatments [33-35]. Increased cellular turnover observed in bacteria and mammalian cells (e.g. osteoblasts) brings into question broader aging and cancer considerations; cells affected by the environment of altered gravity may also be provoked by increased radiation exposure [36-38]. This perhaps couples poorly with the possibility of weak B-Cell surveillance creating a form of immuno-suppression, worsened by their misfunction due to changes in lymphatic fluid dynamics [36-38].

There is of course, with any aging population, the inevitably to consider palliative care requirements in an off-Earth space setting. Unlike older populations on Earth where the conversations

about resource allocation is not one currently considered (in most Western nations), this may become an issue which future space bound clinicians may be forced to discuss [39].

Conditions and diseases that are experienced by older populations on Earth are expected to occur in the same rate in space based aging populations [40, 41]. Without a resolution to create gravity that mimics Earth's, longer space flight scenarios are anticipated to have greater and ongoing impacts on the human body. This discussion gives consideration to altered gravity environments impact on immunological responses, changes to bacterial and viral pathogenesis (with an increased infection risk) and the increased hazard of oestopenia and osteoporosis (occurring at a younger age than which is experienced on Earth), as well as morphological cardio-vascular changes, an older person's potential for cognitive changes, perhaps made worse, by the overall effect on and changes to, the gut microbiome alterations observed in confined habitats. This discussion by no means considers all the issues, both known and predicted, but aims to open the conversation about the challenges of geriatric space travel, which may create, for the geriatric astronaut, the possibly of diminishing health returns in a clinical environment of limited or scarce resources [42-44].

The physiological effects of altered gravity environments

The physiological effects of altered gravity environments on the human body are wide and varied. They include ocular-vestibular changes, blood clotting and wound healing dysfunction, increased cellular turnover and the more widely appreciated cardio-vascular and musculo-skeletal changes [45-47]. There is good evidence to support gene dysregulation, immune dysfunction and disturbances in cellular and immune signaling as the contributors to some of these effects [48]. These effects may or may not be coupled with increased radiation exposure, from which the Earth's gravitational field currently provides humans with protection [49, 50]. In addition, there is the interplay between radiation, altered gravity environments and DNA damage, affecting DNA repair mechanisms. Our current knowledge enables predictions of increased cancer risk, perhaps aided by dysfunctional or lapsed B-Cell surveillance [51-55].

Apoptosis is not spared in altered gravity; the cellular processes may slow or be nonresponsive due to a loss of vital chemical signals that control this process [56-60]. Cancer in an aging space population may present differently as to a clinician's expectations and experience on Earth. Primary presentation may be a relatively short period of time before either tissue invasiveness or metastases. Cancer cell morphology may not be recognisable due to cellular morphological changes and biochemical markers may not be encountered or recognisable due to changes in protein expression or structure. Surveillance and monitoring tools may not be of the same value as on Earth and certain proteins may appear in unexpected volume or at an unexpected timeline for the disease [57-62]. Changes to three dimensional (3D) molecular structures may impact enzymatic and immune functions. Especially if coupled with nutritional changes (e.g. loss of vital nutrient uptake)

due to the impact of a shared generic gastrointestinal microbiome, affecting ecosystems of genetically determined and individually curated microbiomes [63-67]. And there is the consideration that genetic predisposition for some diseases, which might not 'activate' in 1g, may become more prevalent in altered gravity environments,

There are ocular-vestibular and proprioception changes, each sense becoming more disordered the longer the journey in altered gravity [68-72]. Fluid dynamics in altered gravity environments create vision changes thought to be the result of a conformational change in shape of the eyeball and/all some occlusion of the optic nerve. With conformational changes of the eyeball, radiation exposure and altered gravity effect on the ocular-vestibular apparatus results in motion sickness arising from the middle ear. With continued exposure to altered gravity, gravity and proprioception feedback become more disconnected. The vestibular system becomes further deconditioned causing further motion sickness, persisting when astronauts return to 1g. Some of the vision changes can be beneficial, i.e. correct vision, alternatively the new fluid dynamics experienced can also create vision problems, such as myopia and presbyopia.

