Journal of Public Health and Environmental Research, 2(2):1–10, 2026. DOI: 10.58612/jpher221

Journal of Public Health and Environmental Research

ISSN (Online): 3108-3196

Journal homepage: https://fpub.org/journal-details.php?journal-id=41

Review Article

Metabolic Dysregulation in Microgravity: A Focus on Carbohydrate Utilization during Space Missions

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Article Info

Keywords: *Carbohydrate metabolism, Microgravity, Spaceflight, Insulin resistance, Skeletal muscle atrophy.*

Received: *15.06.2026;*
Accepted: *05.07.2026;*
Published: *10.07.2026*

Abstract

Exposure to microgravity during spaceflight induces significant physiological adaptations that disrupt metabolic homeostasis, particularly carbohydrate metabolism. This study reviews current evidence on the effects of microgravity on glucose regulation, insulin sensitivity, skeletal muscle function, and hepatic glucose metabolism. Findings from human spaceflight and ground-based analogs, such as bed rest and head-down tilt studies, consistently demonstrate the development of peripheral insulin resistance under microgravity conditions. This is largely attributed to skeletal muscle unloading, which leads to muscle atrophy, reduced mitochondrial oxidative capacity, and impaired insulin signaling, particularly along the IRS-1/PI3K/Akt pathway, resulting in decreased GLUT4-mediated glucose uptake. In addition, the suppression of contraction-mediated glucose transport further limits glucose utilization in skeletal muscle. Compensatory increases in hepatic glucose production, driven by enhanced gluconeogenesis and glycogenolysis and influenced by hormonal changes, including elevated cortisol and glucagon levels, contribute to altered glucose homeostasis. Although fasting glucose levels often remain within normal ranges, postprandial hyperglycemia and reduced insulin sensitivity are commonly observed. These metabolic alterations closely resemble early features of insulin resistance and type 2 diabetes, albeit developing over a much shorter timescale in microgravity. Current countermeasures, including exercise and nutritional interventions, provide partial mitigation but do not fully restore metabolic function during prolonged exposure. This review highlights the need for integrated strategies to preserve carbohydrate metabolism in long-duration space missions. It underscores the relevance of microgravity research in understanding and managing metabolic disorders on Earth.

1. Introduction

The metabolism of Carbohydrates plays a key role in maintaining cellular energy supply, specifically in skeletal muscle and the central nervous system. Insulin-sensitive peripheral tissues and hepatic glucose production work together to manage glucose homeostasis under normal gravity conditions. About 70–80% of postprandial glucose disposal occurs solely in skeletal muscle, highlighting its crucial role in systemic metabolic control [1]. Therefore, any interference with muscle mass, contractile activity, or insulin signaling significantly affects carbohydrate metabolism throughout the body. The main way microgravity interferes with these regulatory processes is by mechanically unloading skeletal muscle, leading to fast muscle atrophy, diminished oxidative capacity, and altered substrate usage [2].

How To Cite: N.W. Eneh, O.G. Akinwade, H.A. Gumel, M. Akilu, O.A. Otum, Z.I. Suleiman, S.B. Abubakar and Z.O. Idris. Metabolic Dysregulation in Microgravity: A Focus on Carbohydrate Utilization during Space Missions. *Journal of Public Health and Environmental Research*, 2(2):1–10, 2026. https://doi.org/10.58612/jpher221

Human spaceflight causes a peculiar physiological challenge defined by continuous exposure to microgravity, a condition in which gravitational loading is significantly reduced [3]. Even though progress in aerospace medicine has reduced many acute risks of space travel, long-duration missions aboard orbital platforms such as the Intenational Space Station (ISS) continue to reveal complex metabolic adaptations with significant health implications [3]. Among these, distortions in carbohydrate metabolism are a major concern, as they are linked to long-term metabolic dysfunction, insulin resistance, and muscle atrophy [4].

These functional and structural changes are followed by reduced glucose transporter type 4 (GLUT4) translocation, diminished glucose uptake, and impaired insulin signaling, which collectively promote peripheral insulin resistance [5, 6]. In the same vein, hepatic adaptations may exacerbate dysglycemia by altering glycogen storage, increasing gluconeogenic flux, and disrupting insulin signaling pathways, thereby elevating hepatic glucose output [7].

The unique environment of microgravity disrupts the tightly regulated interplay between skeletal muscle and hepatic function that supports carbohydrate metabolism, leading to impaired glucose utilization, altered insulin signaling, and a high risk of metabolic dysfunction. Despite growing evidence of these changes, findings remain fragmented, and mechanisms are not yet fully integrated. Therefore, a comprehensive review is necessary to synthesize current knowledge, clarify underlying pathways, and identify critical gaps, ultimately guiding the development of effective countermeasures to safeguard metabolic health during long-duration spaceflight.

1.1. Overview of Microgravity

The term ”microgravity” refers to a physical state in which very little apparent gravitational force acts on objects, creating an almost weightless environment [8]. Spacecraft and astronauts in orbit experience microgravity because they are both traveling forward at a high orbital speed and falling toward Earth at the same rate. The feeling of weightlessness happens because the spacecraft and everything inside it accelerate at the same rate under Earth’s gravity, making the relative gravitational force.

Figure 1: Life in Microgravity (European Space Agency, 2021, October 23). Floating through the Space Station in 360 (video). ESA

1.2. Real Microgravity

Microgravity is often experienced in outer space when objects are in an orbital motion about a planetary body. In this environment, astronauts and spacecraft are constantly in free fall, which creates a constant microgravity. During orbital missions [9, 10], the International Space Station (ISS), space shuttles, and other orbital laboratories often experience true microgravity. The long-term missions carried out on the International Space Station (ISS) have provided substantial information regarding the biological effects of microgravity exposure. Long-term exposure to microgravity during space flight has been linked to reductions in muscle mass and strength due to a reduction in the mechanical loading of antigravity muscles such as the soleus and quadriceps [2].

1.3. Simulated Microgravity

Simulated microgravity is an experimental technique designed to model some of the biological and physiological consequences of weightlessness under normal conditions. As Earth’s gravitational field does not allow a complete simulation of real microgravity, researchers use specially designed devices and experimental models that minimize the gravitational forces acting on biological systems [11, 12]. The clinostat is a common laboratory simulation tool that continuously rotates biological samples about a horizontal axis. The continuous rotation changes the direction of the gravitational force applied to the sample, causing a reduction in the gravitational effects. Therefore, cells and tissues are submitted to conditions similar to some aspects of microgravity [11, 12].

