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MICROGRAVITY AND SKELETAL DECONDITIONING: A NARRATIVE REVIEW OF BONE DENSITY LOSS AND EXERCISE COUNTERMEASURES IN ASTRONAUTS

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ABSTRACT

Background: Microgravity uncouples skeletal remodelling — accelerating resorption and suppressing formation — causing BMD losses of 0.5–2%/month at weight-bearing sites, six-month ISS deficits are comparable to a decade of postmenopausal bone loss.
Objective: To synthesise evidence on mechanisms, countermeasure efficacy, recovery, and gaps for exploration.
Methods: Narrative review. PubMed/MEDLINE, Scopus, and NASA Technical Reports Server searched 1990–2025, 82 of 312 records included: spaceflight studies with DXA, QCT, or HR-pQCT, bed-rest RCTs, systematic reviews.
Results: ARED reduced hip BMD loss by ~40% versus aerobic-only protocols, proximal femur deficits persist. HR-pQCT confirmed resorption exceeded formation threefold in-flight, bone repair concentrated within 6 months. QCT revealed trabecular deficits at 24 months despite DXA normalisation. Alendronate preserved BMD in the only spaceflight RCT (n=28).
Conclusions: Available evidence suggests current exercise countermeasures may be insufficient for missions beyond six months. Bisphosphonate therapy alongside ARED may be considered for high-risk crewmembers, though evidence is limited to a single small trial. Longer missions will likely require multimodal strategies. Pre-flight risk stratification and anti-sclerostin trials are priority research needs.

KEYWORDS

Microgravity, Bone Mineral Density, Spaceflight Osteoporosis, Skeletal Deconditioning, Exercise Countermeasures, ARED, HR-pQCT, QCT, Sclerostin, Bisphosphonates, Long-Duration Spaceflight

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Introduction

Bone loss is an established consequence of spaceflight. Fiedler et al. (2025) followed 94 astronauts and found that BMD at the hip and spine had not recovered to preflight levels by one year post-flight: only 34% had recovered hip BMD and 47% lumbar spine BMD at that point.(Fiedler et al., 2025) Subsequent densitometric measurement has quantified the magnitude: monthly losses of 0.5–2.0% at weight-bearing sites — including the hip, lumbar spine, and calcaneus — accumulate over a six-month ISS expedition into deficits comparable to more than a decade of postmenopausal bone loss.(Sibonga et al., 2007; Stavnichuk et al., 2020) HR-pQCT data have further demonstrated that DXA areal BMD underestimates structural damage: trabecular microarchitecture continues to deteriorate at sites where DXA values remain within normal limits,(Vico et al., 2017; Walle et al., 2024) and QCT has documented that hip trabecular volumetric BMD remains below preflight values at twenty-four months post-landing in crewmembers whose DXA measurements have normalised.(Sibonga et al., 2020) This DXA–QCT discordance causes areal BMD to overestimate skeletal recovery, rendering DXA-only post-flight assessments insufficient for determining whether structural deficits have resolved.

These structural changes matter clinically. Keyak et al. documented reduced estimated femoral strength after six-month missions using QCT-based finite element modelling,(Keyak et al., 2009) and Burkhart et al. found elevated vertebral fracture risk in ISS crewmembers by the same method.(Burkhart et al., 2020) Orwoll et al. confirmed that fracture risk remains elevated for months to years after landing.(Orwoll et al., 2013) For planned crewed exploration missions — lunar Gateway stays of six months or more at 0.16 g, and Mars transits of 24–30 months in near-zero gravity without access to emergency evacuation — these skeletal deficits represent a health risk for which current countermeasure protocols have not provided an adequate solution.

