Acta Scientific Gastrointestinal Disorders (ISSN: 2582-1091)

Volume 8 Issue 2 February 2025

Research Article

Gut Microbiota Studies Could Improve the Health of the Astronauts for Long Duration Spaceflight

Godard Brigitte*

MEDES, Institut de Médecine et Physiologie Spatiale, France

***Corresponding Author:** Godard Brigitte, MEDES, Institut de Médecine et Physiologie Spatiale, France.

Received: January 06, 2025

Published: January 13, 2025

Abstract

Spaceflight are still fascinating for human even despite the fact they are very challenging for the human body. The life of terrestrial people has been developed to evolve on Earth with the gravity and all the system of the human body have been shaped with gravity.

Cardiovascular system [1] and Musculo skeletal system [2] are may be the most and earlier studied ones because of the direct consequences observed on the human body in space. The lack of gravity exposes the astronauts to osteoporosis increasing faster than after menopausal on the women bodies. After we acquired knowledge from all space mission it has been admitted that spaceflight is a good model for aging and the first system on which it is clearly demonstrated is the Musculo-skeletal system [3].

Nowadays we can easily say that the full body is impacted by the environment of the spaceflight, not only due to microgravity but radiation and confinement inside the ISS (International Space Station).

In this article we would like to highlight the fact that the gastro intestinal tract/system is as well fully impacted by this hostile environment. When we compare the main consequences of a long duration flight on the gut microbiota it has similarities with effect of aging.

In this review we present the changes seen in the gut microbiota of both populations: elderly people [4] and the astronauts [5]. How these changes in the microbiome are impacting human body and are responsible for diseases, linked to immune changes start to be well known. This review shows similarities from spaceflight to elderly people or younger people but sick.

Few studies are showing that improving diet might help restoring the gut equilibrium and probably more, changing the state from pro-inflammatory to a healthier system [6].

Since the first short flight it was obvious that the lack of gravity would affect bone, muscle and all systems also, training with exercise was a minimum to be done to make sure that the astronaut can come back with a minimum of impact on his/her body. It is fully admitted that this countermeasure is crucial but not efficient enough. The new knowledge acquired on the gut microbiome and his impact on the body, is promising to allow us to pursue space exploration beyond the low earth orbit (LEO).

Keywords: Aging; Astronauts; Gut Microbiota; Diet; Immune System; Microgravity

Abbreviations

BGMA: Brain Gut Microbiome Axis; CO_2: Carbon Dioxide; CSA: Canadian Space Agency; ECLSS: Environmental Control and Life Support System; ESA: European Space Agency; EVA: Extra Vehicular Activity; GIT: Gastrointestinal Tract; IFN: Interferon; IL: Interleukine; ISS: International Space Station; JAXA: Japan Aerospace Exploration Agency; LEO: Low Earth Orbit; MUFA: Monounsaturated Fatty Acids; NASA: National Aeronautics and Space Administration; OUT: Operational Taxonomic Units; SANS: Spaceflight Associated Neuro-Ocular Syndrome; SCFA: Short-Chain Fatty Acid; SMS: Space Motion Sickness; T-reg : T Cell Regulator; T-RFLP: Terminal-Restriction Fragment Length Polymorphysm; VIP: Vasoactive Intestinal Peptide

Introduction

The International Space Station (ISS) offers a unique opportunity to study the impact of spaceflight environment on the human being. In 1998 started to be launched astronauts to "this unique giant plateform" built by NASA (National Aeronautics and Space Administration) first followed by the Russian agency and with the participation of the CSA (Canadian space agency), JAXA (Japan aerospace exploration agency) and ESA (European space agency) partners. Since this date, three to more than ten astronauts spent in between 14 days until 12 months to collect data in all field of science: physics, chemistry, radiobiology, biology and physiology. This is a unique place where the astronaut is her/his own experimenter and the subject of the experiment on his body.

If the goal of this review is to focus on the digestive system and mainly the gut microbiota, it is necessary to remind the challenges resulting from this extreme and complex space environment.

Three specifics factors are challenging for a human organism arriving in space/aboard ISS: the radiations, the microgravity and confinement plus other factors linked to the ISS itself. We can find everywhere the impact of these factor on human body but we summarize briefly here the main consequences [7].

Challenges for radiation exposure in space

Exposure to space radiation is one of the main challenges for future long-term and interplanetary space missions. Many uncertainties remain, especially to quantify the risk of radiation-induced cancer. Radiations are different from those we receive on the Earth. They are mainly composed of Proton, electron and heavy particles coming from three main sources: the galactic cosmic rays, the Earth radiation belt and the solar particles. Onboard ISS, astronauts receive an average of 80mSv for a maximum of 6 months of solar activity (when there is a maximum of sunspots and the maximum of solar magnetic fields to deflect particles). Also, this value reaches 160 mSv during the period of minimum solar activity for a stay of 6 months. Although the type of radiation is different on Earth, 1 mSv of radiation in Space is equivalent to the average dose received for three chest x-rays. On Earth we receive an average of 2 mSv each year of all radiation in general [8].

Epidemiological studies of populations exposed to ionizing radiation (primary X-rays or gamma rays) show an increase in the incidence of degenerative tissue damage with, for example, cataracts and cardiovascular diseases (atherosclerosis) [9]. The underlying mechanisms are still poorly understood but involve oxidative and inflammatory damage as well as direct deleterious effects on the tissues [10].

The impact of microgravity

Microgravity has an impact on all the physiological systems of the human body. On the Earth, all living organism adjust and "fight" to resist to the attraction acting between all bodies of matter, the so called gravitational "force". It is difficult to imagine living without, model on the ground are used to simulate this microgravity and to develop countermeasures (means to avoid secondary effects of the microgravity). Those models are the bed rest and dry immersion studies, see other articles for details of such experiments. Another way is during parabolic flight, but the duration of the microgravity is very short (20 seconds repeated 30 times). The well known and most studied impact of weightlessness are on the heart and the musculoskeletal system with atrophy of the muscles, changes in quality and quantity of the muscle fiber, on the bone, with osteoporosis greater than that of postmenopausal women, loss of 1% of bone density per month for an astronaut while this loss is about 1% per year at menopause [11]. These values of course change depending on the individual and the location: it is well known that the carrier bones are the most affected.

Other effects on the vascular system [1] are the stiffness of the vascular wall, from the atrophy of the heart muscle, some degree of heart failure are expected, and orthostatic intolerance to return to Earth is impacting astronaut in the few hours or first day after their landing.

On the neurological system, the first best known challenge is sleep [12], some other symptoms are less mentioned because less impacting such changes in writing, concentration [13]. Headaches is a very common disorder reported in space but not only consequence of the microgravity but can occur with congestion due to elevated CO_2 levels.

The visual system is widely studied nowadays. The discover of changes impacting anatomic or functional vision of crew-member called the SANS (Spaceflight associated neuro-ocular syndrome) shows among other things some abnormalities widely describes in space medicine articles such: flattening of the eyeball, retinal and choroidal folds, enlargement of the sheath of the optic nerve... Most of the time, astronauts do not suffer from any symptoms, except possibly an early presbyopia in flight which is usually arranged on their return to Earth. For the moment the mechanisms are not fully explained but are for sure multifactorial, of course contribution of ionization radiation has to be mentioned too [14].

On the ENT and vestibular system, space sickness was the first annoying symptom mainly for short duration flight in case few EVAs (Extra vehicular activity) would have to be done [15]. Nowadays some preventive measures like medication have considerably reduced the impact. This space motion sickness (SMS) has a neuro-sensory origin and still not clearly explained. Hearing is not in rest but more in relation with the actual environmental conditions aboard ISS rather than microgravity itself. There is a lot of noise on board the station because of the various computer equipment, treadmill on which the astronauts will run, ECLESS (Environmental Control and Life support system), system that provides or controls atmospheric pressure, fire detection and suppression, oxygen levels, proper ventilation, water regeneration system, in order to maintain same conditions of life support than on the ground.

The digestive system is affected in space, its involvement is probably not as visible as the muscle and bone, it will be detailed in this review, among the most frequent symptoms a feeling of fullness in the beginning of the flight with decrease of the appetite, and of course changes in the gut microbiota which is the subject of many scientists 'projects. The gut microbiota would change mainly because of life in a closed environment but because of all factors link to spending time in this hostile environment for the human being (Liu et al. 2020). To be complete, all the system of the human body will be impacted so the sense of smell and taste which will contribute to the alteration of the gut microbiota. The uro-genital, hormonal and immune systems are altered too as describe elsewhere [16].

Other challenge inside the station

Isolation confinement

Indeed, one of the other effects of life aboard the ISS concerns the confinement or isolation from familia and friends that will first have a psychological impact. Astronauts of course on ISS can communicate with families through their iPhone but they have no contact outside the teammates, for at least 6-12 months depending on the duration of their mission [17].

