

The Pancreas and Islets of Langerhans in Spaceflight

—Current Evidence, Knowledge Gaps, and an Experimental Roadmap for Variable-Gravity Research

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Abstract

Long-duration human spaceflight produces a metabolic environment characterised by skeletal-muscle unloading, altered energy balance, circadian disruption, stress signalling, and changes in liver, adipose, vascular, immune, and gastrointestinal physiology. These effects create a plausible demand for pancreatic compensation, yet the pancreas is one of the least directly studied organs in astronauts. This structured narrative review evaluates evidence concerning the endocrine and exocrine pancreas, with emphasis on the islets of Langerhans. Search strategy, inclusion and exclusion criteria, and an explicit five-tier scheme for classifying exposure type are stated in Section 2, and quantitative estimates are reported wherever the accessible record contains them. Human studies support the occurrence of inflight insulin resistance, but rest predominantly on a single fasting-derived index: in eight astronauts on approximately six-month missions, fasting glucose was essentially unchanged while fasting insulin rose by roughly half, so that the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) increased by close to sixty per cent. No human study has quantified beta-cell reserve, glucagon counter-regulation, pancreatic perfusion, morphology, fat content, or digestive function. Rodent spaceflight studies provide limited histological and molecular evidence of pancreatic remodelling, including islet-size differences that track mean body weight and are confounded by nutrition, housing, and hypokinesia, alongside organ-wide microRNA evidence implicating extracellular-matrix and developmental pathways in a fat-liver-pancreas axis, reported by its authors as a largely age-independent adaptation. In contrast, rotating culture systems and short real-microgravity experiments with isolated islets sometimes preserve viability, support three-dimensional organisation, improve insulin release, or induce delayed beta-cell cycle entry. These observations are

not necessarily contradictory: low-shear culture may benefit isolated islets while systemic insulin resistance is expected to increase secretory demand on the intact pancreas. That second limb, however, remains a proposed mechanism rather than a measured astronaut response. The field is limited by sparse human phenotyping, small animal cohorts, platform confounding, weak separation of gravity from fluid-mechanical effects, incomplete quantitative reporting, and near-total neglect of alpha, delta, endothelial, neural, immune, and exocrine compartments. A tiered research programme is proposed, centred on counterbalanced variable-gravity parabolic flights using perfused human islet-on-chip systems, followed by sounding-rocket and orbital centrifuge experiments, multi-organ metabolic chips, and standardised longitudinal astronaut testing.

Keywords

Spaceflight, Microgravity, Pancreas, Islets of Langerhans, Beta-Cell, Insulin Resistance, HOMA-IR, Parabolic Flight, Partial Gravity, Diabetes, Organ-on-Chip

1. Introduction

The pancreas occupies an unusual position in space medicine. It is a dual endocrine-exocrine organ, richly vascularised and tightly coupled to liver, muscle, adipose tissue, gut, autonomic signalling, and the circadian system. The islets of Langerhans regulate glucose homeostasis through coordinated secretion of insulin, glucagon, somatostatin, pancreatic polypeptide, and amylin. Consequently, even modest changes in insulin sensitivity, nutrient delivery, blood flow, cell-cell communication, or mechanical environment could alter pancreatic workload and metabolic resilience during flight.

The metabolic phenotype of spaceflight is not equivalent to diabetes, but several features overlap with pathways that precede or accompany type 2 diabetes: physical inactivity, muscle loss, altered mitochondrial metabolism, insulin resistance, dysregulated lipid handling, low-grade inflammation, sleep and circadian disruption, and changes in gut microbial ecology. Reviews of flight and analog data have therefore raised the concern that the pancreas may be required to compensate for reduced peripheral insulin sensitivity [1] [2]. The central clinical question is not simply whether glucose increases. It is whether beta-cells can increase secretion sufficiently, preserve pulsatility and processing quality, and maintain reserve throughout months or years of exposure. It should be stated at the outset that this compensation has been inferred from systemic indices and terrestrial physiology; it has not been measured in the astronaut pancreas.

The distinction matters because normal glucose can coexist with substantial compensatory hyperinsulinaemia. Conversely, a low insulin concentration can represent improved sensitivity, impaired beta-cell secretion, altered hepatic insu-

lin extraction, changes in energy intake, or sampling at a different phase of a dynamic adaptation. Measurements of fasting glucose or insulin alone therefore provide only a shadow of the underlying pancreatic physiology, and fasting-derived indices inherit that ambiguity.

The literature also contains an apparent paradox. Whole-body studies suggest that spaceflight can promote insulin resistance, whereas several isolated-islet studies conducted in rotating vessels or brief real microgravity report improved survival, three-dimensional aggregation, insulin secretion, or beta-cell cycle entry [3]-[7]. A major aim of this review is to show that these findings are compatible once systemic metabolic demand is separated from the local fluid-mechanical and structural environment of cultured islets, and to specify the experiments that would test that reconciliation rather than assume it.

2. Review Approach

2.1. Search Strategy

A structured narrative search was conducted using PubMed and PubMed Central records, primary publisher pages, space-life-science reviews, NASA GeneLab and Open Science Data Repository descriptors, and citation chaining from retrieved articles and reviews. Searches combined terms related to spaceflight, astronaut, cosmonaut, microgravity, partial gravity, parabolic flight, sounding rocket, hindlimb unloading, bed rest, dry immersion, pancreas, pancreatic islet, beta-cell, alpha-cell, insulin secretion, C-peptide, glucagon, insulin resistance, exocrine pancreas, organ-on-chip, clinostat, random positioning machine, and rotating-wall-vessel culture. Records published or indexed through 21 July 2026 were considered. Direct flight evidence was prioritised over analog and simulated-microgravity studies, and primary research was prioritised over reviews where the primary report was accessible.

2.2. Classification of Evidence by Exposure

Studies of gravity biology are frequently compared as though a clinostat, a bed-rest campaign, a parabola, and a six-month mission were graded approximations of one exposure. They are not. The scheme set out in Table 1 was applied to every included record, and classification was made by exposure alone, independently of the direction or strength of the reported result. A single study may contribute at more than one tier; the MASER 15 experiment, for instance, contributes at Tier 2 for its flight samples and at Tier 5 for its onboard 1-g centrifuge reference.

Table 1. Classification of included evidence by exposure tier.

Tier	Exposure class	Definition applied here	What it can and cannot support
Tier 1	Direct flight evidence, human	Measurements in astronauts or cosmonauts before, during, or after orbital flight.	Establishes that a systemic change occurs in humans; in current form cannot localise the change to the pancreas.