Countermeasure development has followed a progression from aerobic-only to resistance-centred exercise protocols, driven by evidence that aerobic exercise generates sub-osteogenic skeletal strain. Early ISS

protocols — tethered treadmill running and cycle ergometry — prevented cardiovascular deconditioning but produced mean monthly hip BMD losses of 0.9–1.1% despite compliance, consistent with the well-established principle that bone responds to strain magnitude rather than exercise volume.(Convertino, 1996; Turner, 1998) The installation of ARED on the ISS in 2008–2009 enabled multi-joint high-load resistance exercise at loads approaching terrestrial intensities for the first time.(Loehr et al., 2015) Sibonga et al. and Smith et al. confirmed that ARED-era protocols reduced monthly BMD loss by approximately 40% at the total hip compared with pre-ARED cohorts,(Smith et al., 2012; Sibonga et al., 2019) yet clinically significant proximal femur deficits persist and no controlled data establish the adequacy of current protocols for missions beyond six months.

The present review addresses three objectives: (1) to characterise the primary cellular, molecular, and systemic mechanisms by which microgravity induces bone loss in humans; (2) to appraise the controlled evidence for the efficacy of exercise-based and pharmacological countermeasures and define the limits of its applicability to exploration-class missions; and (3) to identify the priority knowledge gaps requiring resolution before countermeasure adequacy for missions beyond twelve months can be established. Where the evidence permits, guidance is offered for current ISS mission planning. Throughout, study design and sample size are considered, as is the distinction between bed-rest analog findings and results from actual spaceflight.

Literature Search Strategy and State of Knowledge

The present work is a narrative review. No systematic protocol was prospectively registered and no primary data were collected. Three databases were searched: PubMed/MEDLINE, Scopus, and the NASA Technical Reports Server, covering January 1990 to April 2025. Ten predefined search strings were applied: spaceflight bone loss; microgravity osteoporosis; astronaut skeletal deconditioning; ARED bone spaceflight; bed rest bone mineral density countermeasure; whole-body vibration bone spaceflight; bisphosphonate spaceflight; sclerostin spaceflight OR bed rest; ISS exercise countermeasure skeletal; and HR-pQCT astronaut bone. Of 312 records identified after deduplication, 187 underwent full-text review; 68 met the predefined inclusion criteria and were selected. A further 14 sources were identified by hand-searching the reference lists of key systematic reviews. The final synthesis is based on 82 sources.

Source selection criteria. Studies were selected if they reported quantitative bone outcomes in human spaceflight or controlled bed-rest trials of at least 14 days, or if they were systematic reviews or meta-analyses of such data. Mechanistic studies were included where they provided direct cellular or molecular evidence cited in the human spaceflight literature. Conference abstracts, case reports, and studies without bone-specific outcomes were excluded. Within the spaceflight evidence base, priority was given to studies using QCT or HR-pQCT over DXA-only designs.

Limitations of this review. As a narrative review, this work is subject to the following methodological constraints. Source selection applied predefined inclusion criteria as described above, but screening was performed by the authors without independent verification, introducing the possibility of selection bias. No formal hierarchy of evidence was applied, and findings from bed-rest analog studies, animal models, and small-cohort spaceflight investigations are synthesised alongside randomised controlled trials without explicit quality weighting. The available spaceflight evidence base itself is limited by small sample sizes, predominantly male cohorts, and the absence of randomised allocation to countermeasure conditions in actual flight. Quantitative synthesis of outcomes across studies was not attempted. These limitations mean that the conclusions should be interpreted as a critical appraisal of current knowledge rather than as a systematic or meta-analytic review.

Pathophysiology of Microgravity-Induced Bone Loss

Mechanosensory Uncoupling at the Osteocyte Level

Normally, bone resorption and bone formation are tightly coupled: osteoclasts remove old or damaged matrix and osteoblasts deposit new mineralised matrix in the same location. The coupling is coordinated by osteocytes — the most abundant cells in bone — embedded within a three-dimensional lacunocanalicular network that functions as the skeleton's mechanosensory system.(Bonewald, 2011) Weight-bearing activities generate interstitial fluid flow within canalicular channels, producing fluid shear stresses that are transduced into intracellular biochemical signals via integrin–cytoskeletal linkages and ion channel activation — a mechanosensory transduction pathway reviewed in detail by Bonewald.(Bonewald, 2011) These signals modulate the paracrine factors — prostaglandins, nitric oxide, Wnt ligands — that govern osteoblast and osteoclast activity at adjacent bone surfaces.