Main factors are involved in the psychological disturbances such, crew changes, work overloaded, social retract, hazardous atmosphere on board with contaminants, technical deficiency « anxiety or anger » against the ground support, conflict among crew members. Consequences are psychological changes and could impact the mission, among the main symptoms are: irritability, depression and sleep disturbances.

To be complete we have to mentioned the factors directly linked to the life on board the ISS. Among those factors are the chronobiological and biorhythms changes

The station flies over the globe every 90 minutes, the consequences is an alternation of day night and all hormonal physiology might be disturbed. Indeed, the hormones are secreted at specific period of times in the day (cortisol in the morning at 8am and melatonin in the evening just as example).

CO_2 level, dust noise and orbital debris are impacting life on board

At the beginning of spaceflight, the CO_2 level was about 10 times higher than on the ground. This has an impact on the concentration and headaches is the most frequent symptom probably with congestion (stuffy nose). A study conducted by NASA [18] showed that each elevation of 1 mmHg of CO_2 level, gives headaches double of normal based. Following this study which furthermore showed that to see a decrease in less than 1% of headaches, it was necessary to have a level of CO_2 lower than 2 mmHg; a lot of effort was made to really decrease the level on board. Nowadays there is a big improvement even so it is not possible to decrease much more.

The quantity of dust increased considerably on board the ISS, despite the fact each crew member is cleaning up two hours per week. Some new rules and changes were implemented and were able to reduce the symptoms and improve the way of life on board [19].

Noise is higher than on the normal environment on Earth. Lot of noise in ISS, is generated by ECLSS system as already mentioned, this system is a very fundamental system to maintain life in the same conditions as on the Earth. Of course, the quantity of computer on board as well the sport exerciser such Treadmill increase the level of noise. Most of the time, the level of noise reaches the conversational level (more than 60 dB) but can be higher in some part of the modules of the station, depending on the activity done! The alarms are another factor for noise, mentioned here because happen more often than we could expect and usually in the night. Hopefully they are false alarms but wake up the crew [20].

Also to conclude the full body is impacted by the new environment and to allow human bodies to stay and work in this extreme environment for human, a multitude of actions have been taken and they are called countermeasures.

The digestive system is widely studied nowadays not only in astronaut population but in all population on Earth specifically elderly or younger adult people with pathology. A huge number of studies show the impact of microbiota changes on the human metabolism, on cardio vascular diseases, osteoporosis, inflammatory and chronicle pathology. Furthermore, we will see how the immune system is directly impacted by the changes in gut microbiota.

The gut microbiome, often described as the "virtual organ of the human body", plays a crucial and significant role in maintaining human health on the ground, as it probably does for astronauts.

The gastrointestinal tract (GIT) alone harbors 100 trillion bacteria, consisting of thousands different species, and million non-redundant microbial genes. These microbial communities, found in and outside our body, are referred to as the "human microbiome", a term first coined in 2001 by Joshua Lederberg to refer to the "ecological community of commensal, symbiotic and pathogenic microorganisms that literally share our body space".

While the terms "human microbiome" and "human microbiota" are often used interchangeably, the latter refers to the microbial taxa associated with humans, while the former refers to the collection of microbial taxa and their genes. The microbial communities that colonize various parts of our body are important in promoting health. If this balance is disrupted even slightly, a breakdown in homeostasis will occur, leading to disease [21].

High microbiome diversity and richness are generally considered a hallmark of a healthy gut ecosystem; however, there is still no consensus on the actual health-related values. Healthy adult humans characteristically harbor more than 1000 species of bacteria, with B*acteroidetes* and *Firmicutes* being the dominant phyla. While *Bacteroidetes* (recently renamed as *Bacteroidota*) are connected with immunomodulation and augmented immune reactions through synthesis of cytokines, *Firmicutes* are involved in the metabolism, nutrition, and regulation of hunger and satiety, via short-chain fatty acid (SCFA) synthesis.

Spaceflight markedly affect the composition and function of the human gut microbiota, implying that the human gut microbiota is sensitive to spaceflight [5].

Since the beginning of long duration spaceflight, we see that the human body and more specifically the musculo-skeletal system follow the same physiologic degradation as what is seen with aging. Of course and fortunately, the changes are reversible for the astronauts quickly after their return on Earth. With the increasing studies on the gut and digestive system on elderly people we are able now to compare the two population. We can learn as well from that studies on the ground in the people how changing the diet can reverse the changes seen in the gut microbiota and may be this could become a new countermeasure but this time not only acting on the digestive system but on the full body. Because these studies are showing the huge impact of the gut microbiota on inflammation, chronicle disorders even on neurology such as seen in elderly with Parkinson or some other diseases. This will drive us to the immune system which probably plays a main role in the human body. Number of studies showed this phenomenon and allows us to expect improvement of our actual countermeasures, which would help space medical/ science community to reach the next step to space, interplanetary missions. More than having an impact on the immune system or micrograviy, all factors impacting life in space might be improved by a safe good harmonious gut microbiota.

Materials and Methods

All the materials and methods that are used to complete the study should be mentioned. A review on articles found in pubmed on both populations, astronauts and adult, mainly elderly population was efficient to resume the main characteristic of the gut microbiome on these two populations. Some other article regarding space confirmed the changes, as explained earlier the ground based modal of gravity or confinement studies showed exactly the same tendency.

The techniques used in main of the articles reviewed for this publication

On the ground the classical technique from the feces with culture can still be used. But for 10 years new gene and DNA/pPCR plus -T-RFLP (Terminal-restriction fragment length polymorphism) completely revolutionized the study of the microbiome. Last techniques nowadays are using metagenomic and metaOMICs. These techniques focused not only on DNA, but also on RNA, protein and small molecules improving comprehension of crosstalk among gut bugs and gut bugs and the host.

Furthermore utilization of primers toward highly conserved region of the gene, 16S for the procaryote and archea and 18S for eukaryotes (including fungi) have massively sequenced and clustered into operational taxonomic units (OTUs).

Thus, Metatranscriptomics describe the functional activity of the gut microbiota expressed at a given time and depending on a specific environmental condition. To be more complete it is interesting to be able to study the proteins because they provides a more representative overview of the final functional activity of the gut community and it has been largely employed to characterize functional roles of gut microbiota in health and disease conditions. This is what is done by metaproteomic. In fact, metaproteomic is defined as the large-scale profiling of the complement of proteins produced by a complex microbial ecosystem.

Together with metaproteomic, metabolomic closes the entire pathway from genes to the functionality of the gut microbiota. Indeed, the study of the final products (metabolites) of bacterial metabolism present in a sample provides a better knowledge of the functionality and physiology. Metabolomic involves the identification and quantification of the metabolites and it can be performed in a targeted (analysis of different classes of previously defined compounds) or untargeted way (a global profile or picture of the metabolic diversity of the sample).

The use and combination of more than one methodology is necessary to analyze the complete metabolome of a sample, because of the diversity in properties and concentrations of the metabolites [22].

For elderly people a wide information was provided by Badal et al. 2020. They reviewed 29 articles and 24 were utilized. 70% of these studies utilized 16S rNA sequencing, the others used the genetic functional pathways and metabolomic [5].

For astronaut population, the review of Tesei at al. in 2022 compiles experiments from space mission on human, on animals and from ground based models. Majority of techniques used as well the 16S rNA sequencing or the Shotgun metagenome sequencing of genomic DNA. Two old studies on human in space were still doing culture of feces.

Following this review, it was clearly mentioned that the already well known consequences on elderly are linked to change in microbiota. For the astronaut this may be explain by the other way round. Indeed, all system almost have been studied and comparison from pre-in and post flight if they show improvement, we can connect the different changes with what is seen as well on the elderly population.

From these two separate populations it is becoming clear that we can make connection in between the pathology in elderly, the tendency seen in astronauts and the changes in the gut microbiota.

A step further would study deeper the change of the gut microbiota with modification of food on board. If we can see that changing the food improves the gut either by some nutrient or by using pre end probiotic as it is on going on the Earth this would be a new promising countermeasure.

Results and Discussion

Results

The digestive system and the gut microbiota in elderly population

Gastro-intestinal tract and aging

The elderly population is increasing over the world and particularly in industrialized countries. The physiological, immunological and cognitive decline occurring in old age are strongly influenced by lifestyle, social habits and nutritional status. Aging is often accompanied by disease and disability.