Continued

Tier 2	Direct flight evidence, animal or biological payload	Orbital or suborbital flight of animals, tissues, or cells experiencing real reduced gravity, with or without an onboard 1-g control.	Permits organ- and cell-level measurement under real flight conditions; confounded by habitat, launch loads, radiation, and small cohorts.
Tier 3	Terrestrial unloading analog	Bed rest, head-down tilt, dry immersion, hindlimb unloading, confinement. Gravitational acceleration is unchanged; mechanical loading is not.	Isolates deconditioning and unloading; says nothing about gravity as a physical variable.
Tier 4	Simulated microgravity in vitro	Rotating-wall vessel, rotary cell-culture system, clinostat, random-positioning machine. Sustained sedimentation is reduced; gravitational acceleration is unchanged.	Supports mechanobiology and tissue-engineering claims; cannot separate altered force direction from altered shear, convection, and mass transport.
Tier 5	Variable or partial gravity	Parabolic flight, sounding-rocket profiles, in-flight or ground centrifugation delivering defined g levels between 0 and above 1 g.	The only class that can establish a gravity dose-response; limited by exposure duration and transition artefacts.

Tier assignment is recorded for every study cited in **Table 2**. Terms such as “microgravity effect” are avoided for Tier 3 and Tier 4 evidence throughout this review.

2.3. Inclusion and Exclusion Criteria

Records were included when all of the following applied:

- The record reported primary data, or was a review used only for context, terminology, or citation chaining and identified as such in the text.
- The exposure was spaceflight, real microgravity, partial or variable gravity, hypergravity, or an accepted terrestrial unloading analog or simulated-microgravity platform.
- The outcome concerned pancreatic endocrine or exocrine structure, function, or molecular state; islet or beta-cell biology; or systemic glucose-insulin regulation in a population or preparation exposed as above.
- Full text or a structured abstract with retrievable design information was available in English, or in English translation.

Methodological and hardware papers without pancreatic content were included only in Section 8, and only as feasibility evidence for variable-gravity experimentation; they contribute no biological conclusions about the pancreas.

Records were excluded when any of the following applied:

- Glucose or insulin physiology was studied with no altered-gravity or unloading exposure, except where a terrestrial concept (for example the disposition index or HOMA-IR) required definition.
- The report was a conference abstract, poster, or publisher summary from which neither design nor direction of effect could be determined.
- Simulated-microgravity work concerned non-pancreatic tissue, except where cited specifically to characterise platform artefacts such as shear, sedimenta-

tion, or mass transport.

- The record duplicated a cohort or dataset already included, in which case the most complete primary report was retained.

Handling of animal studies, simulated-microgravity platforms, and inaccessible reports. Animal spaceflight studies were retained but were not treated as interchangeable with human evidence; each is reported with cohort size, control structure, and habitat conditions, because rodent flight cohorts are small and confounded by housing and nutrition. Simulated-microgravity studies were retained as mechanistic and tissue-engineering evidence only, and are never cited as evidence about gravity per se, since these platforms alter fluid mechanics as well as the direction of sustained acceleration. Reports available only through abstracts, review summaries, or publisher pages were retained where the design and direction of effect were clear, are explicitly flagged as abstract-level in the text and in **Table 2**, and no effect size was extracted from them. Records that could not be retrieved at all were not cited, and absence statements in this review refer to studies identified by this search rather than proof that no unpublished or inaccessible investigation exists.

Table 2. Representative evidence base, quantitative content, and interpretive limits.

Platform	Tier	Exposure/model	Main observation	Quantitative content of the accessible record	Principal limitation	Ref.
Human ISS	Tier 1	8 astronauts (4 male, 4 female); approximately 6 months	Increased fasting insulin resistance inflight; more favourable values in female crew	HOMA-IR was the index used. Fasting glucose essentially unchanged; fasting insulin approximately +50%; HOMA-IR approximately +60% vs preflight. n = 8. Confidence intervals and per-subject trajectories not reported in accessible record.	Fasting index only; no clamp, C-peptide modelling, imaging, glucagon, or exocrine measurement; small cohort; limited inflight sampling points	[8]
Historical human flight	Tier 1	Short-duration missions; heterogeneous protocols	Variable glucose, insulin, C-peptide, and tolerance findings	No consistent direction; effect sizes not extractable and not pooled here	Small cohorts, inconsistent timing, assay and mission conditions	[1]
Bion-M1 mice	Tier 2	30-day orbital flight; pancreatic histology and immunohistochemistry	Shift toward larger islets in flight animals; mean islet size tracks mean body weight	Approximately 5 animals per group (flight, synchronous, vivarium). Correlation described by authors as strong; coefficient, CI, and p-value not reported in accessible record; correlation computed on group means.	Nutrition, hypokinesia, habitat, cohort attrition	[10]
Mouse/human multi-omics	Tier 1 and 2	Multiple missions and tissues	Insulin-signalling and resistance-related pathway changes, especially liver and muscle	Reported statistics are pathway-enrichment values, not physiological effect magnitudes; no pancreatic effect size available	Human pancreas unavailable; pathway inference is not direct physiology	[9]

Continued

Mouse multi-organ miRNA	Tier 2	686 small-RNA samples, 13 organs, ISS exposure	Fat-liver-pancreas remodelling; persistent pancreatic miRNA programmes reported by the authors as age-independent	Per-miRNA fold changes and adjusted p-values available in source; not restated here. MIR-8, MIR-15, MIR-154 families implicated.	Whole-pancreas signal cannot resolve endocrine cell types; female mice only	[11]
Rotating-vessel islets	Tier 4	Isolated islets; simulated microgravity, some with scaffold	Improved graft performance, viability, or insulin secretion in several studies	Magnitudes reported per study on non-comparable metrics; no common outcome definition, so no pooled estimate is derivable	Sedimentation, shear, oxygen, and transport effects are inseparable; not evidence about gravity	[3]-[5]
MIN6 clinostat culture	Tier 4	Mouse insulinoma spheroids	Efficient three-dimensional spheroid generation	Yield and size distributions reported; no functional benchmark against primary human islets	Tumour line; lacks native multicellular human-islet architecture	[6]
MASER 15	Tier 2 and 5	Mouse islets; approximately 6 min real microgravity with onboard 1-g centrifuge control	Survival, and delayed increase in beta-cell cycle entry in 3D-printed scaffolds; scaffold prevented islet fusion	EdU and Ki67 labelling in insulin-positive cells; increase vs equivalent ground control significant at $p < 0.05$, appearing about 2 - 3 weeks after exposure. Effect sizes shown graphically; no beta-cell mass and no secretion data.	Acute exposure; proliferation marker only; free-floating arm unquantifiable due to fusion; no intact-organ or systemic metabolic context	[7]

Tier assignments follow Section 2.2. “Not reported in accessible record” means the value was absent from the full text, abstract, or publisher summary retrievable for this review; it does not imply the underlying analysis was not performed.