For astronauts their peak physical condition is vital, however a long known side effect of altered gravity environments is the rapid onset of osteopenia and corresponding osteoporosis, which is not abated by exercise. Studies show that effect on osteoblasts can occur in as little as two weeks and persist for over 12 months on return to 1g. Further considerations must be given to peri- and post-menopausal women and other individuals genetically prone to such musculo-skeletal disorders when considering crews for long haul space flight.

Human physiology is uniquely adapted for Earth's gravity, the further humans venture into the altered gravity environments, the more health and welfare issues will appear. Research indicates that management challenges, resource and medicine limitations will compound the clinical decision making processes. There is a high probability that new and novel medicines and methodologies will be needed to keep geriatric space travelers healthy for their missions. This paper aims to highlight four areas that space scientists have gathered some data on the impact of altered gravity [73]. It is important to note that the data thus far collected may or may not extrapolate to extended altered gravity environments and/or intergenerational space flight.

Musculo-skeletal changes in altered gravity environments

During space flight (such as short haul or ISS terms) weight-bearing bones lose approximately 1 per cent of their mineralized density per month with an accompanying loss of muscle mass (bulk) [74, 75]. There is a faster decline in altered gravity environments without exercise, leading to the conclusion that the resistance of gravity is required to ensure bone health and muscle bulk [74, 75]. Some astronauts reviewed post ISS and shuttle missions did not recover their pre-flight bone density, after return from their missions, within 12 months of exposure to 1g [76, 77].

There is evidence that the disordered ratio between the action of the osteoblasts and osteoclasts, along with other mechanisms not yet recognized, lead to bone demineralization, most notably in the weight bearing bones of the human body and even vigorously scheduled exercise does not completely abate the issues [78,79]. Ongoing research has not defined the reason for the rapid change in osteocyte behavior [80-85]. Spaceflight induced bone and tissue changes in peri- and post- menopause woman increase the risk of diminishing bone quality and fractures [86-88]. Modern methods of management rely on the balancing ratio of reabsorbing of bone and its minerals, and medications (i.e. bisphosphonates) have been used as bone stabilization medications on Earth for many years. However this medication may not be suitable for space flight due to the increased risk of renal calculi formation, and new alternatives are not yet tested in altered gravity environments [89-92]. Another consideration, apart from the trauma caused by fracture, including the difficulties of surgical intervention in altered gravity environments: blood does not clot, wounds heal poorly, the risk of infection is higher (common benign bacteria change their pathogenesis in microgravity) and pain management is difficult to achieve [93].

Altered gravity environment's effect on the cardiovascular systems

The effect of altered gravity on the heart has long been catalogued; however it is perhaps now with our increased knowledge of the heart that the view of these changes has become more appreciated [94, 95]. The heart changes in size and the chambers change their overall capacity, becoming more the morphology akin to that of a long term sufferer of poorly controlled blood pressure [96-100]. The challenge in altered gravity environments is to maintain the cardiovascular health of astronauts, not only in the shorter term, but also in the longer term with consideration of long haul space flight, where radiation may also have an independent and as yet not catalogued effect [101,102]. This is more complicated when modern pharmacological management of cardiac disease are considered, as the availability of medications and their bioavailability are areas of interest for flight surgeons, particularly if gut microbiome changes impact on the bioavailability [103]. Reactive Oxygen Species (ROS) is increased in altered gravity environments and has an influence on the genetic expression of cardiac and other cells [97-100]. Downstream effects of the change in cardiac morphology concern the heart's compromised 'pumping' ability, causing the development of splenic and upper body congestion, renal failure and lymphatic fluid drainage changes [104,105]. Lymphatic flow is normally supported by both cardiac output and the body's various muscle pumps. The changes to lymphatic fluid dynamics are a double consequence of lack of cardiac output strength as well as change in fluid dynamics in altered gravity. Changes in the lymphatic flow has an obstructive effect on antibodies, peptides, immune complexes, growth factors and all things in the human body that use the lymphatic system as a metaphoric "highway". Unfortunately for humans we do not have the baroreceptors of giraffes [106]. Eventually cardiac changes

lead to baroreceptor dysfunction and blood pressure changes [107-109]. The body's ability to regulate blood pressure deteriorates the longer a person spends in an altered gravity environment; clinically resulting in light-headedness and fainting (on return to 1g), signaling a physical and physiological change in the receptor behaviour [108-110]. These cardiac effects may become complicated medical risks for the geriatric astronaut.