Depending on their social condition, older people will not have the same "status/physiology" regarding their body/organ and specifically their digestive system will be directly impacted by the condition of life [22]. It seems very important that the older people keep social relation which has been proven to be beneficial for their health. Also, if they become isolated, they start to probably be less dynamic, they are doing less physical activities and stay at home. Among other factors, diet and food is a key factor in maintenance a good health. When social activity decrease, spontaneously most of the time the food intake change. The change in food may be explained by dentition alteration with loss of teeth which can be connected with osteoporosis due to low energy intake combine with decrease of motion. Another factor of their decrease in quality of meal is due to the changes in smell and taste. With aging the taste is changing and the number of captors in mouth for the sweet taste is one of the last one to be still present. On contrary, the salty, bitter receptor are decreasing seriously involving change in their preferred selected appetence. They indeed will have tendency to select sweet nutrients because they cannot taste the other nutrients. The tendency is as well to decrease fruit and vegetable consumption. Of course the economic status can play a game in such changes of behavior. With aging we see increase in auto-immune pathology which can give changes in the saliva for example dryness of the mouth. Saliva is a major factor in the function of GIT and mainly first part of the digestion.

In such conditions they start to suffer from constipation, malnutrition, digestions issues and microbiome changes. This is part of the unhealthy ageing compare with older people who are still having normal or equilibrium meals with physical activity all of this more often linked with a social life.

Among other factor linked to food is the medication. Some people suffer from multiple disease and can have secondary effect from the medication (stomach pain, nausea or fell already full when they start their meal).

Some elderly people will have a tendency to have higher blood glucose and insulin resistance. This may be the consequence of bad habits in the food consumption but can be linked to diabetes in that case the quality and quantity of food will be important but not so easy to handle in this age as in younger population. Following such diabetic state will start the chronicle disease linked to it with kidney, liver, cardio vascular and eyes issues as well known. Full review is dedicated to the changes in the GIT in the elderly person with recommendation to avoid malnutrition [24].

The goal is not to be exhaustive in the pathology of aging but focused on alteration which are most likely responsible for changing the microbiota.

See Figure 1 which describe the changes seen in astronaut and older people on the GIT.

Gut microbiota and aging

The gut microbiota changes with aging. Bada et al divided the older population in two branches which is very useful for the following interpretation of status of the person. This team separates the oldest old or centenarian from the old not so old but unhealthy. What makes centenarian living longer? Is the main question. Is there any factor which can explain this longevity of course out of the genetic? The centenarian has gut microbiota criteria closest to the healthy adult compare to the older subject who may be not so old (at least not centenarians) but have more medical issues [4].

This is compatible with what Gosh et al. in 2022 found. They showed how microbiome has a reciprocal relationship with age and they define 3 groups of bacteria which are really three major groups of taxa showing consistent patterns of alteration. Also, the group 1 taxa decreases with age and is associated with healthy aging. Group 2 consists of the pathobionts (Can become pathogenic in certain circumstances) that increased with age and were associated with unhealthy ageing. Group 3 increases with age but were observed to be depleted in unhealthy aging [25].

- **Group 1 contains:** *Faecalibacterium, Roseburia, Coprococcus, Eubacterium,, Bifidobacterium and Prevotella.*
- **Group 2 contains:** *Eggertella, Bilophila, Desulfovibrio, Fusobacterium, Anaerotruncus, Streptococcus, Escherichia.*
- **Group 3 contains:** *Akkermansia, Christhensenellaceae, Odoribacter, Butyrivibrio, Barnesiella, Oscillospira.*

The results of all combine studies show the following tendencies.

Beta diversity distances were significantly different between older adults and younger adults, even between the oldest-old and younger-old adults. Aging associated with increased presence of specific Lactobacillus species. Some specific germs are present in residents in hospital or long term care facilities such

Bacteroides, Proteobacteria, Verrucomicrobia, Actinobacteria, Parabacteroides

Taxonomy varies with studies but an increase in the *Akkernansia* and decrease in *Faecalibacterium, Bacteroidaceiae, Lachnospiraceae* is constantly seen with unhealthy ageing.

In adults, *Firmicutes* is predominant followed by *Bacteroides.* Oldest old adults have the opposite more *Bacteroides less Firmicutes* consistent with previous evidence suggesting that the Firmicutes/Bacteroidetes ratio increases in adulthood but declines again in older age.

Both (Firmicutes or Bacteroides) abnormally elevated and abnormally decreased Firmicutes/Bacteroides ratios are implicated in metabolic and gastro-intestinal disorders.

Oldest old adults have increased SCFA (Short-chain fatty acid) production a complex balance of pro and anti inflammatory features permitting an effective immune response.

Altered microbiota functionality and composition (dysbiosis) contribute to frailty. To avoid too much impact on the health, the diet would be a mean to improve and restore gut microbiota in the senior population (Salazar 2020)

See table 1 which give details of the taxonomy classification of gut microbiota

The digestive system and the gut microbiota in astronaut population

Gastro-intestinal tract and astronauts

The digestive system is really an important system in the human body. His main function is to assume the breakdown of the food in small piece and release the nutrients and permit them to be absorbed by the body. A very classical sentence: « the happiness comes from the belly » is explicit enough to explain that in case of disturbances even though not involving life for most of the time will give enough trouble to the subject. The whole human body needs nutrients in a good quality and quantity to keep homeostasis inside the body on the Earth or in Space.

Adequate nutritional status is critical to maintain crew health during extended-duration space flight and postflight rehabilitation. Despite good and individualized recommendations, most of the time the astronauts experienced reduced energy intake and weight loss during their space flight. This suggests that the space environment has a significant impact on the digestive system of astronauts [26].

According to the current researches, the main reason why weightlessness affects the digestive system may be the change of systemic hemodynamics (fluid shift). Secondly, weightlessness, as source of stress, will cause the coordinated response of the body, thus leading to changes in the functions of various organs of the digestive system [27]. Of course at the beginning of the flight, SMS is responsible for nausea vomiting which explain the reduction of appetite but at least majority of astronauts recover in few days, this would affect about 70% of them.

Yang et al conducted an exhaustive overview of the changes in the digestive system from the mouth to the pancreas occurring during spaceflight. We summarize here what are the main changes at each level inside the intestinal tract, from mouth to large intestine.

Mouth level, oral cavity: the oral cavity, is the first part involved from the digestive tract during food intake. In fact first of all the smell will induce swallowing, which will be the first action coming from eyes and probably from the smell. It is well known that taste would be affected by microgravity … this would be the one of the reason to explain decrease food intake because no tasty food! Of course, the first reason for decrease food intake at early stage of spaceflight is mainly the space motion sickness (SMS) which can give nausea and vomiting. Plus the fluid shift with redistribution of the liquid in the upper part of the body in the face (the so called puffy face) contributes to the congestion and lost of appetite, this should change after few days or weeks in space.

In a microgravity environment it has been demonstrated that the bone density and bone mineral content of the mandible and alveolar bone reduced significantly compared to that in the control group [28]. It has been shown as well an increase in the secreted Immunoglobuline A in the mouth.

At the second level is the Stomach. Same remark can be done regarding the SMS and the fact that astronauts would have with the fluid shift a feeling of full stomach, all of this contribute to low food intake at least at the beginning. Among other symptoms, the astronauts experienced often gastric reflux which may be connected with the weightlessness and fluid shift. Afonin et al. in a Dry Immersion ground modal experiment, studied the stomach evacuation function. The results indicated there was no significant effect on the gastric emptying of liquid food [29]. But this has been reversed in another simulation study, a bed rest study where they show a considerably slow gastric movement rhythm, indicating a dysfunction in the gastric movement rhythm [30].

The activity of gastric and pancreatic secretion (insulin and C-peptide) increased during the early stages after space flight. After 4 months of spaceflight, the level of pepsinogen increase in blood and urine, indicative of gastric hypersecretion in flight.

During the EUROMIR-94 mission, a number of hormones were analyzed, it was found that the fasting plasma levels of motilin, pancreatic polypeptide (PP), vasoactive intestinal peptide (VIP), and secretin increased and the levels of plasma cholecystokinin (CCK) decreased under acute exposure of the astronauts to microgravity [31]. Chen., *et al*. further confirmed the reduction in plasma ghrelin levels and the increase of VIP content in rats under simulated microgravity [32]. The changes in the levels of these hormones reflect the levels of digestive juice secretion, and further affect the digestive ability of the body.

In addition, Zhang et al. reported that the healing rate of experimental gastric ulcers induced by acetic acid significantly reduced under simulated microgravity.

From the animals experiment it is stated that the stomach exhibits gastric motor dysfunction and hypersecretion and is more vulnerable to injury.

The impact on the Intestinal tract: it was reported that the rate of intestinal content emptying was accelerated [29,30].

Relevant studies have demonstrated that the effects of microgravity on blood circulation in the gastrointestinal tract primarily manifest an increased vascular volume and reduced flow velocity in the resting state.

Afonin et al. and Pei and Chang showed a disruption or defects in epithelial integrity which may influence microbial colonization and allow free passage of microorganisms or other substances across the epithelial barrier where they stimulate the immune system and induce inflammation, autoimmunity, allergy, and even carcinogenesis.

Chen et al. confirmed that the expression of tight junction proteins between small intestinal mucosal epithelial cells in tail-suspended mice was reduced significantly, which would subsequently damage the intestinal mucosal barrier, increase intestinal permeability, and increase the risk of colonization by opportunistic pathogens [32].