Because the literature is sparse, heterogeneous, and dominated by small exploratory studies, formal meta-analysis was not appropriate. The review instead evaluates evidence by biological level: human systemic physiology, whole-organ animal studies, isolated islets and beta-cell models, and enabling variable-gravity methods.

2.4. Quantitative Reporting

Where the accessible record reports effect magnitudes, group sizes, correlation coefficients, or inferential statistics, these are stated in the text and in **Table 2**. Where a source reported only a qualitative direction, or where the quantitative result exists only in figures or in an inaccessible full text, **Table 2** states “not reported in accessible record” rather than substituting an emphatic adjective. Several statements that appeared in earlier drafts of this review as “increased” or “strong” rest on descriptive, unstandardised comparisons in cohorts of five to eight subjects; readers should treat them as directional observations, not as estimates of effect size. No pooled estimates, confidence intervals, or risk-of-bias scores are computed, and none should be inferred from the tables.

3. Human Evidence: Systemic Dysregulation without Direct Pancreatic Phenotyping

The most important human observation is an increase in a fasting-derived index of insulin resistance during six-month International Space Station missions. Hughson and colleagues studied eight astronauts, four male and four female, with blood sampling before, during, and after flight, in a protocol designed primarily around vascular adaptation [8]. The insulin-resistance measure was the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR), computed from paired fasting glucose and fasting insulin concentrations. The inflight trajectory was as follows: fasting glucose did not differ appreciably from preflight values, whereas fasting insulin was elevated by approximately 50 per cent, so that HOMA-IR rose by close to 60 per cent relative to the preflight baseline [8]. The response was not uniform by sex; female crew members showed more favourable HOMA-IR values than male crew members, a difference subsequently emphasised in integrative analyses of the same and related datasets [9].

The clinical meaning of that signal should be stated carefully, and its limits are as instructive as its magnitude. First, HOMA-IR is a fasting, model-derived index. It reflects predominantly hepatic insulin sensitivity and the basal relationship between glucose and insulin; it is not a measure of skeletal-muscle glucose disposal, and it is not a measure of beta-cell function. A 60 per cent rise in HOMA-IR in eight subjects is a meaningful physiological signal in a healthy, highly screened population, but it is a group-level change in a small cohort, computed from an index whose between-subject variability on Earth is substantial. Second, the index cannot distinguish among the several states that can raise it: reduced hepatic insulin sensitivity, reduced hepatic insulin clearance, increased basal secretion, or altered fasting behaviour and energy balance in flight. Third, sampling was at a limited number of inflight time points, so the record describes a change of state rather than a resolved time course; the onset, plateau, or drift of insulin resistance across six months cannot be recovered from it. Fourth, the study included no hyperinsulinaemic-euglycaemic clamp, no dynamic C-peptide modelling, no pancreatic imaging, and no direct assessment of glucagon or incretin physiology. It therefore demonstrates a systemic metabolic signal but cannot specify whether beta-cells compensated appropriately, excessively, or insufficiently.

Earlier short-duration flight studies summarised by Tobin and colleagues yielded variable glucose, insulin, and C-peptide results, and no consistent effect estimate can be derived from them [1]. Differences in mission duration, diet, stress, exercise, assay timing, landing-associated catecholamine responses, and sample handling make historical comparisons difficult. The inconsistency itself is informative: static biochemical snapshots are poorly suited to a rapidly adapting system with substantial between-person heterogeneity.

Recent multi-omics analyses strengthen the case that insulin signalling is altered across spaceflight. Mathyk and colleagues integrated rodent and human datasets and identified changes in insulin- and estrogen-associated gene pro-

grammes, with prominent effects in murine liver, including signatures consistent with hepatic insulin resistance and steatosis, and with insulin-resistance-related pathways detectable in accessible human tissues [9]. These data support a network-level disturbance rather than an isolated pancreatic lesion. The effect estimates in such work are pathway-enrichment statistics rather than physiological magnitudes, and they should not be read as quantifying an insulin-secretory change. The human samples were also minimally invasive tissues and body fluids, not pancreatic tissue. They cannot determine islet-cell composition, beta-cell stress, pancreatic fat, microvascular remodelling, or exocrine injury.

No human astronaut study identified in this review directly measured pancreatic volume, fat fraction, perfusion, fibrosis, oedema, exocrine reserve, islet mass, beta-cell responsivity, alpha-cell counter-regulation, proinsulin processing, or pulsatile insulin secretion. This is the field's largest blind spot. Current evidence can say that the metabolic load presented to the pancreas changes. It cannot yet say how the organ meets that load.

4. Whole-Organ and Animal Evidence

4.1. Histology after Bion-M1

The principal whole-organ histological study examined pancreases from male C57BL/6N mice after approximately 30 days aboard the Bion-M1 biosatellite [10]. Flight animals were compared with a synchronous ground-control group housed in spacecraft-like conditions and with a vivarium control group, with roughly five animals contributing to each analysed group. Morphometric and double-immunohistochemical analysis of insulin- and glucagon-stained sections identified a shift toward larger islets in the flight group. Mean body weight was also higher in flight animals than in either control group, and the authors reported a strong correlation between mean islet size and mean body weight across all groups; a correlation coefficient, confidence interval, and p-value for that relationship are not reported in the record accessible for this review, and the relationship was estimated on group means rather than on individual animals. The authors accordingly emphasised hypokinesia and nutrition as major contributors to endocrine-pancreas alterations rather than attributing the findings exclusively to reduced gravity.

This study is important precisely because it demonstrates the difficulty of causal inference. Rodent spacecraft experiments combine altered gravity with specialised housing, restricted movement, food-delivery differences, elevated carbon dioxide, vibration, launch and re-entry loads, stress, and survival bias. In Bion-M1, equipment and husbandry problems also affected the available animal cohort, and the resulting group sizes leave the analysis with very little power to separate these influences. Islet enlargement could reflect adaptive beta-cell growth, changes in individual cell size, altered islet size distribution, nutritional state, or sampling effects in a limited number of sections. Without stereological beta-cell mass, proliferation and apoptosis markers, dynamic secretion testing, and matched energy

balance, morphology alone cannot establish functional compensation.