Another commonly used method is the head-down tilt bed rest model, where human participants consistently lay on a bed tilted at about -6° where the head is below the feet. This position produces physiological responses similar to those experienced in spaceflight including shifts in body fluids toward the head (cephalad), decreased mechanical loading on the musculoskeletal system, and cardiovascular adaptations [13, 14].

The random positioning machine (RPM) is another simulation system, which rotates samples along many axes, thereby randomizing the direction of gravitational forces. It is often used in cellular and molecular biology experiments to study the impact of gravity on cytoskeletal organization, cellular proliferation, gene expression, and intracellular signalling pathways [15, 16].

Parabolic flight experiments are also used in the study of microgravity. Parabolic flights use specially modified aircraft and follow a parabolic trajectory to produce short bursts of free fall lasting about 20 to 30 seconds. These missions permit researchers to perform experiments in real microgravity conditions without having to travel to space, though the microgravity exposure is short [17].

2. Effects of Microgravity on Glucose Homeostasis

Disruption of systemic glucose homeostasis emerged as a consistent finding across both spaceflight and ground-based microgravity analogs [7]. Earlier studies demonstrated that specimens subjected to simulated microgravity exhibit impaired glucose tolerance, as evidenced by higher plasma glucose concentrations following intravenous or oral glucose challenges [18].

In head-down bed rest studies, related changes have been repeatedly documented, showing that reduced gravitational loading rather than other space-specific factors is the primary determinant [19]. Studies have provided strong evidence that microgravity induces peripheral insulin resistance within relatively short timeframes. Mathyk et al. [20] reported a remarkable decrease in whole-body insulin sensitivity following spaceflight. Further, bed rest studies also showed comparable declines following 5–7 days of unloading [21]. These discoveries demonstrate that carbohydrate metabolism is highly responsive to mechanical unloading and decreased muscle contractile activity.

Fasting plasma glucose levels are often only slightly raised or remain normal. However, postprandial glucose excursions are elevated. This shows that microgravity primarily affects insulin-mediated glucose disposal rather than basal glucose regulation. This discovery is closely related to early-stage insulin resistance observed in sedentary individuals and older adults on Earth [22].

2.1. Mechanism of the Effects of Microgravity on Energy Metabolism

The body's production, utilization, and regulation of energy (ATP) from the breakdown of carbohydrates are all affected by microgravity. The muscles, liver, adipose tissue, mitochondria, and hormone regulation are also affected in the microgravity environment [23, 24]. Detailed mechanisms by which microgravity affects carbohydrate metabolism include:

Reduced Mechanical Loading leading to Altered Energy Demand

Skeletal muscles, especially antigravity muscles like the soleus and quadriceps, are constantly used to maintain posture and movement under normal gravitational conditions. Skeletal muscle experiences functional unloading in microgravity due to the near-complete loss of gravitational force, which significantly lowers contractile activity. Consequently, there is a significant decrease in ATP demand as muscle contraction frequency and intensity decrease [25]. Since mitochondrial respiration is primarily driven by ATP usage, decreased ATP hydrolysis instructs the cell to decrease energy output instead of maintaining a high metabolic flux. Muscle cells have an energy sensor called AMP-activated protein kinase (AMPK), which triggers pathways that provide additional energy when muscles contract and utilize ATP. AMPK is less active in microgravity due to a decrease in ATP use, which lowers signals for energy synthesis [26]. Without insulin, muscle contractions aid in the entry of glucose into cells; less glucose enters muscle cells in microgravity due to fewer contractions, which lowers the amount of energy derived from sugar [27]. Overall effect results in reduced muscle activity, which lowers ATP use, slows energy-producing pathways, and decreases the efficiency of fat and glucose utilization.

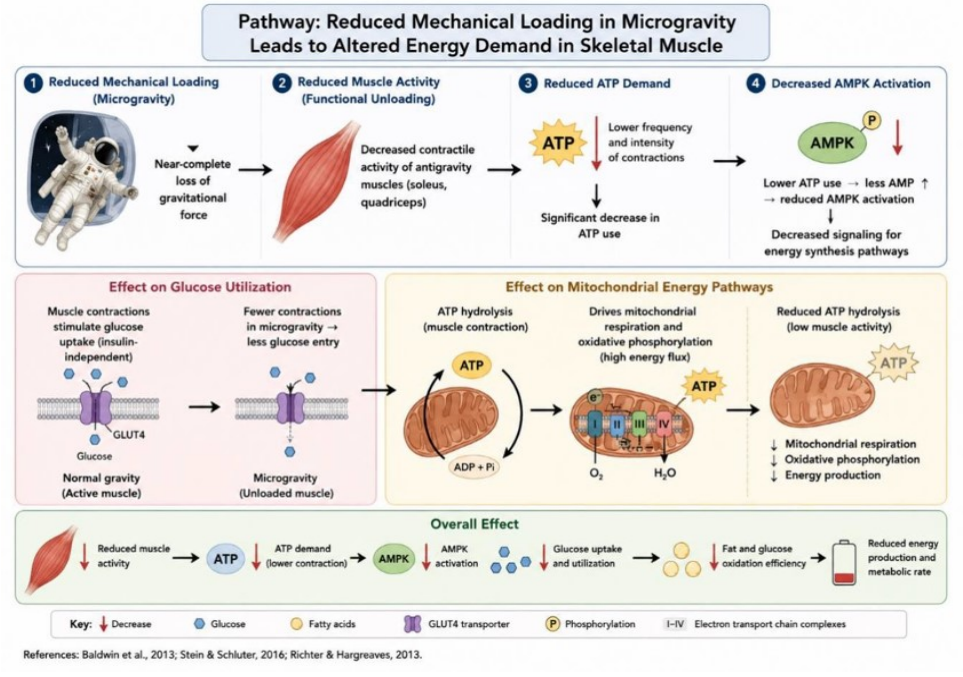

Figure 2: Pathway illustrating how microgravity leads to altered energy demand in skeletal muscles. (image generated using ChatGPT in response to "generate image supporting this paragraph" prompt)

Mitochondrial Dysfunction in Microgravity

Since mitochondria are the primary locations where ATP is produced by oxidative phosphorylation, any disruption can have a substantial impact on energy homeostasis [28]. Under microgravity, the mitochondria's ability to generate ATP efficiently through oxidative phosphorylation is impaired. Studies have shown reduced activity of ATP synthase and other enzymes in mitochondria, which slows the conversion of ADP to ATP [29]. Consequently, cells increasingly rely on anaerobic glycolysis, which produces less ATP per glucose molecule and accumulates lactate [30]. It has been demonstrated that microgravity reduces the number of mitochondria in muscle and other tissues, reducing their density, potentially as a result of reduced mechanical stress and altered gene expression that controls mitochondrial biogenesis [31]. Fewer mitochondria limit the overall capacity for ATP production. The activity of electron transport chain complexes I–IV is down-regulated in microgravity, compromising the proton gradient needed for ATP production. This contributes to energy deficits and metabolic shifts [32]. Impaired ETC activity causes electron leakage and increased ROS production [33].