Shao et al. demonstrated that under a simulated microgravity environment, *L. acidophilus* exhibited enhanced acid resistance and reduced sensitivity to cefuroxime, gentamicin sulfate, penicillin sodium, and other antibiotics [33]. In addition, Chopra et al. confirmed that the virulence of *Salmonella sp.* increased.

Notably, NASA's space experiment confirmed the increased resistance of certain intestinal microbes to antibiotics [27]. This undoubtedly increases the challenges of treating infections in a microgravity environment. Li et al. suggested that the intestinal microflora and the innate immune system both respond to simulated microgravity and contribute to the proinflammatory shift in the gut microenvironment. The data also emphasize the necessity of evaluating the susceptibility to inflammatory bowel diseases in astronauts [34]. As astronauts execute space missions, intestinal disorders in them may affect their health adversely, and may severely affect the implementation of space missions.

Although direct evidence is lacking, astronauts are recommended to maintain a regular intake of probiotics to reverse these changes and maintain a micro ecologic balance.

The Liver is impacted as well. Multiple studies have reported that the levels of proteins and glycogen, as well as the functional structure of various enzymes, changed in the liver under a simulated microgravity environment. The oxidative stress in the liver also increased. The blood flow in the portal veins are reduced and the levels of endotoxins increased.

The liver is the largest human organ associated with metabolism and detoxification, its functions depend on the complex metabolic processes in hepatocytes. Abraham et al in 1981 showed the accumulation of glycogen in hepatocytes and reduction in the levels of hexadecenoic and hexadecenoic acids.

The metabolic and detoxification potential of the liver are closely related to the remarkable regenerative ability of the liver. Specifically, the liver can rebuild 70% of lost tissue within a few weeks, which depends on the activation, trans differentiation, metaplasia, or compensatory proliferation of quiescent hepatocytes.

On one side, a series of studies have demonstrated that under a weightless environment, the proliferative potential of hepatocytes undergoes reduction. On the other side, Cui et al. showed that weightlessness was closely related to hepatocyte apoptosis, and the expression of p53 in the hepatic tissues of rats under weightless conditions was consistent with that observed during hepatocyte apoptosis [35].

Du et al in 2015 confirmed that prolonged exposure to microgravity induced significant damage to the liver and triggered hepatocyte apoptosis.

The liver's remarkable metabolic function is inseparable from its unique dual blood supply system comprising the hepatic artery and portal vein. The liver receives approximately two-thirds of its blood supply from the portal vein, nearly 75% of which is routed through the mesenteric vein. This implies that once the intestinal barrier is damaged, a large number of bacteria and their products can enter the liver via the portal vein. The imbalance between intestinal flora and the intestinal mucosal barrier in a weightless environment has been described earlier.

Zhou., *et al*. demonstrated that subjects who were continuously under-6° head-down bedrest exhibited a reduction in the maximum portal vein flow velocity with time, and the portal vein flow velocity gradually recovered after they returned to the upright position, and was nearly normalized on the 7th day.

A recent article from Vinken in 2022 confirmed the animal level changes in the liver which might explain the metabolic alteration seen in astronauts.

- Disturbance of hepatic homeostasis in experimental animals, resulting in liver injury and inflammation with apoptosis and oxidative stress.
- Spaceflight and simulated microgravity compromise carbohydrate metabolism in the liver of experimental animals, which may explain the diabetogenic phenotype observed in astronauts.
- Accumulation of lipids in the liver of experimental animals, which suggests an increased risk of developing non-alcoholic fatty liver disease in astronauts.
- Spaceflight and simulated microgravity in experimental animal alter hepatic biotransformation capacity in experimental animals, which suggests the need for personalized pharmacological therapy of astronauts

The pancreas, as the major secretory gland in the human body, has fundamental function which primarily consists of the secretion of pancreatic juice necessary for digestion and various hormones necessary for the regulation of homeostasis in the internal physiological environment.

As the primary function of the pancreas is to secrete pancreatic juice, which contains a variety of digestive enzymes, and insulin, which regulates blood sugar levels. A number of studies suggest that microgravity can affect the state of the pancreas and glucose metabolism.

The fluctuations in blood glucose levels and irregularities in the insulin and glucagon levels in weightless environments may be the eventual result of the body's self-regulatory activity in a stressful environment. Already reported in 1994 by Stein et al. on astronauts who developed insulin resistance during a short space mission. Fortunately the reverse few days after their return on the ground.

Moreover, although the reasons are not entirely clear, insulin resistance and glucose intolerance are frequently observed both in short- and longer-term space missions, and in analog missions.

In 2016 Hughson and his team studied blood parameters and arterial stiffness with measurement done pre in and post flight on 9 astronauts. If the change in the glucose level was not significant, there was a significant increase in the insulin resistance index in all astronauts. The primary mechanisms underlying these changes is probably related to the chronic elevation in carotid artery blood pressure and physical inactivity which might affect blood biomarkers associated with increased carotid arterial stiffness [1].

In addition, Li and his team reported a study on rat showing the same results but they studied the impact on the brain. Because, insulin exhibits obvious memory-enhancing effects and has been demonstrated to play a key role in chronic cognitive impairment in various pathological conditions, such as neurodegenerative diseases, aging, diabetes and dementia. Peripheral insulin resistance is known to contribute to metabolic disorders and inflammation, which are significant factors in the development of brain insulin resistance.

Therefore, it is suggestive that hippocampal insulin resistance may be associated with neuronal damage and cognition dysfunction in weightlessness, and an early intervention aimed at improving insulin sensitivity in long-term spaceflight may be an effective approach for safeguarding astronauts' brain health. They recommend to use berberine. Berberine has several pharmacological properties, such as immunomodulatory, antioxidative, cardioprotective, hepatoprotective, and nephroprotective effects. Berberine (in animal model) has been shown to enhance insulin sensitivity in diabetes and other conditions. In addition, berberine can cross blood-brain barrier and is potent in ameliorating cognitive impairment through regulating the insulin signaling in diabetic rats. Berberine looks beneficial but we need to conduct more studies and of course prove the same efficiency and first of all check the mechanism in human being is it the same as in animals?.

Gut microbiota and space

Specific space environment factors, such as microgravity and radiation, are thought to also induce changes in microbiome composition (i.e., dysbiosis) [36].

The gut microbiome, often described as the "virtual organ of the human body" [104], will play a crucial and significant role in maintaining astronaut health during space travel, as it does for humans on Earth.

High microbiome diversity and richness are generally considered a hallmark of a healthy gut ecosystem; Healthy adult humans characteristically harbor more than 1000 species of bacteria, with Bacteroidetes and Firmicutes being the dominant phyla.

While *Bacteroidetes* (recently renamed as *Bacteroidota* [37] are connected with immunomodulation and augmented immune reactions through synthesis of cytokines, *Firmicutes* are involved in the metabolism, nutrition, and regulation of hunger and satiety, via short-chain fatty acid (SCFA) synthesis [38].

Alterations in the composition and functionality of the gut microbiome can be induced even by short-term space travel. [5], showed that spaceflight led to increased abundance of Bacteroides. By contrast, the probiotic taxa.

Lactobacillus and *Bifidobacterium* appeared reduced, possibly affecting host immune function Early analyses of the microbiome revealed a reduction in the number of nonpathogenic bacteria and an increase in the number of opportunistic pathogens in the nasal flora of astronauts.

Voorhies et al. (2019) showed that the microbiome composition of skin, nose and tongue, such as the gut microbiome, changes in microgravity, and additionally, becomes more similar between astronauts [39].

A reduced caloric intake like that often experienced by astronauts, may also lead to a restructuring of the gut microbiome similar to that observed in association with very-low-calorie diet (Figure 2). Accordingly, a low-calorie intake and the consequent weight loss may be paralleled by a decrease in bacterial abundance, impaired nutrient absorption, and enrichment in endogenous enteric pathogens (e.g., *Clostridioides difficile*), suggesting that diet-induced shifts in the gut microbiome may influence colonization resistance and thus host physiology.

As a matter of fact, crewmembers do experience adverse medical events of varying severity during spaceflight missions, related to infectious diseases, which include cold sores, skin and urinary tract infections, lymphadenitis and pharyngitis [40].

An altered microbiome is not only associated with the onset of infections but with noninfectious diseases as well, such as inflammatory bowel disease, systemic metabolic disorder (e.g., type 2 diabetes and obesity) and allergic reactions and sensitivities.

In addition to the aforementioned functions of the microbiome in supporting host physiology, research has more recently shed light on the relationship between the gut microbiome and mental health through what is known as the brain–gut–microbiome axis (BGMA). Furthermore, microbiome would have an impact on sleep physiology, with microbiome diversity being positively correlated with increased sleep efficiency and total sleep time.

See Figure 2 which compare both populations to explain the main reason of these changes in the gastro intestinal tract.