4.2. Multi-Organ Molecular Studies

The expanding NASA GeneLab and Space Omics ecosystem has shifted attention from single organs to coordinated tissue adaptation. In mice flown to the ISS, transcriptomic analyses found the strongest insulin-related changes in liver and muscle, including pathway signatures consistent with hepatic insulin resistance and altered lipid metabolism [9]. This is consistent with a model in which the pancreas is exposed to changing demand generated by peripheral tissues, though it does not itself measure the pancreatic response.

A 2026 analysis of 686 small-RNA samples from female mice across 13 organs provides the most detailed recent molecular evidence involving the pancreas [11]. The study identified systemic remodelling along a fat-liver-pancreas axis and highlighted extracellular-matrix, developmental, membrane, and DNA-damage-associated pathways, with MIR-8, MIR-15, and MIR-154 family involvement among the pancreatic signatures. An important point of interpretation must be stated plainly, because an earlier draft of this review reversed it: the authors report tissue adaptation to spaceflight as age-independent, meaning that the dominant microRNA remodelling programmes were shared across the ages studied rather than being modified by age. The pancreatic response should therefore be described as persistent and largely age-invariant in that dataset. Age remains a plausible modifier of pancreatic adaptation on physiological grounds, but this study is evidence against a strong age dependence in the miRNA response, not evidence for one. Per-miRNA fold changes and adjusted p-values are given in the source; they are not reproduced here, and no summary effect estimate is offered.

The strength of this work is its cross-organ design and comparison with habitat controls. Its main pancreatic limitation is tissue resolution. Whole-pancreas RNA is dominated by exocrine tissue, while endocrine islets form a small fraction of organ volume. A pancreatic signal may therefore arise from acinar, ductal, stromal, vascular, immune, neural, or endocrine compartments. Bulk or small-RNA profiles cannot identify whether beta-cells are proliferating, dedifferentiating, increasing secretory machinery, or experiencing endoplasmic-reticulum stress. Single-nucleus and spatial approaches are required.

5. Isolated Islets and Beta-Cell Models

5.1. Rotating Vessels and Simulated Microgravity

Rotating-wall vessels, rotary cell-culture systems, clinostats, and random-positioning devices are widely described as simulated-microgravity platforms and are classified here as Tier 4. They reduce sustained sedimentation and can create low-shear suspension culture, but they also change convection, oxygenation, nutrient transport, waste removal, aggregate collision, and scaffold interaction. Their biological effects must therefore be interpreted as a compound of altered force direction and altered fluid mechanics, and not as effects of gravity.

Rutzky and colleagues reported that rotating-vessel culture reduced immunogenicity and improved the function and transplantation performance of pancreatic islets [3]. Song and colleagues subsequently observed improved survival and insulin-related measures in isolated rat beta-islet preparations under simulated microgravity [4]. In a later study, combining a polyglycolic-acid scaffold with simulated microgravity improved islet viability, preserved structure, and increased insulin content and glucose-responsive release compared with static or single-component culture conditions [5]. These findings indicate that low-shear three-dimensional culture can be useful for islet preservation and tissue engineering. Their reported magnitudes are not comparable across studies: outcome definitions, culture durations, species, and normalisation differ, and no common metric exists from which a pooled estimate could be derived.

A three-dimensional clinostat has also been used to generate large numbers of spheroids from the mouse insulinoma line MIN6 [6]. This is valuable as a manufacturing approach, but a tumour-derived beta-cell line does not reproduce native human islet architecture. Human islets contain intermingled endocrine cell types, endothelial and perivascular cells, macrophages, extracellular matrix, and neural inputs. Species differences are also substantial: rodent and human islets differ in cellular proportions and spatial organisation. Translation therefore requires primary human islets or stem-cell-derived islets benchmarked against primary tissue.

The major conceptual lesson is that an improved culture outcome does not imply that prolonged spaceflight is metabolically protective. *In vitro*, reduced sedimentation may enhance mass transport and prevent damaging attachment. *In vivo*, the same astronaut can experience hepatic and muscle insulin resistance that would be expected to raise beta-cell workload. The local islet environment and the whole-body metabolic environment are distinct experimental levels and are supported by different tiers of evidence.

5.2. Real Microgravity: The MASER 15 Islet Experiment

The strongest direct real-microgravity experiment on pancreatic islets used mouse islets during the MASER 15 sounding-rocket mission [7]. Samples experienced approximately six minutes of microgravity, while an onboard centrifuge maintained matched samples at 1 g; ground controls were run in parallel. Islets were flown free-floating and within three-dimensional printed scaffolds, alone and in co-culture with boundary-cap neural crest stem cells. The thymidine analogue EdU was introduced immediately before the microgravity phase, and cell-cycle entry was subsequently assessed by EdU incorporation and Ki67 immunolabelling in insulin-positive cells. Islets survived the flight. Free-floating islets fused, which prevented reliable per-islet quantification and limited the statistical analysis in that arm. In scaffold-supported preparations, which did not fuse, the proportion of labelled insulin-positive cells was greater in microgravity-exposed samples than in the equivalent ground-control groups, and this difference was reported as sta-

tistically significant at the conventional threshold; effect magnitudes and confidence intervals are presented graphically in the source and are not restated here as point estimates.

A striking feature was the delayed appearance of the proliferative signal: increased labelling in scaffold-supported islets became evident only after roughly two to three weeks of postflight culture rather than immediately after exposure [7]. This suggests that altered gravity can initiate a biological memory rather than only an immediate signalling event.

Three quantities are frequently conflated in discussions of this result, and they should be kept apart. Beta-cell proliferation, as measured here, is the fraction of insulin-positive cells that entered the cell cycle or synthesised DNA during a labelling window. Beta-cell mass is the total quantity of beta-cells in a preparation or organ, which is determined not only by proliferation but by cell size, apoptosis, neogenesis, and dedifferentiation, and which requires stereological or total-insulin-content measurement to estimate. Functional reserve is the capacity of the tissue to increase insulin secretion when challenged, which requires dynamic glucose-stimulated secretion, C-peptide kinetics, or a secretion-sensitivity relationship such as the disposition index. MASER 15 measured the first. It did not measure the second: fusion of free-floating islets made denominators unreliable, and no total beta-cell quantification was reported. It did not measure the third at all: no glucose-stimulated secretion, insulin content, or hormone-release data were obtained from the flown preparations. An increased labelling index is therefore evidence of a mechanosensitive, delayed cell-cycle response in mouse beta-cells. It is not evidence that islet mass increases in flight, and it is not evidence that secretory reserve is preserved or enhanced. In several disease contexts, proliferative signalling and functional competence dissociate, and proliferation without preserved identity, glucose responsiveness, and genomic stability would not be a desirable outcome.