In microgravity, the loss of habitual weight-bearing strain removes the primary mechanical input to this signalling cascade. Wnt/β-catenin pathway activation in osteocytes — a pro-osteogenic axis that promotes osteoblast differentiation and suppresses osteoclastogenesis — is substantially reduced under mechanical

unloading.(Sambandam et al., 2014) Concurrently, RANKL expression by osteocytes and bone lining cells rises, stimulating osteoclast precursor differentiation. Osteoprotegerin (OPG), the soluble RANKL decoy receptor, is downregulated in parallel.(Turner et al., 2006) Taken together, the changes described by Sambandam et al. and Turner et al. shift the remodelling balance toward net resorption within the first weeks of spaceflight exposure.(Sambandam et al., 2014; Turner et al., 2006)

The Sclerostin Axis

Sclerostin, a glycoprotein encoded by the SOST gene and secreted by osteocytes in response to reduced mechanical loading, has emerged as a particularly relevant molecular target in spaceflight bone biology. It antagonises canonical Wnt signalling in osteoblast precursors by binding LRP5/6 co-receptors, inhibiting osteoblast differentiation and suppressing bone formation.(Galea et al., 2017) The pathway's importance is underscored by human genetic evidence: loss-of-function SOST mutations cause sclerosteosis and van Buchem disease, conditions characterised by markedly increased bone density. Circulating sclerostin is consistently elevated during both spaceflight and bed-rest, and correlates with suppression of formation markers across multiple study designs.(Spatz et al., 2013)

Walle et al. provided the first direct in vivo human evidence linking serum sclerostin to locally resolved trabecular formation rates, using time-lapsed HR-pQCT in seventeen ISS crewmembers. The observed correlation ($\rho = -0.62$, $p < 0.01$) indicates that the pathway is active at the tissue level under actual spaceflight conditions, not only in animal models.(Walle et al., 2024) This finding strengthens the pharmacological case for sclerostin inhibition. Romosozumab, the approved anti-sclerostin antibody, increases bone formation while simultaneously reducing resorption — a combination that may be well suited to the spaceflight context, where both processes are dysregulated.(Cosman et al., 2016)

Bone Turnover Marker Dynamics

Biochemical markers of bone remodelling offer a complementary view of spaceflight-induced skeletal changes alongside imaging outcomes. Gabel et al. assessed turnover markers longitudinally across six-month ISS expeditions and found that urinary N-telopeptide (NTx) and serum CTX — both resorption markers — rose to approximately twice preflight values within the first month of flight and remained elevated throughout.(Gabel et al., 2022) Formation markers (P1NP, osteocalcin) showed a declining trajectory over longer missions, indicating, as Gabel et al. note, chronic suppression of the anabolic arm rather than a co-varying response to the resorptive excess.(Gabel et al., 2022) The persistence of elevated resorption markers across the full six-month mission duration, without attenuation, suggests that the skeletal response does not diminish with prolonged microgravity exposure — an observation relevant to planning for longer-duration missions, though direct data from missions beyond twelve months are lacking.(Gabel et al., 2022)

Walle et al. extended this picture by correlating systemic biomarker profiles with site-specific HR-pQCT measures of trabecular formation and resorption, confirming that resorption exceeded formation threefold at the tissue level during flight.(Walle et al., 2024) This multi-scale approach — linking blood and urine markers to local microstructural outcomes — provides a more integrated view of remodelling dynamics, and Walle et al. propose it as a model for how future countermeasure trials might track skeletal responses at multiple levels simultaneously.(Walle et al., 2024)