Discussion

Comparison between the two populations

Gut microbiota in astronauts has key commons alteration with the gut microbiota of elderly people

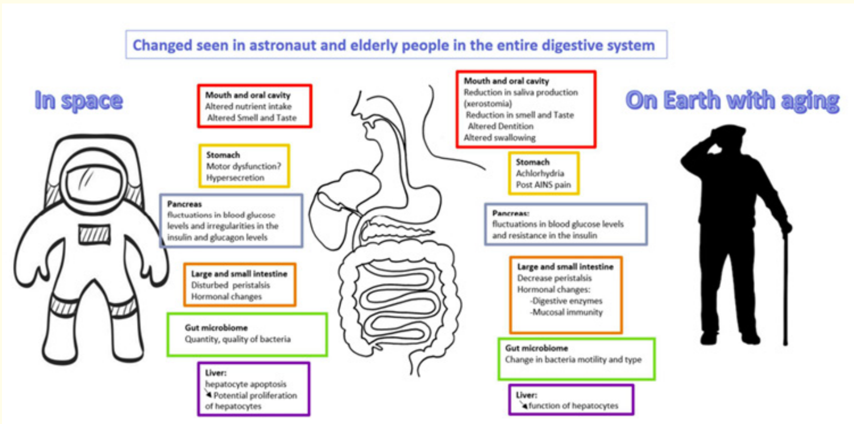

Figure 1: Comparison between the astronaut on the left and the elderly people on the right regarding the changes seen in the digestive system.
All the digestive tracts are impacted in both subjects. From the oral cavity going through oesophagus, stomach and finally in the intestinal tract.
The liver and pancreas have an important function in digestion and are affected too. The microbiome is studied fully separately.

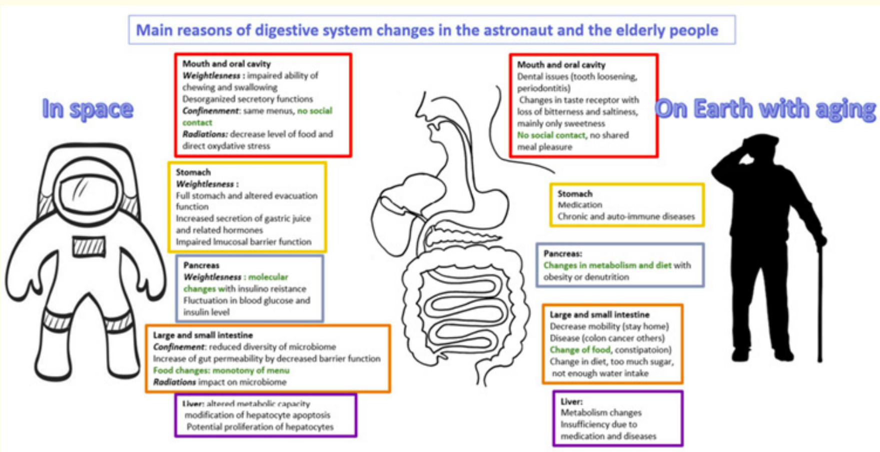

Figure 2: Comparison between the astronaut on the left and early people on the right regarding the reason for changes seen in the digestive system.
All the digestive tracts are impacted in both subjects. Because spending time in space is a "Model of aging" it is not surprising to find a huge number of common alterations like, social isolation, less mobility, taste and smell changes are highlighted in green.

It is well known that spaceflight is a good modal of ageing at least on the Musculo-skeletal system but if we compare the changes in digestive system and in the microbiome this confirms such statement.

Figure 1 compares both population in term of digestive changes. There are some basic common changes first in the oral cavity with the low energy intake in both populations. Of course, astronauts normally do not suffer of dental loss but of course with a longer flight duration and increasing osteopenia could bring some dental disorders. Both populations exhibit loss of smell and taste for the elderly people this is connected to internal factor, decrease in the receptor function, for astronauts directly due to fluid shift following microgravity. At the level of the stomach the changes are not always the same. For astronauts gastric reflux is often reported, in older people, they suffer more from gastric pain linked to medication which result in achlorhydria.

On the large and small intestine are common changes in both populations like reduction in peristalsis and change in the permeability membrane. Such as a consequences we found same gut microbiota changes (see Figure 3) with decrease in Bacteroides and increase in Firmicutes. Moreover, a decrease in the production of SCFA is seen in both populations.

In general, two main factors seem important to keep a safe gut microbiota and avoiding dysbiosis. First a high microbial diversity is important for intestinal homeostasis, favoring the tolerance of the microbial environment. Second from many studies, it appears that the concentrations of SCFA in the colon are critically important for immunoregulation [41] and for maintaining gut and overall health in all populations [21,35].

Consequences in elderly

In ageing, the changes are due to the physiological alterations impacting the body this may be internal factor like the alteration of the human body which is the normal evolution of the body called senescence but some external factor probably more linked to the social status of the individual such physical inactivity (of course internal factor may impact depending on their pathology, arthrosis …), decrease in the meal, use of medication (against blood pressure against pain..).

It has been estimated that between 2% and 16% of institutionalized elderly people present an inadequate intake of protein and calories [22], which could increase the risk of malnutrition and exert an important impact on gut microbiota.

Diet with a high content of protein and animal fat were associated with a B*acteroides* enterotype, those with a higher proportion of carbohydrates were dominated by *Prevotella*. Mainly as explained earlier, older people have a tendency to increase their carbohydrate intake. In institution if they should have the adequate nutrition, it might well be that still older people on their own do not eat properly with all factor previously mentioned. Also, modification in eating patterns frequently occur, because of physiological and physical changes, which frequently involve a relative state of malnutrition that, in its turn, exerts a negative impact on the gut microbiota, the immune system and the cognitive state.

It is therefore urgent to develop new nutritional strategies able to positively modulate the composition and functionality of the intestinal microbiota in order to promote healthy ageing that allow to dignify life in the elderly and to manage health-care costs.

Consequences for astronauts

For the astronaut weightlessness mainly and confinement plus radiation at a second level are responsible for the changes. The changes are reversible quickly in between some days and week after landing. For the actual ISS mission, the impact is not so important. It is difficult to have fresh food aboard ISS, but still feasible with cargo bringing it up regularly to the station. Considering longer mission with no possibility to send cargo a new way has to be found, like cultivate on the planet or station which will host the astronauts. May be been able to know the gut microbiota and offer to astronauts the best probiotics to improve their gut microbiota would be the easier and best solution.

See Figure 3 where are discussed the changes of the gut microbiota with differenciation in between healthy and unhealthy old people. This figure tries to explain how the changes in the gut microbiota can directly drive to pathology. Is astronaut belongs to healthy or unhealthy old population and what are the factors which are responsible for such belonging.

The main changes in the three population are changes in the *Firmicutes* and *Bacteroides* ratio. Either this ratio increases or decreases. This mins that the two Familiae are important and their ratio should be kept. In the three it is generally admitted that we see a loss in bacteria diversity but if it is too important this raises the pathology level like in unhealthy elderly people. In general

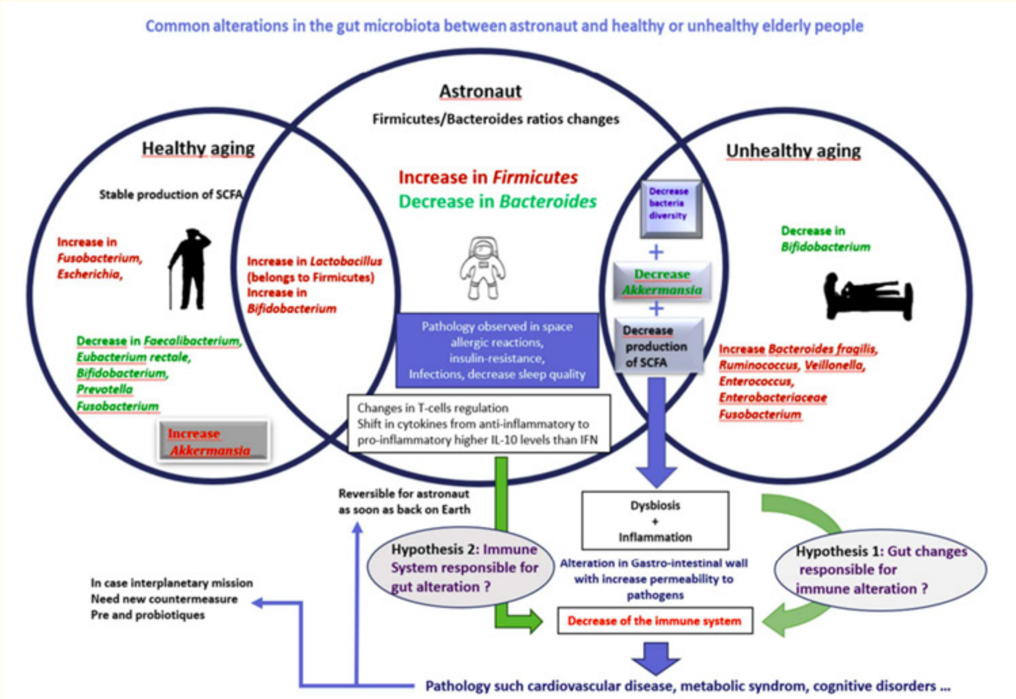

Figure 3: Common alterations in the gut microbiota between astronaut and healthy or unhealthy elderly people.