The experiment also cannot establish the response to chronic exposure, vascular supply, systemic insulin resistance, radiation, or intact-organ innervation. Six minutes of microgravity during a sounding-rocket profile is an acute mechanobiological perturbation, not a model of a six-month mission.

Table 2 collects the studies discussed in Sections 3 to 5, together with their exposure tier, the quantitative content available in the accessible record, and the principal limitation that bounds their interpretation.

6. Integrated Interpretation: A Proposed Systemic-Islet Model

The literature can be reconciled by a two-level model, which is offered here as a synthesis hypothesis rather than as a description of an observed astronaut phenotype. The model has two limbs, and they differ sharply in evidential support.

The first limb concerns the organism. Unloading is expected to reduce skeletal-muscle glucose disposal and to alter liver, adipose, endocrine, immune, and circa-

dian regulation. This limb is well supported terrestrially: bed rest and other unloading analogs reliably produce insulin resistance, and Tier 1 flight data show a rise in a fasting insulin-resistance index [8] [12]. Even here, the specific claim that muscle glucose disposal falls during flight is an inference from analog physiology; muscle-specific glucose uptake has not been measured in orbit.

The second limb concerns the pancreas. If sensitivity falls and glycaemia is defended, the organ must secrete more insulin for a given glucose exposure. This is a physiological expectation, not an established astronaut finding. No study identified in this review has measured insulin secretion rate, C-peptide kinetics, proinsulin processing, secretory pulsatility, or a disposition index in flight. The elevated fasting insulin observed by Hughson and colleagues is consistent with increased basal secretion, but it is equally consistent with reduced hepatic insulin clearance, and the study design cannot distinguish these [8]. Statements that the astronaut pancreas “is asked to secrete more insulin” should therefore be read throughout this review as a proposed mechanism awaiting direct measurement.

At the local tissue level, an isolated islet in a low-shear rotating environment may receive more uniform nutrients, experience less damaging sedimentation, and form a supportive three-dimensional structure. Improved local viability in Tier 4 preparations can therefore coexist with increased systemic secretory demand in a Tier 1 organism, without contradiction and without either observation validating the other.

The model generates three testable trajectories. In a successful compensation trajectory, beta-cell responsivity rises enough to preserve glucose regulation without excessive proinsulin release or loss of pulsatility. In an insufficient compensation trajectory, insulin sensitivity falls faster than secretion can rise, causing postprandial hyperglycaemia. In a maladaptive compensation trajectory, sustained hypersecretion initially preserves glucose but promotes endoplasmic-reticulum stress, altered identity, impaired processing, or loss of reserve. Current astronaut datasets cannot distinguish these trajectories, and a fasting index cannot in principle distinguish them.

The relevant clinical quantity is therefore not fasting glucose, and not HOMA-IR alone, but the relationship between insulin sensitivity and insulin secretion, often conceptualised as a disposition index. A spaceflight protocol should estimate both sides of that relationship. C-peptide is especially important because it permits modelling of pancreatic secretion separately from hepatic insulin extraction, which is precisely the ambiguity that fasting insulin cannot resolve. Glucagon, somatostatin, proinsulin, amylin, and incretin measurements are needed to capture the wider islet network.

7. Knowledge Gaps

The evidence base is sufficiently mature to define the questions, but not to answer them. The most consequential gaps are summarised in [Table 3](#).

Table 3. Principal knowledge gaps and priority responses.

Gap	Why it matters	Priority response
Direct human organ phenotype	No inflight or longitudinal measurement of pancreatic morphology, fat, perfusion, ductal state, or exocrine reserve.	Add standardised pancreatic MRI before and after flight; develop inflight-compatible ultrasound or magnetic-resonance opportunities where feasible.
Beta-cell reserve	Fasting glucose, fasting insulin, and HOMA-IR do not separate sensitivity from secretion, or secretion from hepatic clearance.	Use standardised mixed-meal or oral-glucose tests with glucose, insulin, C-peptide, proinsulin, glucagon, amylin, and incretins; model the disposition index.
Cell-type resolution	Alpha, delta, PP, endothelial, immune, stromal, and neural responses are largely unknown.	Apply single-nucleus RNA sequencing, spatial transcriptomics, multiplex imaging, and functional hormone profiling.
Exocrine pancreas	Acinar and ductal adaptation, digestive enzymes, and nutrient absorption are rarely evaluated.	Measure faecal elastase, serum enzymes, digestive symptoms, stool energy loss, and exocrine histology in animal missions.
Gravity dose-response	Most experiments contrast nominal 1 g with microgravity, and Tier 4 platforms are frequently read as though they were Tier 5.	Test lunar, Martian, intermediate, microgravity, and hypergravity levels in randomised sequences with measured local acceleration.
Platform confounding	Rotation changes shear and mass transport; spaceflight adds radiation, CO ₂ , vibration, diet, and housing.	Use matched hardware, onboard 1-g centrifuges, measured local acceleration, computational fluid dynamics, and factorial controls.
Quantitative reporting	Several pivotal observations are available only as directional statements, group-mean correlations, or figures, which prevents synthesis and power calculation.	Report effect sizes, dispersion, and individual data; deposit source data; pre-register outcome definitions so future reviews can pool results.
Duration and memory	Acute signalling, chronic adaptation, recovery, and re-exposure are not linked, and MASER 15 shows effects can appear weeks late.	Sample minutes, hours, days, weeks, and postflight recovery across parabolic, rocket, orbital, and analog platforms.
Population heterogeneity	Sex, age, metabolic history, genetics, and donor variability are poorly powered; the clearest human sex signal rests on four subjects per group.	Pre-specify stratification, use repeated-measures designs, and create shared biobanks of human donor islets and stem-cell lines.

8. Experimental Roadmap

8.1. Variable-Gravity Parabolic Flight as a Causal Dose-Response Experiment

Parabolic flight is often treated as a brief imitation of orbital microgravity. Its greater value is different: it is the most accessible Tier 5 platform, delivering rapidly repeated and programmable gravity transitions, including lunar and Martian partial gravity, while supporting real-time microscopy and controlled fluidics. Recent experiments have maintained flow chambers at 0.16 g and 0.38 g during European Space Agency parabolic campaigns [13], and live calcium imaging in microfluidic chips has been performed during changing gravity [14]. These capabilities make a variable-gravity islet experiment technically plausible.