Insulin Resistance Development in Microgravity

During spaceflight, microgravity induces insulin resistance, a condition in which skeletal muscle and adipose tissue fail to respond efficiently to circulating insulin. This effect contributes to alteration in glucose homeostasis, increased blood glucose levels, and altered energy metabolism, which in turn compromise an astronaut's health during long-duration missions [34, 35]. The translocation of GLUT-4 transporters to the muscle cell membrane in response to insulin is reduced upon exposure to microgravity. GLUT-4 is essential for insulin-mediated glucose uptake; reduced translocation limits glucose entry into skeletal muscle, leading to hyperglycemia [36]. Insulin receptor substrate (IRS-1/IRS-2) and downstream PI3K-Akt signaling are among the insulin receptor signaling pathways that are altered by spaceflight [37]. Insulin-mediated metabolic responses are less effective when receptor sensitivity is compromised, which further restricts the absorption of glucose in muscle and adipose tissue.

Altered Insulin Signaling Pathways and Sensitivity

Impairments in conventional insulin signaling pathways serve as the molecular basis for microgravity-induced insulin resistance. Reductions in insulin receptor substrate-1 (IRS-1) phosphorylation and downstream phosphoinositide 3-kinase (PI3K) activity have been shown in a number of investigations using skeletal muscle samples before and after bed rest or spaceflight [5]. A crucial node in insulin-mediated glucose absorption, Akt (also known as protein Kinase) activation is slowed down by these changes. Abnormal Akt signaling has relative negative effect on glucose transporter type 4 (GLUT4) translocation to the sarcolemma. Normally, insulin stimulation enhances GLUT4 migration from intracellular vesicles to the plasma membrane, facilitating the absorption of glucose into muscle fibers. This process is affected by microgravity, which lowers the amount of GLUT4 at the cell surface and the ability to transport glucose [38, 39]. Notably, these signaling abnormalities seem to be unaffected by variations in the amounts of insulin in the blood, suggesting that microgravity causes insulin resistance at the tissue level as opposed to endocrine failure. This effect is worsened by decreased muscle contractile activity because muscle contraction typically activates insulin-independent glucose uptake pathways, which are mostly missing in unloaded muscle [40]. Generally, the above evidence shows that microgravity negatively affects insulin signaling through both molecular downregulation of insulin-responsive pathways and diminished mechanical stimulation, leading to reduced glucose uptake by skeletal muscle.

2.2. Skeletal Muscle Atrophy and Carbohydrate Utilization

Skeletal muscle is the primary site of insulin-stimulated glucose disposal, which accounts for 70–80% of postprandial glucose uptake under normal physiological conditions. As such, the structural and metabolic integrity of skeletal muscle is essential for preserving whole-body glucose homeostasis [41, 42]. Exposure to microgravity or the simulated analogs (bed rest, hindlimb unloading, clinostat) causes fast and profound skeletal muscle atrophy, particularly in the soleus and quadriceps (antigravity muscles), which depends highly on mechanical loading for maintenance of mass and function [25, 43]. Systemic insulin resistance is exacerbated by this decrease in muscle cross-sectional area, which directly restricts the amount of tissue accessible for insulin-mediated glucose uptake. Microgravity causes notable qualitative changes in skeletal muscle phenotype in addition to the quantitative loss of muscle mass. The transition from oxidative, fatigue-resistant type I fibres to more glycolytic, fast-twitch type II fibres after extended unloading is a well-documented adaptation [44, 45]. This transition is associated with lowered mitochondrial density, capillarization, and oxidative enzyme activity, collectively impairing aerobic metabolism. As a result, the metabolism is reprogrammed to rely more on anaerobic glycolysis, which is less effective for long-term glucose oxidation and leads to lactate buildup and metabolic rigidity [46]. Microgravity-induced unloading alters mitochondrial homeostasis, a crucial factor in metabolic health, at the cellular and molecular levels. Research has shown decreased levels of mitochondrial biogenesis regulators such as PGC-1 α, as well as decreased oxidative phosphorylation capacity and increased formation of reactive oxygen species (ROS) in the mitochondria [47]. As a result of these mitochondrial defects, ATP production efficiency is reduced, and glucose oxidation pathways are compromised. This limits effective utilization of glucose by the skeletal muscles. Concurrently, unloading elevates deficiencies in glucose utilization by downregulating important enzymes involved in carbohydrate metabolism, such as pyruvate dehydrogenase and citrate synthase.

The duration of time spent in microgravity significantly impacts the degree of muscle atrophy and related metabolic abnormalities. Despite the use of exercise countermeasures, long-duration missions, like those on the International Space Station, are linked to progressive reductions in muscle mass, strength, and insulin sensitivity [48, 49]. Resistance and aerobic exercise regimens can reduce muscle loss and partly maintain metabolic function, but they do not completely prevent impairments in glucose metabolism, suggesting that current countermeasures are insufficient to fully mitigate metabolic alterations caused by microgravity [50]. Collectively, skeletal muscle atrophy is a key mechanistic connection between exposure to microgravity and poor metabolism of carbohydrates. Reduced muscle mass, fiber-type changes, mitochondrial dysfunction, and compromised insulin signaling all work together to restrict glucose elimination and increase systemic insulin resistance [2]. These results highlight the significance of creating more potent countermeasures that address metabolic health and muscle preservation during extended space missions [51].