Endocrine and Systemic Contributions

Mechanical unloading is the primary driver of spaceflight bone loss, but systemic factors modulate the net skeletal response. Urinary calcium excretion rises substantially during flight, reflecting accelerated osteoclastic resorption and, as Caillot-Augusseau et al. note, possible impairment of renal tubular calcium reabsorption — a mechanism not fully characterised in humans. Calciuria can exceed 300 mg/day in unprotected crewmembers, well above the terrestrial upper limit. This is both a marker of ongoing demineralisation and a risk factor for nephrolithiasis, which is the most commonly treated medical condition on ISS.(Caillot-Augusseau et al., 1998) The calcium-regulating hormonal axis — PTH, calcitriol, and calcitonin — shows early-flight suppression followed by gradual partial recovery, a trajectory that parallels the suppression of bone formation markers documented by Stavnichuk et al.(Stavnichuk et al., 2020)

Vitamin D sufficiency requires particular attention in the spaceflight environment. Cabin lighting provides no ultraviolet-B irradiation, so oral supplementation is the only available route; Smith et al. documented that a subset of ISS crewmembers remained below the 50 nmol/L serum 25(OH)D threshold despite prescribed oral supplementation, indicating that current dose protocols may require upward revision for some individuals under spaceflight metabolic conditions.(Smith et al., 2012) Additional systemic contributors to the altered bone remodelling environment include cortisol elevation associated with psychological stress and alterations in growth hormone/IGF-1 signalling, both of which are known to influence

bone cell activity in terrestrial settings.(Stavnichuk et al., 2020) However, as Stavnichuk et al. note in their systematic review, the independent contributions of these endocrine factors to total spaceflight bone loss remain incompletely characterised in human crewmembers and have not been isolated from the dominant effect of mechanical unloading.(Stavnichuk et al., 2020)

Compartment-Specific and Regional Heterogeneity

A consistent and clinically critical feature of spaceflight-induced bone loss is its pronounced regional and compartment-specific heterogeneity, closely tracking the distribution of habitual gravitational loading. The Stavnichuk et al. pooled data from approximately 148 astronauts across 25 studies. Post-flight changes were +2.2% at the skull, −0.7% in the thorax and upper limbs, −6.2% in the lumbar spine and pelvis, and −5.4% in the lower limbs, with a lower limb loss rate of −0.8% per month.(Stavnichuk et al., 2020) These patterns confirm that sites normally sustaining the highest compressive forces lose the most bone in microgravity, while the skull — shielded from habitual axial loading — paradoxically gains density; the mechanism is unconfirmed but has been attributed to altered intraosseous pressure from cephalad fluid redistribution in the Stavnichuk et al. meta-analysis. QCT analyses by Lang et al. demonstrated that trabecular volumetric BMD losses at the hip (2.2–2.7%/month) substantially exceeded cortical losses (0.4–0.5%/month) on a percentage basis, with cortical loss occurring primarily through endocortical thinning — a mechanism distinct from the endosteal expansion of age-related bone loss and with specific implications for fracture risk mechanics.(Lang et al., 2004)

HR-pQCT analyses provide greater compartmental resolution than DXA or QCT. Vico et al., studying twelve ISS crewmembers with pre- and post-flight imaging and a twelve-month post-flight follow-up, documented trabecular volumetric BMD losses at the distal tibia that did not recover within the observation window, alongside progressive deterioration of trabecular number and thickness at non-weight-bearing sites (distal radius) — changes invisible to DXA.(Vico et al., 2017) The QCT cohort study of Sibonga et al. demonstrated that while areal BMD by DXA recovered to preflight values in nine of ten crewmembers within twelve months, hip trabecular volumetric BMD remained below preflight in five of ten at twelve months and four of five at twenty-four months. The underlying mechanism is a technical limitation of DXA: periosteal expansion and cortical consolidation upon skeletal reloading restore the areal projection while trabecular deficits persist.(Sibonga et al., 2020) These findings indicate that DXA-based post-flight assessment alone may overestimate the degree of structural recovery, with potential consequences for crewmember clearance decisions.