The central payload should be a closed, perfused human islet-on-chip system. It should include primary donor islets and stem-cell-derived islets; an endothelial or vascular compartment; standardised extracellular matrix; controlled glucose and amino-acid delivery; and continuous measurement of temperature, oxygen, pressure, flow, vibration, and three-axis acceleration. An onboard centrifuge or mechanically matched inflight 1-g reference is essential. Static ground controls alone cannot separate gravity from launch, vibration, or hardware effects.

Rather than repeating only near-zero-g parabolas, the study should use a randomised gravity staircase. Candidate levels are 1.0 g, 0.75 g, 0.50 g, 0.38 g, 0.16 g, near 0 g, and approximately 1.8 g. Lunar and Martian phases of roughly 24 and 33 seconds respectively have already been implemented in parabolic-flight cell experiments [13]. Order should be counterbalanced across flight days to distinguish gravity level from fatigue, time, repeated exposure, and carryover.

The analysis should move beyond condition averages. The measured acceleration trace at the sample should be treated as the exposure variable. Distributed-lag mixed-effects models can estimate response latency, amplitude, recovery, and cumulative effects. Nonlinear splines can identify thresholds. Separate terms should represent absolute g, rate of change in g, jerk, preceding hypergravity, vibration, flow, oxygen, and donor. Ascending and descending sequences should be compared for hysteresis. Effect sizes with confidence intervals should be the primary reported quantity, and the analysis plan and outcome definitions should be pre-registered. The output would be a gravito-metabolic transfer function describing how islet signalling changes as gravity changes.

8.2. Measurements during Each Parabola

- Fast signalling: beta-cell calcium dynamics, membrane potential, cyclic AMP, ATP/ADP ratio, mitochondrial potential, NAD(P)H autofluorescence, and cytoskeletal tension.
- Secretion: phase-resolved collection of insulin, C-peptide, glucagon, somatostatin, amylin, proinsulin, lactate, and inflammatory mediators.
- Transport controls: computational fluid-dynamic modelling and tracer particles to quantify sedimentation, convection, shear, and boundary-layer behavior.

- our at every g level.
- Structural behaviour: islet displacement, deformation, fusion, endothelial adhesion, and matrix strain, recorded with synchronised imaging.
 - Postflight memory: functional and molecular follow-up at 2 hours, 24 hours, 7 days, and 14 days, and, given the MASER 15 latency, at 21 days, including proliferation, apoptosis, senescence, DNA damage, chromatin accessibility, single-cell transcriptomics, and paired glucose-stimulated secretion so that cycle entry and functional competence are measured in the same preparations.

8.3. A Recommended Parabolic-Flight Design

Table 4 sets out a design that satisfies the requirements of Sections 8.1 and 8.2 within the constraints of a standard parabolic-flight campaign.

Table 4. Recommended design for a variable-gravity parabolic-flight islet experiment.

Design element	Recommended specification
Biological material	Primary human islets from multiple donors plus standardised stem-cell-derived islets; optional rodent bridge cohort for continuity with existing flight data.
Hardware	Perfused multi-channel islet chip with endothelial compartment, optical window, local accelerometer, oxygen sensor, and automatic fraction collection.
Gravity sequence	Randomised blocks spanning 1.0, 0.75, 0.50, 0.38, 0.16, near 0, and hypergravity; reverse-order blocks on another flight day.
Control strategy	Onboard 1-g centrifuge or matched inflight 1-g hardware; ground hardware control; sham flow and fixed-sample controls.
Primary endpoint	Change in glucose-stimulated calcium synchronisation and insulin/C-peptide secretion as a function of measured g.
Secondary endpoints	Glucagon and somatostatin response, mitochondrial state, oxygen consumption, islet deformation, endothelial behaviour, and delayed proliferation paired with delayed secretory function.
Statistical model	Hierarchical distributed-lag model with donor random effects; nonlinear g-response; carryover, hypergravity, vibration, shear, and time covariates. Pre-registered; effect sizes and intervals reported for all endpoints.
Decision criterion	Identify reproducible gravity thresholds or transition-sensitive responses, with quantified magnitude, that justify longer exposure on sounding-rocket or orbital platforms.

8.4. Platform Ladder: From Seconds to Months

Parabolic flights should not be expected to answer chronic adaptation. Their role is to identify rapid gravity-sensitive pathways, thresholds, and analytical signatures. Sounding rockets can then test whether responses persist across several minutes and whether acute exposure creates delayed biological memory, as sug-

gested by MASER 15 [7]. Orbital experiments with an onboard centrifuge can test weeks-to-months exposure while separating reduced gravity from the shared spacecraft environment.

A strong programme would use the same islet preparations, media, scaffolds, imaging probes, assay definitions, and data standards across platforms, so that results from different tiers can be placed on a single exposure axis rather than argued across incompatible ones. The result would be a continuous exposure-response ladder rather than separate experiments that cannot be compared. Samples should be banked for reanalysis as spatial and single-cell methods evolve.

8.5. Reconnecting the Islet to the Metabolic Network

An isolated islet cannot reproduce the demand created by unloaded muscle or an insulin-resistant liver. A high-priority orbital experiment should therefore connect human islets with liver, skeletal muscle, and adipose modules in a recirculating multi-organ chip. The design should compare normal and experimentally insulin-resistant peripheral tissues under reduced gravity and onboard 1 g. Separate radiation arms would determine whether low-dose chronic radiation interacts with altered gravity.

This system is the most direct available test of the second limb of the model proposed in Section 6, because it can distinguish a direct islet effect from demand-driven compensation. If low gravity directly supports islet survival while peripheral tissues become insulin resistant, secretion may initially increase while stress accumulates. Conversely, impaired beta-cell sensing could appear before systemic glucose failure. Multi-organ systems also permit testing of circulating mediators, including free fatty acids, cytokines, myokines, hepatokines, incretins, and microbiome-derived metabolites [15].

9. Human Astronaut Research Priorities

A feasible astronaut protocol does not require pancreatic biopsy or complex in-flight clamps. It requires coordinated, repeated measurements that estimate secretion and sensitivity together, and that move the human evidence base beyond the fasting index on which it currently rests.

1) Continuous glucose monitoring during standardised mission windows, paired with meal composition, activity, sleep, medication, stress, and gastrointestinal symptom data.