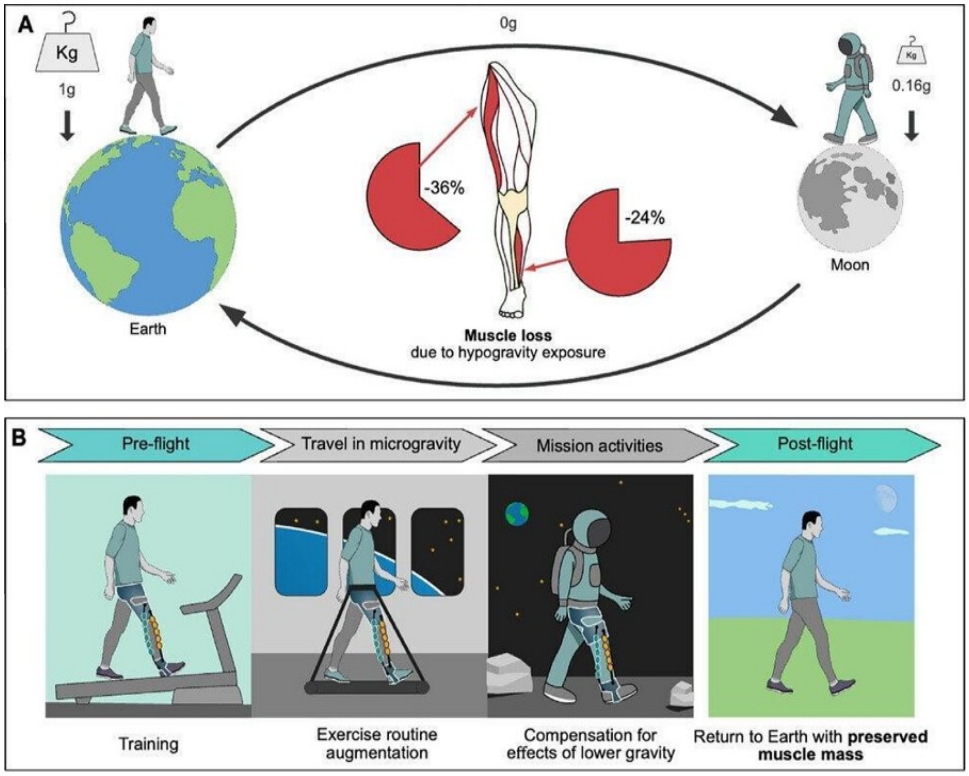

Figure 3: Effects of Hypogravity Exposure on Skeletal Muscle Loss and Exercise Countermeasures During Spaceflight [52]. Effects of hypogravity on skeletal muscle mass and countermeasure strategies during spaceflight. Communications Biology, 6, Article 467)

2.3. Hepatic Glucose Metabolism as a Compensatory Mechanism

Maintaining systemic glucose homeostasis under microgravity or simulated unloading circumstances is a crucial compensatory function of the liver [53]. Hepatic glucose synthesis and peripheral glucose uptake, especially by insulin-sensitive tissues like skeletal muscle, work together to carefully manage glucose balance under normal physiological conditions [53]. Reduced mechanical loading in microgravity, however, results in decreased skeletal muscle glucose utilization, which makes an adaptive increase in hepatic glucose output necessary to maintain euglycemia, particularly during fasting and postabsorptive states [27]. Under unloading conditions, gluconeogenesis becomes a more significant contributor to endogenous glucose synthesis, according to emerging data from stable isotope tracer studies and bed rest analogs. Changes in important hormone regulators of metabolism are thought to cause this change. In particular, hepatic gluconeogenic pathways are stimulated through the upregulation of enzymes like phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G6Pase) due to increases in counter-regulatory hormones like cortisol and glucagon and relative decreases in insulin action in peripheral tissues [54, 55]. Further supporting increased hepatic glucose production is the availability of gluconeogenic substrates, such as lactate and alanine from muscle proteolysis and decreased oxidative metabolism [2].

This compensatory increase in glucose production may eventually become maladaptive, even though hepatic insulin sensitivity seems to be generally retained during brief microgravity exposure or the early stages of unloading. The hallmarks of spaceflight-associated dysglycemia, such as fasting hyperglycemia and decreased glucose tolerance, can be caused by prolonged increase of hepatic glucose production in the context of persistent peripheral insulin resistance [55]. Microgravity may cause subtle hepatic metabolic reprogramming, including changes in mitochondrial function, lipid metabolism, and circadian regulation, all of which may indirectly affect glucose homeostasis, according to recent omics-based and spaceflight studies [56, 57].

This peripheral hepatic difference is significant because it highlights the integrative nature of metabolic regulation in microgravity. The liver's compensatory increase in glucose production is crucial for maintaining the systemic energy supply, but it may potentially worsen metabolic dysregulation during extended missions, even when skeletal muscle insulin resistance is the major issue [58]. As a result, remedies like resistance training or neuromuscular stimulation that just aim to restore muscle function may not be adequate. To completely normalize carbohydrate metabolism in spaceflight conditions, a more all-encompassing strategy that targets both peripheral glucose disposal and hepatic metabolic control, possibly through combined exercise, nutritional, and pharmacological strategies, is probably needed [59, 60].

2.4. Interaction between microgravity, diet, and energy balance

During spaceflights and space missions, when coordination between energy intake, expenditure, and substrate use is drastically altered, nutritional intake serves as a key regulator of metabolic adaptation. Neuroendocrine processes involving appetite-regulating hormones (such as leptin and ghrelin) and peripheral metabolic signals carefully regulate energy balance under normal gravity conditions. However, concomitant changes in physical activity, hunger, and physiological stress responses disturb this control in microgravity [61, 62]. These changes directly affect carbohydrate metabolism and the preservation of glucose homeostasis.

A constant decrease in intentional calorie intake is a distinguishing characteristic of spaceflight. "Space anorexia," a disorder marked by decreased appetite, changed taste perception, and early satiety, is common among astronauts and is probably caused by changes in gastrointestinal function, fluid shifts, and vestibular disturbances [63]. Because of this, energy intake frequently falls short of metabolic

needs, resulting in a persistent negative energy balance. Astronauts ingested about 1,900 kcal per day while expending over 3,000 kcal per day, leading to large caloric deficits, according to studies using doubly labeled water techniques during Space Shuttle missions [64]. This long-term energy shortage affects metabolic pathways, including the use of carbohydrates, and leads to decreases in body mass, especially lean muscle tissue.