Phylum	Class	Order	Family	Genus
Firmicutes (Bacillota)	Clostridia	Clostridiales	Clostridiaceae	Faecalibacterium
				Clostridium
			Ruminococcaceae	Ruminococcus
			Lachnospiraceae	Roseburia
	Bacilli	Bacillales	Enterococcaceae	Enterococcus
			Staphylococcaceae	Staphylococcus
		Lactobacillales	Lactobacillaceae	Lactobacillus
Bacteroidota	Bacteroidia	Bacteroidales	Bacteroidaceae	Bacteroides
			Prevotellaceae	Prevotella
Actinomycetota	Actinomycetia	Mycobacteriales	Corynebacteriaceae	Corynebacterium
		Bifidobacteriales	Bifidobacteriaceae	Bifidobacterium
Proteobacteria	Gammaproteobacteria	Enterobacterales	Enterobacteriaceae	Escherichia
Verrucomicrobiota	Verrucomicrobiae	Verrucomicrobiales	Akkermansiaceae	Akkermansia
Fusobacteriota	Fusobacteriia	Fusobacteriales	Fusobacteriaceae	Fusobacterium

Table 1: Taxonomic classification of gut microbiota. Bacteria are categorized into hierarchical taxonomic levels including phyla, classes, orders, families, genera, and species. The Firmicutes and Bacteroidetes phyla represent the predominant bacterial taxa in the gut microbiome.

astronaut like healthy aging has a decrease in *Bacteroides* and increase in some *Firmicutes* but the Genres may be different depending on the studies done. A very important fact is that *Akkernansia* increase in healthy elderly people and it is very interesting to see it is decreasing in astronauts as in unhealthy elderly people. Furthermore, the data we have from spaceflight show a immune change as decrease in T cells regulation and shift in between the pro and anti-inflammatory cytokines. Such the pro-inflammatory cytokines are increasing.

Moreover, another regular change in unhealthy and in astronaut is the decrease in the SCFA production. This is another crucial data because it is directly linked with pathology.

Astronauts experience sometime pathology in flight and outside the Musculo-skeletal injuries, the main disorders are the decrease time and quality of sleep for many reasons, but allergy are frequent with skin rash and infections happen. From the blood draw the level of glucose are changing but more steadily there is an increase in insulin-resistance. More and more studies on Earth population are showing the link in between those pathologies and the gut dysbiosis.

But one question we might ask is what is the first factor? Is immune change causing changes in the gut microbiota or is the change in the gut microbiota acts directly on the immune system?

This time would the model of ageing help astronaut to find a new countermeasure because some studies show already an improvement with the use of pre or probiotics. But in fact, it is very challenging because each individual will have his own gut microbiota so a full identity and personalized medicine is crucial to find the good probiotic [48].

For astronaut the actual duration of the mission is nowadays not impacting too much even one year as seen with the NASA twin study showed that he recovers in few weeks so no consequent pathology on the gut microbiota. But what about a longer duration mission?

The example of the centenarian people is really a good prove that they have a better equilibrium in their bacteria in their gut which avoid the diseases we see in unhealthy not so old people.

Impact on the gut microbiota on human body

Microbiome and insulin/glucose changes

Regarding the impact of glucose on gut microbiota, Wu and his team compared the gut microbiota in different group (variation in age, blood parameters, gender, quality of sleep…,) they showed that dysbacteriosis is closed associated with aging and abnormal blood glucose level. Among all blood parameter, the glucose was the only one significant statistically. The glucose blood level is highly linked with some gut bacteria and linked with age. After 76 years old, they have more *Lactobacillus* and *Bifidobacterium* with higher level of glucose than before 75 years old.

This is probably in favor of a weaker immune system because it is well known that as the blood glucose level changes, the concentration of SCFA (which have significant immune system effects in the intestinal mucosae) decreases while concentration of LPS (lipopolysaccharide) from gram negative bacteria increases. As a result pro-inflammatory signal transduction pathway is activated and consequently causes chronic low-grade inflammatory status, reduced insulin sensitivity and a series of signs that eventually lead to the occurrence of Type 2 diabete [42].

The impact of the gut microbiota on the immune system

Dysbiosis of the gut microbiome has been associated with a dysregulated immune system.

With ageing, *Proteobacteria*, which has been previously associated with increased gut inflammation and dysbiosis, was more abundant and even much in oldest-old adults than in young-old or younger adults [4]. Additionally, *Faecalibacterium*, which has an important role in the production of the SCFA butyrate, was less abundant in oldest-old adults. At first glance, these patterns appear to be conflicting and counterintuitive to the picture of longevity.

It has been previously noted that exceptionally long-living individuals exhibit a complex balance of pro- and anti-inflammatory features, permitting an effective immune response that is counterbalanced by robust anti-inflammatory activity.

In spaceflight, it is well known that the immune system is altered [5,21,50].

During their spaceflight, many astronauts experience uncharacteristic allergies and skin rashes, with some requiring antihistamines or steroids to manage these reactions [40].

The studies done on the immune system in space show that these hypersensitivities may result from a TH2 shift in the immune system occurring in spaceflight. Results show a significantly higher IL-10 levels than IFN, which suggests a shift towards a TH2 response. This tendency is also observed among astronauts upon landing [43].

Many immune responses and resulting medical issues encountered by astronauts during spaceflight could be linked to abnormal microbiomes. The cytokine IL-10 and IFN are those secreted from immune cells, which are regulated by the gut microbiome.

Additionally, astronauts experience spaceflight-related reductions in certain SCFA-producing bacteria in their gut microbiome, such as *Pseudobutyrivibrio* and *Akkernansia* [5]. Same as in elderly population. Furthermore, it is interesting to note that the A*kkernansia* bacteria could be a good marker of unhealthy old person and astronaut because if it is difficult to have a good tendency on all bacteria in the gut microbiota from all studies mentioned and this *Akkenansia* parameter is decreasing mainly in majority of astronauts studies and in the old unhealthy population. On contrary, the centenarian exhibits an increase in *Akkenansia.*

Moreover, SCFAs produced by the gut microbiota are important in immune system regulation, as they have a role in CD4+ and CD8+ T cell function, generation and cytokine secretion [25].

We should remind here that gut microbes, especially probiotic strains, ferment complex carbohydrates and produce short-chain fatty acid (SCFA) metabolites like acetate, butyrate, and propionate. They play a vital role in maintaining intestinal homeostasis and have been associated with numerous health benefits. Acetate serves as an important energy source for various cells, including colonocytes, supporting gut barrier integrity. Butyrate acts as a key energy substrate for colonocytes and has anti-inflammatory effects. It enhances gut barrier function, modulates immune responses, and promotes the differentiation and apoptosis of colon cancer cells. Propionate regulates hepatic gluconeogenesis and lipid metabolism, contributing to metabolic health [44].

Butyrate, for example, has been identified in reducing gastrointestinal inflammation through the induction of IL-10, inhibiting the secretion of pro-inflammatory cytokines, and regulating innate immune cells and Treg cells. Regarding T cell function, it is affected in space, but the response differs depending on the flight duration, as short-term missions increase T cell function and long term missions cause T cell function to decrease upon landing [45].

The impact of gut microbiota on bone health

With increased understanding of the influence of the microbiome to overall health, many studies have revealed that the gut microbiome can also specifically influence bone health.

Proteins and SCFAs produced by the gut microbiome have been shown to promote bone formation. Butyrate, a short-chain fatty acid produce by Lactobacillus of the gut microbiome, promotes bone formation through T cell signaling inducing differentiation of osteoblasts in the bone marrow [47].

The gut microbiome is also a rich source of vitamin K2, which is required for the activation of osteocalcin, a protein produced by osteoblasts during bone formation. Gut microbiome dysbiosis has been linked to bone disease in humans with osteoporosis and osteopenia.

As we have mentioned, the stressors of spaceflight can stimulate astronaut microbiome dysbiosis. One such change during spaceflight is the decrease in immune system and shift in the cytokine profile with anti-inflammatory properties in the gut microbiome and the increase in *Parasutterell*a, known to be associated with chronic inflammation [45].

But, what is really the responsible factor of bone density decrease in space? We would assume that microgravity would be the main factor to explain osteopenia? [46].

This would have to be clarified. The immune changes are probably coming from the microgravity with the high ionized particle from space are these combine factor responsible for gut changes in astronauts? [21,47].