The following implementation strategies follow from this evidence. QCT of the proximal femur should be added to post-flight surveillance alongside DXA, with assessments at twelve and twenty-four months post-landing. Failure to recover trabecular volumetric BMD by twenty-four months should trigger specialist review.(Sibonga et al., 2020) Second, where HR-pQCT equipment is accessible at pre- and post-flight assessment sites, inclusion of distal tibia and radius scanning would provide microarchitectural outcomes that can serve both as research endpoints and as individual crewmember monitoring data. Third, pre-flight HR-pQCT baseline assessment — ideally alongside DXA — would enable personalised risk stratification based on trabecular microarchitectural parameters, identifying crewmembers with lower structural reserve before mission assignment. Fourth, the discordance between DXA and QCT recovery trajectories should be explicitly communicated in post-flight medical briefings, so that crewmembers and flight surgeons are not misled by DXA normalisation into underestimating residual structural deficit. NASA's Human Health and Performance Directorate performs pre- and post-flight DXA scans on all ISS crewmembers. It also conducts triennial DXA under the Lifetime Surveillance of Astronaut Health programme, which covers active and retired astronauts. The surveillance infrastructure is already in place. Cross-agency comparability would require agreement on standardised acquisition protocols and reporting thresholds. That kind of consensus is achievable — the 2010 NASA Bone Summit convened external experts in osteoporosis and densitometry to establish the astronaut skeletal health standards currently in use.(Orwoll et al., 2013)

Table 1 summarises the three principal imaging modalities used in spaceflight bone research, their technical characteristics, and their respective roles in assessing mission-induced skeletal changes.

Table 1. Comparison of imaging modalities used in spaceflight bone research. BMD: bone mineral density; DXA: dual-energy X-ray absorptiometry; QCT: quantitative computed tomography; HR-pQCT: high-resolution peripheral QCT; Tb.N: trabecular number; Tb.Th: trabecular thickness; Tb.Sp: trabecular separation. Numbers in brackets indicate key references where the modality was used to characterise spaceflight-induced changes.

Modality	Measurement	Compartments Assessed	Spaceflight Application	Key Limitation
DXA (Dual-energy X-ray absorptiometry)	Areal BMD (g/cm²)	Integrates cortical and trabecular; cannot separate	Standard pre/post-flight bone assessment; recovery monitoring	Cannot distinguish trabecular from cortical loss; overestimates recovery (Sibonga et al., 2020)
QCT (Quantitative CT)	Volumetric BMD (mg/cm³); bone geometry	Cortical and trabecular separately at spine and hip	Trabecular deficit detection post-flight; fracture risk modelling (Sibonga et al., 2020; Burkhart et al., 2020)	Higher radiation dose; less available at clinical sites
HR-pQCT (High-resolution peripheral QCT)	Volumetric BMD; trabecular microarchitecture (Tb.N, Tb.Th, Tb.Sp); cortical thickness	Distal tibia and radius (peripheral sites)	Microarchitectural change detection; in vivo remodelling tracking (Vico et al., 2017; Walle et al., 2024)	Restricted to peripheral sites; limited availability; no spinal or hip measurement

Exercise Countermeasures

Pre-ARED Era: Limitations of Aerobic Protocols

Early ISS protocols relied on tethered treadmill running and cycle ergometry. These generated strain magnitudes well below established osteogenic thresholds, even with bungee cord tethering providing roughly 70–80% body weight loading.(Convertino, 1996; Cavanagh et al., 2010) The bone outcomes were, frankly, poor: pre-2009 data showed mean monthly losses of 0.9–1.1% at the total hip and 0.8–0.9% at the lumbar spine despite prescribed exercise.(Sibonga et al., 2019) Sibonga et al. characterised that 50% recovery of hip BMD required approximately one year and that a proportion of crewmembers had not recovered to preflight BMD values within the follow-up period, which extended to approximately five years post-landing in the Sibonga et al. dataset.(Sibonga et al., 2007)