Astronaut meals are specifically designed to meet macronutrient needs while taking into account the particular limitations of space travel, such as food stability, ease of preparation, and restricted storage. About 50–55% of the energy in standard spaceflight diets comes from carbs, with the remaining energy coming from proteins and fats [65]. This comparatively high percentage of carbohydrates is meant to supply easily oxidizable energy substrates that sustain specified workout regimens, mission-critical tasks, and cognitive function. In order to mitigate microgravity-induced muscle atrophy and metabolic deterioration, it is especially crucial to maintain glycogen stores and sustain exercise performance through adequate carbohydrate intake [66].

Despite these dietary recommendations, the relationship between macronutrient consumption and metabolic adaptation in microgravity is complex. Substrate consumption patterns change with time, according to data from long-duration missions on the International Space Station (ISS) [67]. During extended spaceflight, the Energy study found a decrease in lipid oxidation and an increase in carbohydrate oxidation [68]. Both nutritional composition and physiological adaptations, such as decreased mitochondrial oxidative capacity and modified hormonal regulation of metabolism, may be responsible for this change.

The relationship between nutrition and energy balance in space is further complicated by hormonal changes. Adipokines, cortisol levels, and insulin signaling have all been shown to change during spaceflight and ground-based analogs like bed rest studies [58]. For example, decreased insulin sensitivity restricts glucose absorption in peripheral tissues, whereas elevated cortisol may encourage gluconeogenesis and muscle protein breakdown [58]. A metabolic milieu that promotes hyperglycemia and poor energy use is produced by these endocrine alterations, nutritional deficiencies, and decreased mechanical loads. The interplay of energy balance, nutrition, and microgravity as a whole poses a complex threat to metabolic equilibrium. Carbohydrate metabolism is significantly affected when reduced calorie intake, altered macronutrient utilization, decreased physical activity, and hormonal dysregulation come together [58, 61]. The cumulative physiological stressors associated with long-term spaceflight make it more important to comprehend these interactions as space missions grow in length and distance, especially with proposed missions to Mars and beyond [69]. In order to preserve astronaut health and performance over extended exposure to microgravity, future nutritional solutions must not only guarantee sufficient caloric intake but also maximize macronutrient composition and metabolic efficiency [70].

2.5. Health Implications of the effect of microgravity on carbohydrate metabolism

The development of insulin resistance linked to spaceflight is among the most frequently documented effects of exposure on metabolic health. Reduced insulin sensitivity, characterized by decreased glucose uptake and altered insulin signaling pathways, has been observed in studies conducted during both short- and long-duration missions [7]. Although these alterations are often reversible upon returning to Earth, they mirror the early stages of type 2 diabetes mellitus [71].

Skeletal muscle unloading, which lowers glucose disposal because of reduced muscle mass and GLUT4 transporter function, is a significant contributing factor.Systemic glucose homeostasis is severely disrupted by skeletal muscle atrophy, which accounts for 70–80% of postprandial glucose absorption [1]. Furthermore, encouraging gluconeogenesis and impeding insulin action, microgravity-induced hormonal changes, such as increased cortisol and modified catecholamine levels, can worsen insulin resistance [72]. Long-term microgravity exposure may likely increase the risk of metabolic problems like altered lipid metabolism and reduced glucose tolerance, in addition to insulin resistance. These metabolic abnormalities draw attention to possible hazards for extended missions, as those intended for Mars exploration, even though astronauts are generally healthy and physically fit [65].

Crucially, these results are applicable on Earth. Physical inactivity, age, and prolonged bed rest are all linked to metabolic dysfunctions, and microgravity provides a model for these conditions. Studies using bed rest, the common ground-based analogs, have shown that insulin sensitivity rapidly decreases within days of immobility [21]. Interventions for sedentary populations and age-related metabolic illnesses on Earth can therefore benefit from an understanding of metabolic adaptations in space.

3. Countermeasures and Interventions

3.1. Exercise Countermeasures

In space, exercise is still the best way to maintain metabolic health. Maintaining muscle mass, improving insulin sensitivity, and encouraging glucose uptake are all aided by resistance and aerobic exercise. Astronauts on the International Space Station engage in high-intensity resistance exercises thanks to equipment like the Advanced Resistive Exercise Device (ARED) [50]. Exercise compensates for reduced insulin signaling in microgravity circumstances by stimulating GLUT4 translocation without the need for insulin.

3.2. Nutritional Strategies

Maintaining energy balance and metabolic function requires optimizing nutritional intake. To maintain energy demands and avoid an over-reliance on protein and fat metabolism, a sufficient intake of carbohydrates is required. Furthermore, low glycemic meals enhance insulin sensitivity and help regulate blood glucose levels [61]. The potential of supplementing with nutrients like antioxidants and omega-3 fatty acids to lower inflammation and enhance metabolic results is also being investigated.

3.3. Pharmacological Approaches

Although their application in space is yet experimental, pharmacological therapies like insulin sensitizers (like metformin) have been suggested as viable countermeasures. During extended missions, these medications may assist in controlling glucose metabolism and lower the risk of insulin resistance [73].

Figure 4: An astronaut exercises aboard the International Space Station using the Advanced Resistive Exercise Device (ARED). (NASA. (2013, November 18). Astronaut Rick Mastracchio with ARED [Photograph]. National Aeronautics and Space Administration

3.4. Artificial Gravity and Emerging Technologies

Centrifugation-generated artificial gravity is a viable strategy to mitigate the various physiological impacts of microgravity, including metabolic dysfunction. Artificial gravity may support the maintenance of regular muscular activity and metabolic processes by mimicking gravitational loads [9]. Neuromuscular electrical stimulation for stimulating physical exercise and wearable resistance devices are some new tactics. To successfully reduce metabolic disruptions in space, a multimodal strategy that combines exercise, diet, and technological advancements is required.