The main changes in the three are changes in the *Firmicutes* and *Bacteroides* ratio. Either this ratio increases or decreases. This mins that the two Familiae are important and their ratio should be kept. In the three it is generally admitted that we see a loss in bacteria diversity but if it is too important this raises the pathology level like in unhealthy elderly people. In general astronaut like healthy aging has a decrease in *Bacteroides* and increase in some *Firmicutes* but the Genres may be different depending on the studies done. A very important fact that *Akkernansia* increase in healthy elderly people and it is very interesting to see it is decreasing in astronauts as in unhealthy elderly people. Furthermore, the data we have from spaceflight show a immune change as decrease in T cells regulation and shift in between the pro and anti-infalmatory cytokines. Such the pro-inflammatory cytokines are increasing.

Moreover, another regular change in unhealthy and in astronaut is the decrease in the SCFA production. This is another crucial data because it is directly linked with pathology.

Astronauts experience sometime pathology in flight and outside the Musculo-skeletal injuries, the main disorders is the decrease time and quality of sleep for many reasons, but allergy are frequent with skin rash and infections happen. From the blood draw the level of glucose are changing but more steadily there is an increase in insulin-resistance. More and more studies on Earth population is showing the link in between those pathology and the gut dysbiosis.

But one question we might ask is what is the first factor immune change causing change in the gut microbiota or the change in the gut microbiota acts directly on the immune system.

This time would the modal of ageing help astronaut to find a new countermeasure because some studies show already an improvement with the use of pre or probiotics. But in fact it is very challenging because each individual will have his own gut microbiota so a full identity and personalized medicine is crucial to find the good probiotic [48].

For astronaut the actual duration of the mission is nowadays not impacting too much even one year as seen with the NASA twin study shoed that they recover he recovers in fews week so no consequent pathology on the gut microbiota. But what about a longer duration mission?

The example of the centenarian people is really a good prove that they have a better equilibrium in their bacteria in their gut which avoid the diseases we see in unhealthy not so old people.

Finally we would need to have a full picture of the gut microbiota, so not only the microbes themselves but as well the microbial production and their metabolites. It is obvious that all three playing a game in the host defense and changes in the immune system.

A good example regarding the metabolite of the microbe is coming from the SCFA if butyrate, acetate or producer different pathology are seen as well different bacteria.

New perspective and new countermeasures

Recommandation on the food intake

If it is recommended to improve food in elderly people, starting first with improving their social condition (treat the teeth, increase physical activities …) some nutrient could have an impact to at least see a change in the main factor like decreasing A*kkenansi*a and increase the SCFA products. It is important to keep a high bacterial diversity in the gut. We would recommend to increase fresh fruit and vegetable, cereals.

For space, the food is mainly normally prepared to follow the energy level and nutrient recommendation. But they are still missing fresh fruit and vegetable, the problem will even increase with the duration of the mission. Until know cargo send equipment and food to the station. It is not possible to keep fresh food a long time on board so regular cargo can facilitate it. For interplanetary mission, astronaut would need to have a "green garden" to have this kind of food!

Fruits, vegetables and cereals are food groups containing different mixtures of fibers and phytochemicals that may have shown a positive modulatory effect on some intestinal bacterial populations.

Specifcally, there is recent evidence on a positive association between the frequency of consumption of fruits and vegetables and some intestinal microorganisms such as Lactobacillus, *Bl. coccoides* and *Prevotella* [49].

Besides, fruit and vegetables contain sources of vitamin C and carotenoids, compounds that have known anti-inflammatory activity and also provide other bioactive compounds, such as polyphenols, that are involved in the regulation of some metabolic conditions linked to inflammation and oxidative stress.

On ageing population, some nutrients have been linked to a better immune response: monounsaturated fatty acids (MUFA), beta-carotene, vitamins A, B6 , C and D, and bioactive compounds [50]. In addition, in the elderly some macro- and micro-nutrients fall frequently below the recommended intake levels : proteins, fiber, iron, B group vitamins (including folic acid) and vitamin D.

It is currently clear that the impact of diet on the microbiota is more important in the elderly than in young adults and the same remark can be made for astronauts.

To conclude, the reduction in microbial diversity, the shift in dominant species and the reduced levels of some groups of bacteria such as those producing butyrate, the increase of facultative anaerobic bacteria, the decreased levels and imbalanced production in the gut of SCFA, and increased levels of lactate, methane and branched-chain fatty acids are generally considered relevant targets for intervention.

Relevant nutritional strategies for improving intestinal function include the design of diets adapted to the elderly as well as the use of selected probiotics, prebiotics, symbiotic (combined use of pro- and prebiotics), supplements and bioactive compounds.

Pharmacology and gut microbiota

While human physiological changes and reduced drug self-life during spaceflight can alter drug disposition in space, the gut microbiome can also contribute to differential drug efficacy and safety, by enzymatically transforming drug structure and altering drug bioavailability, bioactivity, or toxicity [5].

This has important implications for the crew as a carefully considered "microbiome diet" could help ameliorate any negative effects that may be imposed by a dynamic and changing microbiome caused by spaceflight.

The gut microbiome can also promote drug activation, which was first discovered in 1937, with the antibiotic prontosil, which required bacterial azoreductases in the gut to cleave the drug into its active form

To date, over 270 drugs have been recognized as being susceptible to gut microbiome metabolism, leading to inactive, active or toxic forms.

The 20 years of human studies conducted on the ISS have provided invaluable knowledge of how the human body adapts to the space environment, but more work is needed to understand how the human body

will function and adapt to space conditions beyond LEO [7].

Conclusion

From these two separate populations it is becoming clear that we can make a connection between the pathology in elderly, the tendency seen in astronauts and the changes in the microbiota. As bone in space is a good model of aging, gut microbiota would be a good model of aging.

Currently, there is solid scientific evidences about the importance of adequate nutritional status for the maintenance of good health in all stages of life, and particularly among the elderly [25], and on astronaut population too [2], in order to prevent the appearance and progression of several chronic diseases.

Among the external factors, nutritional requirements and other factors very common in the elderly, such as a sedentary lifestyle, loneliness or depression age-related changes are intrinsically linked to the functioning of the digestive system and to the modifications of dietary patterns that occurs from adulthood to senescence. Internal factors, senescence like, appearance of dysgeusia and xerostomia or the deterioration in dentition may impact the appetite in many ways and alter food choices, which can lead long term to malnutrition [48]. We have the same factor in astronauts but those factors are mainly connected to space extreme complex and hostile environment (radiation, microgravity and confinement). We show previously all the consequences on the astronauts due to microgravity, radiation and isolation [5,21].

All nutritional factor greatly influences the gut microbial composition, diversity and functionality.

The gut microbiota of astronaut has a high number of similarities with the elderly population mainly decrease in diversity and decrease in SCFA. If it is difficult to really extract common bacteria in both populations. It seems that one major bacteria, *Akkernansia* could be a key point. *Akkernansia* is missing or decreasing in unhealthy old people like in astronauts, although *Akkernansia* is increasing in healthy old people and even in centenarian [4,25].

The maintenance of a high dietary variety is essential for an overall optimal nutritional status and health outcomes in frail elderly people. In spite of this, foods with low palatability, such as vegetables and fruits, and those difficult to chew or to digest, like meats, are often excluded from the diet or are reduced with aging.

As gut microorganisms are pivotal for homeostasis in the intestine, the regulation of the immune system [5] and the prevention of major chronic non-communicable inflammatory and metabolic disorders [25], diet could be one of the environmental factors with a greater impact on the future health of the elderly population and of astronauts for LEO.

A step further for astronauts would be to evaluate the change of the gut microbiota with modification of food on board. The food can definitively improve the gut either by adding some nutrient or either by using pre and probiotic as ongoing studies show it on the Earth. This could be a new promising countermeasure.

But probably to be efficient as we saw the gut microbiota is very individual, we would need to perfectly know the tendency in each one, we need the "gut microbiota" of the individual. May be this is less true in space, because studies show how after some days aboard the gut microbiota in between all subjects between more homogeneous [39].

Acknowledgements

A short acknowledgement section can be written acknowledging the sources regarding sponsorship and financial support. Acknowledging the contributions of other colleagues who are not included in the authorship of this paper should also be added in this section. If there are no acknowledgements, then this section need not be mentioned in the paper.

Conflict of Interest

I declare I have no conflict of interest.