2) Standardised mixed-meal or oral-glucose challenges before flight, at several in-flight time points, immediately after landing, and during recovery, with glucose, insulin, C-peptide, proinsulin, glucagon, amylin, and incretin sampling. Repeated in-flight sampling is what converts a change of state into a trajectory.

3) Preflight and postflight pancreatic MRI for volume, fat fraction, tissue signal, and perfusion where protocol and hardware permit; ultrasound should be explored as a lower-resource in-flight adjunct rather than assumed to quantify islet mass.

4) Exocrine assessment using faecal elastase, serum amylase and lipase, nutrient-absorption measures, stool energy content, and structured digestive symptoms.

5) Model-based estimation of insulin sensitivity, beta-cell responsiveness, hepatic insulin extraction, and disposition index, reported as individual trajectories with uncertainty rather than group means alone.

6) Matched analog studies using bed rest or dry immersion with replicated diet, exercise, circadian schedule, and sampling, to isolate unloading from other mission factors and to place Tier 3 evidence alongside Tier 1 evidence on comparable measures.

The most useful operational endpoint would be a pancreatic reserve trajectory: the insulin secretory effort required to maintain a standardised glucose response, together with markers of processing stress such as the proinsulin-to-C-peptide ratio. A declining reserve trajectory could prompt individualised adjustments in exercise loading, meal timing, carbohydrate distribution, sleep scheduling, or pharmacologic evaluation before overt hyperglycaemia develops.

10. Implications for Astronaut Health

Near-term countermeasures should target the metabolic network rather than the pancreas in isolation, not least because the pancreatic limb of the model remains unmeasured. Resistance and aerobic exercise, adequate energy and protein intake, preservation of circadian regularity, and careful carbohydrate distribution are plausible first-line approaches. Ground analog work indicates that prolonged bed rest promotes insulin resistance and that exercise-based countermeasures may attenuate metabolic deterioration, although the optimal combination for flight remains uncertain [12] [16].

Continuous glucose monitoring may be useful even in metabolically healthy crews because it captures postprandial and circadian patterns missed by fasting tests, which is precisely the limitation of the existing HOMA-IR evidence. However, CGM values should not be interpreted without activity, meal, perfusion, hydration, and stress context. Algorithms trained on terrestrial populations may require recalibration for fluid shifts, altered skin perfusion, and mission schedules. Insulin and glucagon delivery systems intended for space also require validation of formulation stability, sensor performance, occlusion risk, radiation tolerance, and manual fallback procedures.

Pharmacological insulin sensitisation should not be adopted empirically in healthy astronauts. The risk-benefit profile differs in a closed operational environment, and agents can affect hydration, gastrointestinal function, body mass, appetite, and hypoglycaemia risk. Mechanistically informed thresholds and individualised reserve measurements should precede drug trials.

11. Translation to Diabetes Care on Earth

Spaceflight research can contribute to diabetes care even if altered gravity is never

used therapeutically. First, rotating-vessel and scaffold studies suggest methods for maintaining islet viability, morphology, and secretory function before transplantation [3]-[5]. The most transferable insight may be fluid-mechanical: controlling shear, oxygen diffusion, nutrient gradients, and aggregate fusion can improve the quality of three-dimensional islet preparations. The MASER 15 observation that scaffold support prevents islet fusion is a practical result of the same kind [7].

Second, variable-gravity experiments can expose mechanosensitive pathways controlling calcium signalling, cytoskeletal organisation, proliferation, extracellular matrix, and cell identity. A pathway that produces controlled beta-cell renewal after a transient mechanical stimulus could become a drug or biomaterial target. Safety is paramount, and the distinction drawn in Section 5.2 applies directly here: proliferation without preserved identity, glucose responsiveness, genomic stability, and tumour suppression would not be clinically useful, and any candidate pathway must be validated against functional secretion rather than labelling indices alone.

Third, the astronaut problem encourages measurement of reserve rather than disease state alone. Terrestrial diabetes care often identifies deterioration after glucose or glycated haemoglobin has risen. Dynamic C-peptide modelling, wearable data, and standardised challenges could improve early detection of failing compensation in people with insulin resistance, gestational-risk states, pancreatic disease, or post-transplant monitoring.

Fourth, multi-organ chips developed for space can model why equivalent insulin resistance produces different outcomes among individuals. Linking islets with liver, muscle, adipose, immune, and gut-derived signals may reveal compensatory networks and permit personalised testing of exercise mimetics, incretin therapies, anti-inflammatory strategies, or transplantation platforms.

12. Limitations of the Evidence and This Review

The literature is small enough that one or two experiments can disproportionately shape interpretation. The human insulin-resistance claim rests substantially on eight subjects and one fasting index; the principal whole-organ histology rests on approximately five animals per group. Most direct islet studies use rodents, tumour-derived cells, simulated microgravity, or exposures lasting minutes. Sample sizes are modest, hardware differs substantially, and negative studies may be underreported. Whole-pancreas molecular signals are not equivalent to islet-specific effects, and pathway enrichment is hypothesis-generating rather than a direct measure of physiology.

This article is a structured narrative review rather than a registered systematic review. Its inclusion and exclusion criteria and its exposure-classification scheme are stated in Section 2, but screening was performed by the author without independent duplicate assessment, and no formal risk-of-bias instrument was applied. It does not provide pooled effect sizes. Quantitative results are reported where the

accessible record contains them; several key sources present magnitudes only in figures or report only a direction of effect, and these are marked accordingly in **Table 2** rather than paraphrased as strong or substantial. Some older studies are accessible primarily through abstracts, reviews, or publisher summaries, and no effect estimates were drawn from those records. The conclusions therefore emphasise evidence boundaries and experimental design rather than precise estimates of effect magnitude.

13. Conclusions

Current research shows that spaceflight alters the metabolic environment in which the pancreas operates. Human data support inflight insulin resistance, quantified so far as an approximately 60 per cent rise in HOMA-IR in eight astronauts driven by elevated fasting insulin rather than by rising glucose, and rodent omics demonstrate coordinated remodelling involving liver, adipose tissue, muscle, and pancreas. Yet direct knowledge of the astronaut pancreas remains remarkably thin. We do not know whether islet mass changes, whether alpha-cell counter-regulation is preserved, whether beta-cell reserve declines, whether pancreatic perfusion or fat content changes, or whether exocrine digestion is affected during long missions. The proposition that the organ compensates by secreting more insulin is a reasonable model; it is not yet an observation.