4. Knowledge Gaps and Future Research Directions

Despite tremendous progress, there are still several unanswered questions regarding how microgravity affects the metabolism of carbohydrates. First, due to financial and logistical limitations of space missions, most research is constrained by small sample sizes. This limits how far the results may be applied and emphasizes the need for bigger, more complete datasets. Furthermore, a lot of studies use ground-based analogs or short-duration trips, which might not accurately mimic the physiological conditions of extended spaceflight [13]. Second, the molecular mechanisms underlying insulin resistance in microgravity are poorly understood. Although changes in GLUT4 expression and insulin signaling pathways have been noted, more research is needed to determine the exact relationships between mechanical unloading, mitochondrial function, and metabolic control. Third, there is a dearth of long-duration mission data, especially for missions outside of low Earth orbit. A deeper knowledge of chronic metabolic adaptations is required because future exploration missions to the Moon and Mars would subject astronauts to extended durations of microgravity or partial gravity. Lastly, combining powerful computational modeling with omics technologies (metabolomics, proteomics, and genomics) may reveal new treatment targets and offer a deeper understanding of systemic metabolic alterations.

In order to ensure astronaut safety and successful missions, as well as to reproduce spaceflight research into Earthly healthcare uses, these gaps must be filled.

5. Conclusion

The metabolism of carbohydrates is severely disrupted by microgravity, resulting in altered hepatic function, decreased insulin sensitivity, and poor glucose management. These alterations resemble insulin resistance on Earth and are usually caused by skeletal muscle atrophy, physical inactivity, and hormonal abnormalities. Exercise and dietary interventions play a crucial role in mitigating these effects; however, current evidence indicates that they are insufficient to fully counteract metabolic disturbances during extended-duration missions on their own. Emerging approaches such as personalized therapeutic interventions and artificial gravity show considerable promise; however, they require further investigation to establish their effectiveness and feasibility for long-duration space missions. Overall, understanding metabolic adaptations to microgravity is essential for maintaining astronaut health over prolonged space missions, and it will provide insightful information on the management and prevention of metabolic problems on Earth.

Article Information

Author Contributions: N.W.E. - Conceptualization, Methodology, Data curation, Formal analysis, Writing – original draft, Writing – review & editing; O.G.A. - Data curation, Formal analysis, Writing – original draft; H.A.G. - Data curation, Formal analysis, Writing – original draft; M.A. - Writing – review & editing, Supervision; O.A.O. - Data curation, Formal analysis; Z.I.S. - Data curation, Formal analysis; S.B.A. - Data curation, Formal analysis; Z.O.I. - Data curation, Formal analysis.

Funding / Financial Support: The authors received no external funding.

Conflict of Interest (Competing Interests): The authors declare no competing interests.

Disclaimer (Artificial Intelligence): The author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.), and text-to-image generators have been used during writing or editing of manuscripts.

Competing Interests: Authors have declared that no competing interests exist.

References

[1] R. A. DeFronzo and D. Tripathy. Skeletal muscle insulin resistance is the primary defect in type 2 diabetes. *Diabetes Care*, 32(Suppl 2):S157–S163, 2009.

[2] R. H. Fitts, D. R. Riley, and J. J. Widrick. Functional and structural adaptations of skeletal muscle to microgravity. *Journal of Experimental Biology*, 204:3201–3208, 2010.

[3] L. H. Winkler. Human physiological limitations to long-term spaceflight and living in space. *Aerospace Medicine and Human Performance*, 94(6):444–456, 2023.

[4] E. Le Roux, A. Zahariev, I. Chery, D.A. , Schoeller, P. Bourdier, A. Maillet, C. Thevenot, G. Garnotel, M. Gauquelin-Koch, L. Van Den Berghe, S. Blanc, C. Simon, and A. Bergouignan. Substrate metabolism in male astronauts onboard the international space station. *NPJ Microgravity*, 2024.

[5] S. S. Rudrappa, D. J. Wilkinson, P. L. Greenhaff, K. Smith, and P.J. Idris, I. Atherton. Human skeletal muscle disuse atrophy. *Journal of Applied Physiology*, 120(8):911–921, 2016.

[6] J. Van Gerwen, A. S. Shun-Shion, and D. J. Fazakerley. Insulin signalling and GLUT4 trafficking in insulin resistance. *Biochemical Society Transactions*, 51(3), 2023.

[7] F. Strollo, S. Gentile, A. M. V. Pipicelli, A. Mambro, M. Monici, and P. Magni. Space flight-promoted insulin resistance as a possible disruptor of wound healing. *Frontiers in Bioengineering and Biotechnology*, 10:868999, 2022.

[8] V. Pletser. *Gravity, weight, and their absence*. Springer, Singapore, 2018. Pages 67–84.

[9] G. Clément and A. Bukley. *Artificial gravity*. Springer, 2015.

[10] LeBlanc. A., V Schneider, L. Shackelford, S. West, and A. Voronin L. Oganov, V. Bakulin. Bone mineral and lean tissue loss after long-duration spaceflight. *Journal of Musculoskeletal and Neuronal Interactions*, 7(2):157–160, 2007.

[11] R. Herranz, R. Anken, J. Boonstra, M Braun, P.C. Christianen, M. de Geest, J. Hauslage, R. Hilbig, R.J. Hill, M. Lebert, F.J. Medina, N. Vagt, O. Ullrich, and Hemmersbach R. van Loon, J.J. Ground-based facilities for simulation of microgravity. *Microgravity Science and Technology*, 25:1–17, 2013.

[12] J. J. Van Loon. The random positioning machine. *Advances in Space Research*, 39:1161–1165, 2007.

[13] A. Pavy-Le Traon, M. Heer, M. V. Narici, J. Rittweger, and J. Vernikos. From space to Earth: Advances in human physiology from spaceflight research. *European Journal of Applied Physiology*, 101(2):143–194, 2007.

[14] A. R. Hargens and L. Vico. Long-duration bed rest as an analog to microgravity. *Journal of Applied Physiology*, 120:891–903, 2016.

[15] J. Pietsch, J. Bauer, M. Egli, M. Infanger, and D.G. Grimm. Simulated microgravity using random positioning machines. *Cell Communication and Signaling*, 9:17, 2011.

[16] G. Aleshcheva, J. Sahana, X. Ma, J. Hauslage, R. Hemmersbach, M. Egli, M. Infanger, and D. Grimm. Changes in gene expression in human endothelial cells during spaceflight. *FASEB Journal*, 30(2):567–576, 2016.

[17] F. Karmali and M. Shelhamer. The dynamics of parabolic flight. *Journal of Vestibular Research*, 18:169–175, 2008.

[18] K. M. Ong, J. J. Rossitto, K. Ray, Q. A. Dufurrena, and R. S. Blue. Blood glucose alterations and continuous glucose monitoring in centrifuge-simulated spaceflight. *Aerospace Medicine and Human Performance*, 93(9):688–695, 2022.