Cognitive changes

Mood disorders in the older patient can have a severe affect on their interactions, insight, contribution and maintenance of relationships [111-113]. The acquired skill and knowledge held by the geriatric astronauts, who may still be working at full capacity in their work team environment, will be challenged further by enclosed spaceship environments, where changes to cognition may cause a range of unanticipated issues [114,115]. Like all patients, physiological causes for changes in mood and social interaction would need to be ruled out/treated and any correctable nutrient, endocrine or metabolic contribution, including gastrointestinal microbiome imbalance affecting uptake of nutrients and/or medications, would need to be corrected [116-119]. Mood disorders, however, are a complex condition, which often reaches beyond nutrition and physiological causes. Clinicians will require tools to maintain their patient's activities and contributions. It may be the case that space clinicians will require sub-specialty skill sets to keep older valued members of the mission team in peak condition [120-122].

In the space environment a change in gastrointestinal microbiome (from individual to generic) can have implications for the uptake of nutrients, and one such nutrient, Vitamin D, is cardinal for healthy minds and the immune system in older patients and therefore older astronauts [4, 123-127]. There are age related changes which occur to the human anterior pituitary's ACTH secretion, noting that ACTH is an important component of the hypothalamic-pituitary-adrenal axis. As a chemical signaler, ACTH's principal effects are increased production and release of cortisol and androgens, stimulating the cortex and medulla of the adrenal gland as well as a role in the maintenance of the circadian rhythm in many organisms [128-134]. ACTH is also produced in response to biological stress (along with its precursor corticotrophin-releasing hormone from the hypothalamus). Biological changes to ACTH either by disease, age related changes or radiation and the high stress environment of space flight could contribute to potential dysfunction, and in this could be catastrophic not only to the individual but the entire crew [135-137].

There is an overlay between the neuro-immune status of an individual and the onset and progression of neurodegenerative disorders and disease [138-141]. The aging process in these cells may be accelerated or decelerated in altered gravity environments; the consequence of this mechanism of aging is not yet explored in altered gravity [142,143]. Treatment regimens may need to include pharmacological, psychological, psychiatric or physical, such as SAD treatment with UV radiation [144-146]. Cognitive decline may be attributable to change in cerebral blood flow/changed fluid

dynamics due to altered gravity effects on the cardio-vascular system [157-160]. However if the base ingredient, medication or other treatment options are not available, treating clinicians may be quite challenged to manage excesses or deficiencies contributing to any mood disorder or cognitive decline. Cognitive decline is a condition that clinicians grapple with on Earth, in altered gravity environments it may be more perfuse and diffuse, with the potential to significantly impact on the mission parameters and safety [161-163]. Early studies appear to indicate a range of brain cells are adversely and perhaps selectively affected by altered gravity environments, as well as exposure to radiation [164,165]. On Earth this radiation is kept at bay by the Earth's gravitational field, in space there is no such protection that our current collective level of technology can offer.

A topic not often broached in modern Western medicine is resource allocation. In the finite environment that space missions present, along with forecasted limited resources, scenarios surrounding rationing of medicine and treatments may be something that requires external (to medicine) protocols and procedures [147-149]. The cardinal question of value of single individual and that of the "greater good" is not a comfortable discussion for modern day clinicians but may be a pragmatic consequence of resource management in space exploration [150-152]. Considerations that are beyond our current technology, such as hibernation chambers, enforced sleep or gross disturbances to the circadian rhythm, may require intensive investigation before they are implemented due to the known effects these may have on mood and cognitive functions [93, 99-100, 153-156].