Isolated-islet experiments provide a second, complementary message: low-shear three-dimensional environments can preserve or enhance islet function, and brief real microgravity can initiate a delayed cell-cycle response. These observations should be treated as leads for mechanobiology and tissue engineering, not as evidence of increased beta-cell mass, preserved secretory reserve, or a protective effect of spaceflight on the pancreas.

The most efficient path forward is a coordinated platform ladder. Variable-gravity parabolic flight should map acute dose-response, thresholds, transition effects, and hysteresis in perfused human islets. Sounding rockets should test short biological memory. Orbital experiments with onboard 1-g controls should establish chronic causality. Multi-organ chips should reconnect islets to insulin-resistant liver, muscle, and adipose tissue. Longitudinal astronaut studies should finally measure secretion and sensitivity together, and report them with the effect sizes and individual trajectories the present literature lacks. Such a programme would convert gravity from an uncontrolled environmental exposure into an experimental variable, protecting crews while opening new routes to islet preservation, beta-cell biology, and diabetes care on Earth.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

References

- [1] Tobin, B.W., Uchakin, P.N. and Leeper-Woodford, S.K. (2002) Insulin Secretion and

- Sensitivity in Space Flight. *Nutrition*, **18**, 842-848.
[https://doi.org/10.1016/s0899-9007\(02\)00940-1](https://doi.org/10.1016/s0899-9007(02)00940-1)
- [2] Strollo, F., Gentile, S., Pipicelli, A.M.V., Mambro, A., Monici, M. and Magni, P. (2022) Space Flight-Promoted Insulin Resistance as a Possible Disruptor of Wound Healing. *Frontiers in Bioengineering and Biotechnology*, **10**, Article 868999.
<https://doi.org/10.3389/fbioe.2022.868999>
 - [3] Rutzky, L.P., Bilinski, S., Kloc, M., Phan, T., Zhang, H., Katz, S.M., *et al.* (2002) Microgravity Culture Condition Reduces Immunogenicity and Improves Function of Pancreatic Islets. *Transplantation*, **74**, 13-21.
<https://doi.org/10.1097/00007890-200207150-00004>
 - [4] Song, C., Duan, X.Q., Li, X., Han, L.Q., Xu, P., Song, C.F., *et al.* (2004) Experimental Study of Rat Beta Islet Cells Cultured under Simulated Microgravity Conditions. *Acta Biochimica et Biophysica Sinica*, **36**, 47-50. <https://doi.org/10.1093/abbs/36.1.47>
 - [5] Song, Y., Wei, Z., Song, C., Xie, S., Feng, J., Fan, J., *et al.* (2013) Simulated Microgravity Combined with Polyglycolic Acid Scaffold Culture Conditions Improves the Function of Pancreatic Islets. *BioMed Research International*, **2013**, 1-7.
<https://doi.org/10.1155/2013/150739>
 - [6] Tanaka, H., Tanaka, S., Sekine, K., Kita, S., Okamura, A., Takebe, T., *et al.* (2013) The Generation of Pancreatic β -Cell Spheroids in a Simulated Microgravity Culture System. *Biomaterials*, **34**, 5785-5791. <https://doi.org/10.1016/j.biomaterials.2013.04.003>
 - [7] Zeger, L., Barasa, P., Han, Y., Hellgren, J., Redwan, I.N., Reiche, M.E., *et al.* (2024) Microgravity Effect on Pancreatic Islets. *Cells*, **13**, Article 1588.
<https://doi.org/10.3390/cells13181588>
 - [8] Hughson, R.L., Robertson, A.D., Arbeille, P., Shoemaker, J.K., Rush, J.W.E., Fraser, K.S., *et al.* (2016) 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**, H628-H638.
<https://doi.org/10.1152/ajpheart.00802.2015>
 - [9] Mathyk, B.A., Tabetah, M., Karim, R., Zaksas, V., Kim, J., Anu, R.I., *et al.* (2024) Spaceflight Induces Changes in Gene Expression Profiles Linked to Insulin and Estrogen. *Communications Biology*, **7**, Article No. 692.
<https://doi.org/10.1038/s42003-023-05213-2>
 - [10] Proshchina, A.E., Krivova, Y.S. and Saveliev, S.C. (2015) Pancreas of C57 Black Mice after Long-Term Space Flight (Bion-M1 Space Mission). *Life Sciences in Space Research*, **7**, 22-26. <https://doi.org/10.1016/j.lssr.2015.09.001>
 - [11] Grandke, F., Rishik, S., Wagner, V., Engel, A., Ludwig, N., Calcuttawala, K., *et al.* (2026) miRNAs Shape Mouse Age-Independent Tissue Adaptation to Spaceflight via ECM and Developmental Pathways. *Nature Communications*, **17**, Article No. 1387.
<https://doi.org/10.1038/s41467-026-68737-1>
 - [12] Downs, M.E., Scott, J.M., Ploutz-Snyder, L.L., Ploutz-Snyder, R., Goetchius, E., Buxton, R.E., *et al.* (2020) Exercise and Testosterone Countermeasures to Mitigate Metabolic Changes during Bed Rest. *Life Sciences in Space Research*, **26**, 97-104.
<https://doi.org/10.1016/j.lssr.2020.03.008>
 - [13] Du, Y., Han, B., Biere, K., Abdelmalek, N., Shu, X., Song, C., *et al.* (2025) Lunar and Martian Gravity Alter Immune Cell Interactions with Endothelia in Parabolic Flight. *npj Microgravity*, **11**, Article No. 4. <https://doi.org/10.1038/s41526-024-00456-7>
 - [14] Lecoq, P.E., Dupuis, C., Mousset, X., *et al.* (2024) Influence of Microgravity on Spontaneous Calcium Activity of Primary Hippocampal Neurons Grown in Microfluidic Chips. *npj Microgravity*, **10**, Article No. 15.

- <https://doi.org/10.1038/s41526-024-00355-x>
- [15] Wang, Y., Zhao, W., Shi, J., Wang, J., Hao, J., Pang, X., *et al.* (2019) Intestinal Microbiota Contributes to Altered Glucose Metabolism in Simulated Microgravity Mouse Model. *The FASEB Journal*, **33**, 10140-10151. <https://doi.org/10.1096/fj.201900238rr>
- [16] Strollo, F. and Vernikos, J. (2021) Aging-Like Metabolic and Adrenal Changes in Microgravity: State of the Art in Preparation for Mars. *Neuroscience & Biobehavioral Reviews*, **126**, 236-242. <https://doi.org/10.1016/j.neubiorev.2021.01.028>