[19] J. P. Scott, A. Kramer, N. Petersen, and D. A. Green. The role of long-term head-down bed rest in understanding inter-individual variation in response to the spaceflight environment: A perspective review. *Frontiers in Physiology*, 12:614619, 2021.

[20] B. A. Mathyk, M. Tabetah, R. Karim, V. Zaksas, J. Kim, R. I. Anu, and A. Beheshti. Spaceflight induces changes in gene expression profiles linked to insulin and estrogen. *Communications Biology*, 7(1):692, 2024.

[21] M. L. Dirks, B. T. Wall, T. Snijders, C. L. P. Ottenbros, L. B. Verdijk, and L. J. C. van Loon. Neuromuscular electrical stimulation prevents muscle disuse atrophy. *Acta Physiologica*, 216(1):231–243, 2016.

[22] A. Bergouignan, F. Rudwill, C. Simon, and S. Blanc. Physical inactivity is the culprit of metabolic inflexibility. *Journal of Applied Physiology*, 111(4):1201–1208, 2011.

[23] B. L. Dickerson, R. Sowinski, R. B. Kreider, and G. Wu. Impacts of microgravity on amino acid metabolism during spaceflight. *Experimental Biology and Medicine*, 248(5):380–393, 2023.

[24] O. M. Manna, S. Burgio, D. Picone, A. Carista, A. Pitruzzella, A. Fucarino, and F. Bucchieri. Microgravity and human body: Unraveling the potential role of heat-shock proteins in spaceflight and future space missions. *Biology*, 13(11):921, 2024.

[25] K. M. Baldwin, F. Haddad, and C. E. Pandorf. Alterations in muscle mass and function in spaceflight. *Comprehensive Physiology*, 3(1): 77–101, 2013.

[26] T. P. Stein and M. D. Schluter. Energy metabolism in spaceflight. *Nutrition*, 2016.

[27] E. A. Richter and M. Hargreaves. Exercise, GLUT4, and skeletal muscle glucose uptake. *Physiological Reviews*, 93(3):993–1017, 2013.

[28] J. Smith, K. Lee, and R. Martinez. Spaceflight stressors and mitochondrial dysfunction: Implications for cellular energy metabolism. *npj Microgravity*, 12, 2026.

[29] A. Michaletti, M. Gioia, U. Tarantino, and L. Zolla. Effects of microgravity on osteoblast mitochondria: A proteomic and metabolomics profile. *Scientific Reports*, 7(1):15376, 2017.

[30] G. Aubert et al. Mitochondrial dynamics and the regulation of oxidative metabolism in skeletal muscle. *Frontiers in Physiology*, 7: 1–12, 2016.

[31] Q. Shi, Y. Song, J. Cao, J. Na, Z. Yang, X. Chen, others, and L. Zheng. Inhibition of mitochondrial fission reverses simulated microgravity-induced osteoblast dysfunction by enhancing mechanotransduction and epigenetic modification. *Research*, 8:0602, 2025.

[32] N. Baecker et al. Spaceflight-induced changes in mitochondrial structure and function. *Journal of Applied Physiology*, 126(2):512–523, 2019.

[33] Y. Tominaga et al. Microgravity-induced oxidative stress in human cells. *Redox Biology*, 37:101729, 2020.

[34] S. M. Smith, S. R. Zwart, M. Heer, and E. K. Hudson. Human physiological responses to microgravity. *Advances in Space Research*, 41(12):1824, 2008.

[35] S. R. Zwart, C. R. Gibson, and S. M. Smith. Spaceflight and insulin resistance: Countermeasures and underlying mechanisms. *Journal of Applied Physiology*, 103(3), 2007.

[36] M. Jaconelli. Dynamic measures of human protein metabolism with stable isotopes and mass spectrometry (Doctoral dissertation, University of Nottingham). 2023.

[37] F. Hakuno, T. Fukushima, Y. Yoneyama, H. Kamei, A. Ozoe, H. Yoshihara, and S. I. Takahashi. The novel functions of high-molecular-mass complexes containing insulin receptor substrates in mediation and modulation of insulin-like activities: Emerging concept of diverse functions by IRS-associated proteins. *Frontiers in Endocrinology*, 6:73, 2015.

[38] R. H. Fitts, S. W. Trappe, D. L. Costill, et al. Prolonged space flight induced alterations in skeletal muscle fibers. *Journal of Physiology*, 588(18):3567–3592, 2010.

[39] E. C. Kirkpatrick. The roles of muscle contraction and pharmaceuticals on restoring glucose uptake in a mouse skeletal muscle model of immobilization (Doctoral dissertation, University of Nottingham). 2023.

[40] A. Ramos-Jiménez, M. Rubio-Valles, J. Guereca-Arvizuo, M. A. Juárez-Oropeza, J. A. Ramos-Hernández, I. A. Chávez-Guevara, and R. P. Hernández-Torres. Canonical and alternative pathways (insulin and exercise) of GLUT4 synthesis, signaling, intracellular clustering, and recruitment to the plasma membrane. 2026.

[41] N. A. Hulett, R. L. Scalzo, and J. E. Reusch. Glucose uptake by skeletal muscle within the contexts of type 2 diabetes and exercise: An integrated approach. *Nutrients*, 14(3):647, 2022.

[42] S. B. Jani. Dietary Manipulation of Glucose and Fat Metabolism in Skeletal Muscles and Liver. 2023.

[43] A. Bosutti, B. Ganse, N. A. Maffiuletti, R. C. Wüst, G. J. Strijkers, A. Sanderson, and H. Degens. Microgravity-induced changes in skeletal muscle and possible countermeasures: What we can learn from bed rest and human space studies. 2025.

[44] R. Demangel, L. Treffel, G. Py, et al. Early structural and functional changes in human skeletal muscle following bed rest. *Journal of Physiology*, 595(11):3509–3526, 2017.

[45] R. Qaisar, A. Karim, and A. B. Elmoselhi. Muscle unloading: A comparison between spaceflight and ground-based models. *Acta Physiologica*, 228(3):e13431, 2020.

[46] H. Eshima et al. Effects of disuse on muscle metabolism and mitochondrial function. *Journal of Applied Physiology*, 128(3):720–734, 2020.