Immuno-suppression and infection

There is a complex picture of acquired immuno-suppression and poor wound healing experienced in altered gravity environments. The increased infection risk, aided and abetted by the changes in the bacterial growth rates (recorded to be increased up 4-6 times faster on the ISS when compared to Earth's 1g) are accompanied by morphological, behavioural and virulence changes [4, 47, 166-171]. Friendly commensals of the skin microbiome can morph to into an organism of pathogenesis in a very short period of time [172,173].

There also appears to be a poorly understood direct insult on the human immune system, creating T-Cell dysfunction that continues up to 12 months on return to 1g [174-177]. This has been considered as a cause for the reactivation of latent infections, such as *H. simplex*, experienced in space flight [178,179]. It is now known that altered gravity environments have an influence on gene regulation; however to what extend these impacts on both the immune system, bacterial and viral behaviour is not yet clear [180-182]. The affect of altered gravity environments on apoptosis, programmed cell death, may or may contribute to cancerous growths and affect the mechanisms of apoptosis [183,184].

Altered gravity environments impact on gene regulation and may affect cellular and molecular signaling, hindered by the changes in fluid dynamics and pseudo obstruction to lymphatic flow

[185,186]. There is also consideration for the changes to the three dimensional molecular structure of immunoglobulin's perhaps losing the 'lock and key' specificity [4, 187]. The interrupted fluid dynamics of the lymphatic system lead to a suffused upper body which is resistant to diuretic treatments [188]. Whilst endocrine dysfunction is not well catalogued, it is noted that insulin secretion demonstrates changed dynamics, causing an independent immunosuppressive effect [189, 190].

B-Cells have demonstrated changes in their surveillance efficiencies and this may be due to the effect of altered gravity on the lymphatic system or changes to fluid dynamics within the lymph system [11, 191-194]. T-Cells, it is presumed, may take over some of the immunological duties, leading to inflammatory cascades, which in itself is thought to promote early aging [195-197]. Evidence for this may lie in the rise of inflammatory makers in other mammals in simulated altered gravity environments, with corresponding inflammatory issues and increased cardiovascular risk [198-200].

The spectra of rapid growth rate, behavioural changes and increased virulence of bacterial and viral pathogens, along with dysfunctional T-Cells and suppressed B-Cells lead inevitably to a situation of immuno-suppression with increased infection risk and rapid antimicrobial resistance [4, 201-203]. Antibiotics unfortunately do not have the same efficiency as the do in 1g, increased bacterial and viral replication lead to rapid, short generational timeframes and an effective resistance [4, 204-208]. A concern for future scientists and physicians may well be the reactivation of viral infections, including SARS-Co-V2, within the enclosed environment of a space ship [4, 205]. Finally, there is the threat of new and exotic diseases, pathogens and life forms not yet imagined, and that for which we are not yet prepared to encounter [4, 152].

Conclusion

Space travel is no doubt one of humankind's greatest adventures; to reach the outer solar system and beyond with our current propellants and technology it is predicted that space flight will progress to long haul as well as intergenerational flights and . Crews may well be required to work into older age, as part of mission teams. Evident from the planetary population's brief foray into altered gravity environments, growth, development and aging in space will present major challenges to the human species survival in an innately hostile environment.

Threats to humans surviving and thriving will come from a multiple of fronts, such as diseases and syndromes associated with aging, nutritional maintenance for optimal functioning, immune system senescence, post-menopausal changes and increase risk of diseases (i.e. osteoporosis) and cancers (i.e. breast cancer). Changes to DNA repair mechanisms, immune signally and responses, as well as the potential for reactivation of latent diseases (i.e. *H. simplex* infections) are all omnipotent health risk factors. Aging presents increased challenges for the clinicians working in space who may be required to ration limited resources, medications and

treatment options. In short, the much needed skills of a specialist Geriatrician may well be the principle specialty, for those doctors wishing to contribute to human space exploration.

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