Bibliography

1. Hughson RL., *et al*. "Increased postflight carotid artery stiffness and inflight insulin resistance resulting from 6-mo spaceflight in male and female astronauts". *American Journal of Physiology-Heart and Circulatory Physiology* 310.5 (2016): H628-638.
2. Smith SM., *et al*. "Benefits for bone from resistance exercise and nutrition in long-duration spaceflight: Evidence from biochemistry and densitometry". *Journal of Bone and Mineral Research* 27.9 (2016): 1896-906.
3. Bettis T., *et al*. "Impact of muscle atrophy on bone metabolism and bone strength: implications for muscle-bone crosstalk with aging and disuse". *Osteoporosis International* 29.8 (2018): 1713-1720.
4. Badal VD., *et al*. "The Gut Microbiome, Aging, and Longevity: A Systematic Review". *Nutrients* 12.12 (2020): 3759.
5. Liu Z., *et al*. "Effects of spaceflight on the composition and function of the human gut microbiota". *Gut Microbes* 11.4 (2020): 807-819.
6. García-Montero C., *et al*. "Nutritional Components in Western Diet Versus Mediterranean Diet at the Gut Microbiota-Immune System Interplay. Implications for Health and Disease". *Nutrients* 13.2 (2021): 699.
7. Tomsia M., *et al*. "Long-term space missions' effects on the human organism: what we do know and what requires further research". *Frontiers in Physiology* 15 (2024): 1284644.
8. Maalouf M., *et al*. "Biological Effects of Space Radiation on Human Cells: History, Advances and Outcomes". *Journal of Radiation Research* 52 (2011): 126-146.
9. Chancellor JC., *et al*. "Space Radiation: The Number One Risk to Astronaut Health beyond Low Earth Orbit". *Life (Basel)* 4.3 (2014): 491-510.
10. Restier-Verlet J., *et al*. "Radiation on Earth or in Space: What Does It Change?" *International Journal of Molecular Sciences* 22.7 (2021): 3739.
11. Vico L., *et al*. "Cortical and Trabecular Bone Microstructure Did Not Recover at Weight-Bearing Skeletal Sites and Progressively Deteriorated at Non-Weight-Bearing Sites During the Year Following International Space Station Missions". *Journal of Bone and Mineral Research* 32.10 (2017): 2010-2021.
12. Barger LK., *et al*. "Prevalence of sleep deficiency and use of hypnotic drugs in astronauts before, during, and after spaceflight: an observational study". *Lancet Neurology* 13.9 (2014): 904-912.
13. Gilles C. "Fundamentals of space medicine. The neuro sensory-system in space. P45-192. Springer Edition 2 (2011).
14. Mader TH., *et al*. "Optic disc edema, globe flattening, choroidal folds, and hyperopic shifts observed in astronauts after long-duration space flight". *Ophthalmology* 118.10 (2011): 2058-2069.
15. Carriot J., *et al*. "Challenges to the vestibular system in space: How the brain responds and adapts to microgravity". *Frontiers in Neural Circuits* (2021).
16. Tipton CM., *et al*. "Neuroendocrine and immune system responses with spaceflights". *Medicine and Science in Sports and Exercise* 28.8 (1996): 988-998.
17. Marazziti D., *et al*. "Space missions: psychological and psychopathological issues". *CNS Spectrums* 5 (2022): 536-540.

18. Law J., *et al*. "Relationship between carbon dioxide levels and reported headaches on the international space station". *Journal of Occupational and Environmental Medicine* 56.5 (2014): 477-483.

19. Mora M., *et al*. "Resilient microorganisms in dust samples of the International Space Station-survival of the adaptation specialists". *Microbiome* 4.1 (2016): 65.

20. Buckey JC., *et al*. "Hearing loss in space". *Aviation, Space, and Environmental Medicine* 72.12 (2001): 1121-1124.

21. Tesei D., *et al*. "Understanding the Complexities and Changes of the Astronaut Microbiome for Successful Long-Duration Space Missions". *Life (Basel)* 12.4 (2016): 495.

22. Salazar N., *et al*. "Microbiome: Effects of Ageing and Diet". *Current Issues in Molecular Biology* 36 (2020): 33-62.

23. De Luca d'Alessandro E., *et al*. "Aging populations: the health and quality of life of the elderly". *Clinical Therapeutics* 162.1 (2011): e13-18.

24. Rémond D., *et al*. "Understanding the gastrointestinal tract of the elderly to develop dietary solutions that prevent malnutrition". *Oncotarget* 6.16 (2010): 13858-13898.

25. Ghosh TS., *et al*. "The gut microbiome as a modulator of healthy ageing". *Nature Reviews Gastroenterology and Hepatology* 19.9 (2022): 565-584.

26. Smith SM., *et al*. "The nutritional status of astronauts is altered after long-term space flight aboard the International Space Station". *The Journal of Nutrition* 135.3 (2005): 437-443.

27. Yang JQ., *et al*. "The effects of microgravity on the digestive system and the new insights it brings to the life sciences". *Life Sciences in Space Research (Amst)* 27 (2020): 74-82.

28. Rai B., *et al*. "Bone mineral density, bone mineral content, gingival crevicular fluid (matrix metalloproteinases, cathepsin K, osteocalcin), and salivary and serum osteocalcin levels in human mandible and alveolar bone under conditions of simulated microgravity". *Oral Science* 52.3 (2010): 385-390.

29. Afonin BV., *et al*. "[Investigation of the evacuatory function of the gastrointestinal tract in 5-day dry immersion]". *Aviakosmicheskaia i Ekologicheskaia Meditsina* 45.6 (2011): 52-57.

30. Pei J., *et al*. "Observation of EGG parameters during -6 degrees head-down bedrest for 21 days". *Space Medicine and Medical Engineering* 10.6 (1997): 413-416.

31. Riepl RL., *et al*. "Influence of microgravity on plasma levels of gastroenteropancreatic peptides: a case study". *Aviation, Space, and Environmental Medicine* 73.3 (2002): 206-210.

32. Chen Ying., *et al*. "Effects of simulated weightlessness on tight junction protein occludin and Zonula Occluden-1 expression levels in the intestinal mucosa of rats". *Journal of Huazhong University of Science and Technology [Medical Sciences]* 31.1 (2011): 26-32.

33. Shao D., *et al*. "Simulated microgravity affects some biological characteristics of Lactobacillus acidophilus". *Applied Microbiology and Biotechnology* 101.8 (2017): 3439-3449.

34. Li P., *et al*. "Simulated microgravity disrupts intestinal homeostasis and increases colitis susceptibility". *FASEB Journal* 29.8 (2016): 3263-3273.

35. Vinken M. "Hepatology in space: Effects of spaceflight and simulated microgravity on the liver". *Liver International* 42.12 (2022): 2599-2606.

36. Jiang P., *et al*. "Reproducible Changes in the Gut Microbiome Suggest a Shift in Microbial and Host Metabolism during Spaceflight". *Microbiome* 7 (2019): 113.

37. Shreiner AB., *et al*. "The Gut Microbiome in Health and in Disease". *Current Opinion in Gastroenterology* 31 (2015): 69.

38. Siddiqui R., *et al*. "Effect of Microgravity Environment on Gut Microbiome and Angiogenesis". *Life* 11 (2021): 1008.

39. Voorhies AA., *et al*. "Study of the impact of long-duration space missions at the International Space Station on the astronaut microbiome". *Scientific Reports* 9.1 (2019): 9911.

40. Crucian B., *et al*. "Incidence of clinical symptoms during long duration orbital spaceflight". *International Journal of General Medicine* 9 (2016): 383-439.

41. Tang TWH., *et al*. "Loss of Gut Microbiota Alters Immune System Composition and Cripples Postinfarction Cardiac Repair". *Circulation* 139.5 (2016): 647-659.

42. Enqi W., *et al*. "Age-stratified comparative analysis of the differences of gut microbiota associated with blood glucose level". *BMC Microbiology* 19.1 (2019): 111.

43. Lv H., *et al*. "Microgravity and immune cells". *Journal of The Royal Society Interface* 20.199 (2023): 20220869.

44. Ramos-Nascimento A., *et al*. "Human gut microbiome and metabolite dynamics under simulated microgravity". *Gut Microbes* 15.2 (2023): 2259033.

45. Capri M., *et al*. "Long-term human spaceflight and inflammaging: Does it promote aging?" *Ageing Research Reviews* 87 (2023): 101909.

46. D'Amelio P and Sassi F. "Gut Microbiota, Immune System, and Bone". *Calcified Tissue International* 102.4 (2018): 415-425.

47. Waldbaum JDH., *et al*. "Association between Dysbiosis in the Gut Microbiota of Primary Osteoporosis Patients and Bone Loss". *Aging and Disease* 14.6 (2013): 2081-2095.

48. Mangiola F., *et al*. "Gut microbiota and aging". *European Review for Medical and Pharmacological Sciences* 22.21 (2018): 7404-7413.

49. Ahmad Kendong SM., *et al*. "Gut Dysbiosis and Intestinal Barrier Dysfunction: Potential Explanation for Early-Onset Colorectal Cancer". *Frontiers in Cellular and Infection Microbiology* 11 (2021): 744606.

50. Turroni S., *et al*. "Gut Microbiome and Space Travelers' Health: State of the Art and Possible Pro/Prebiotic Strategies for Long-Term Space Missions". *Frontiers in Physiology* 11 (2020): 553929.