[47] P. H. Lee, M. Chung, Z. Ren, D. B. Mair, and D. H. Kim. Factors mediating spaceflight-induced skeletal muscle atrophy. *American Journal of Physiology-Cell Physiology*, 322(3):C567–C580, 2022.

[48] S. Trappe et al. Exercise in space: Human skeletal muscle after 6 months aboard ISS. *Journal of Applied Physiology*, 106(4):1159–1168, 2009.

[49] K. L. English et al. High intensity training during spaceflight: Results from the NASA Sprint Study. *npj Microgravity*, 6(1):21, 2020.

[50] J.A Loehr, M.E. Guilliams, N. Petersen, N. Hirsch, S. Kawashima, and H. Ohshima. Physical training for long-duration spaceflight. *Aviation, Space, and Environmental Medicine*, 86(12):A14–A23, 2015.

[51] J. A. Loehr, M. E. Guilliams, N. Petersen, N. Hirsch, S. Kawashima, and H. Ohshima. Physical training for long-duration spaceflight. *Aerospace Medicine and Human Performance*, 86(12):A14–A23, 2015.

[52] National Aeronautics and Space Administration. Effects of hypogravity on skeletal muscle mass and countermeasure strategies during spaceflight. *Communications Biology*, 6, 2023. Article 467.

[53] J. Ramirez, A. Periyakaruppan, S. Sarkar, G. T. Ramesh, and S. C. Sharma. Effect of simulated microgravity on the activity of regulatory enzymes of glycolysis and gluconeogenesis in mice liver. *Microgravity Science and Technology*, 26(5):303–309, 2014.

[54] G. Biolo, M. Heer, M. Narici, and F. Strollo. Microgravity as a model of ageing. *Current Opinion in Clinical Nutrition and Metabolic Care*, 11(1):31–40, 2008.

[55] A. Bergouignan, F. Rudwill, C. Simon, and S. Blanc. Physical inactivity as the culprit of metabolic inflexibility: Evidence from bed-rest studies. *Journal of Applied Physiology*, 111(4):1201–1210, 2011.

[56] W. A. da Silveira, H. Fazelinia, S. B. Rosenthal, E. C. Laiakis, M. S. Kim, C. Meydan, Y. H. Kidane, K. S. Rathi, S. M. Smith, B. Stear, and E. C. da Silveira. Comprehensive multi-omics analysis reveals mitochondrial stress as a central biological hub for spaceflight impact. *Cell*, 183(5):1185–1201, 2020.

[57] E. Afshinnekoo, R. T. Scott, M. J. MacKay, E. Pariset, E. Cekanaviciute, R. Barker, S. Gilroy, D. Hassane, S. M. Smith, S. R. Zwart, E. Christopher, and Mason. Fundamental biological features of spaceflight: Advancing the field to enable deep-space exploration. *Cell*, 183(5):1162–1184, 2020.

[58] A. Bergouignan, I. Momken, D. A. Schoeller, S. Normand, A. Zahariev, B. Lescure, C. Simon, S. Blanc, and Stéphane Blanc. Regulation of energy balance during long-term physical inactivity induced by bed rest with and without exercise training. *Journal of Clinical Endocrinology Metabolism*, 101(3):1045–1053, 2016.

[59] J. A. Loehr, S. M. C. Lee, K. L. English, J. Sibonga, S. M. Smith, B. A. Spiering, and R. D. Hagan. Musculoskeletal adaptations to training with the advanced resistive exercise device. *Medicine Science in Sports Exercise*, 47(1):146–156, 2015.

[60] J. P. R. Scott, T. Weber, and D. A. Green. Introduction to the special issue on the physiology of exercise in space. *Journal of Applied Physiology*, 126(5):1367–1369, 2019.

[61] S. M. Smith, S. R. Zwart, M. Heer, E. K. Hudson, L. Shackelford, and J. L. Morgan. Nutritional biochemistry of spaceflight. *Advances in Clinical Chemistry*, 68:1–32, 2014.

[62] H. W. Lane, D. L. Feeback, and S. M. Smith. Nutrition in space: Lessons from the past applied to the future. *Advances in Nutrition*, 11 (6):1466–1474, 2020.

[63] M. Heer and W. H. Paloski. Nutrition and fluid balance in microgravity. *Gravitational and Space Biology Bulletin*, 19(2):3–18, 2006.

[64] T. P. Stein. The relationship between dietary intake, exercise, energy balance, and the spacecraft environment. *Pflügers Archiv*, 441 (2-3):R21–R31, 2000.

[65] *Human integration design handbook (HIDH)*. NASA, 2017.

[66] S. M. Smith, M. Heer, L. C. Shackelford, J. D. Sibonga, L. Ploutz-Snyder, and S. R. Zwart. Benefits for bone from resistance exercise and nutrition in long-duration spaceflight. *Journal of Bone and Mineral Research*, 27(9):1896–1906, 2012.

[67] S. M. Smith, S. R. Zwart, M. Heer, E. K. Hudson, L. Shackelford, and J. L. Morgan. Nutritional status and human health during spaceflight. *Nutrition*, 70:110617, 2020.

[68] J. Rittweger, H. M. Frost, H. Schiessl, H. Ohshima, B. Alkner, P. Tesch, and D. Felsenberg. Muscle atrophy and bone loss in space: The role of nutrition and exercise. *NPJ Microgravity*, 4(10):5, 2018.

[69] S. M. C. Lee, A. H. Feiveson, and S. H. Platts. Physiological adaptation to long-duration spaceflight. 2022.

[70] E. Le Roux, A. Zahariev, I. Chery, D. A. Schoeller, P. Bourdier, A. Maillet, and A. Bergouignan. Substrate metabolism in male astronauts onboard the International Space Station: The ENERGY study. *NPJ Microgravity*, 10:39, 2024.

[71] R. L. Hughson, A. Helm, M. Durante, and J. S. McPhee. Oxidative stress and cardiovascular regulation during long-duration spaceflights. *Aging (Albany, NY)*, 8(11):2825–2836, 2016.

[72] M. Czupalla, G. Horneck, and H. J. Blome. The effect of microgravity on human physiology. *Acta Astronautica*, 98:1–9, 2014.

[73] T. P. Stein. Weight, muscle, and bone loss during space flight: Another perspective. *European Journal of Applied Physiology*, 113(9): 2171–2181, 2013.