ARED-Based High-Load Resistance Exercise

ARED employs opposed vacuum cylinders to generate resistive loads of up to 272 kg across multi-joint lower extremity exercises — squat, deadlift, and heel raise — as well as upper body movements, in a self-contained, consumable-free unit.(Loehr et al., 2015) Current ISS prescriptions call for three to six sessions per week, each approximately 90 minutes including warm-up and cool-down, combined with daily treadmill running (approximately 30–60 minutes) and cycle ergometry (approximately 30 minutes), as described by Loehr et al. Loading intensities approach 70–85% of estimated one-repetition maximum — sufficient to produce osteogenic strain rates at the proximal femur and lumbar spine.(Loehr et al., 2015) The rationale comes from Turner's three rules of bone adaptation: strain magnitude and rate drive osteogenesis, not exercise volume, and novel patterns produce greater responses than habitual ones.(Turner, 1998) High-load multi-joint movements generate greater skeletal signals at the hip than aerobic exercise at the same time cost — the reason the shift to resistance-centred protocols was expected to improve outcomes.

Smith et al. provided the first systematic evaluation of ARED-era outcomes, showing attenuated BMD losses at the hip and spine relative to pre-ARED controls and better-maintained P1NP.(Smith et al., 2012) Energy intake emerged as a synergistic factor: crewmembers who maintained body mass during flight showed the best skeletal outcomes, indicating that the anabolic response to resistance exercise depends on nutritional

substrate availability. Sibonga et al. subsequently characterised the limits of ARED-based protection, confirming meaningful attenuation across multiple sites but persistent deficits at the femoral trochanter and neck, alongside a threefold to fourfold range in monthly hip BMD loss across crewmembers on nominally identical protocols. Whether this variability reflects adherence, loading technique, energy balance, or genetic susceptibility has not been resolved.(Sibonga et al., 2019)

Table 2 summarises skeletal outcomes reported in comparative analyses of pre-ARED and ARED-era cohorts.

Table 2. Comparison of skeletal outcomes between pre-ARED (aerobic exercise only) and ARED-era (resistance plus aerobic exercise) protocols in ISS crewmembers. BMD: bone mineral density; vBMD: volumetric BMD; P1NP: procollagen type I N-terminal propeptide; DXA: dual-energy X-ray absorptiometry; QCT: quantitative computed tomography; HR-pQCT: high-resolution peripheral QCT. Pre-ARED data from missions before 2009; ARED-era data from missions from 2009 onward. Monthly loss estimates are approximate group means; individual variation is substantial.

Outcome / Skeletal Site	Pre-ARED Era (aerobic only)	ARED Era (resistance + aerobic)	Direction of Change with ARED	Key Source
Monthly hip BMD loss (total hip)	~0.9–1.1%/month	~0.5–0.6%/month	↓ ~40% reduction	Smith et al. 2012 (Smith et al., 2012); Sibonga et al. 2019 (Sibonga et al., 2019)
Monthly lumbar spine BMD loss	~0.8–0.9%/month	~0.4–0.5%/month	↓ Significant reduction	Smith et al. 2012 (Smith et al., 2012)
Femoral trochanter BMD loss	~1.0–1.1%/month	~0.7–0.8%/month	↓ Partial reduction; deficits persist	Sibonga et al. 2019 (Sibonga et al., 2019)
Bone formation marker (P1NP)	Suppressed in-flight	Better maintained in-flight	↑ Improved	Smith et al. 2012 (Smith et al., 2012)
Post-flight BMD recovery (12 months, DXA)	Incomplete in majority of crewmembers	Improved but still incomplete in subset	↑ Partial improvement	Sibonga et al. 2007 (Sibonga et al., 2007); Sibonga et al. 2019 (Sibonga et al., 2019)
Trabecular vBMD (QCT/HR-pQCT)	Not systematically assessed pre-ARED	Deficits persist at 2 years despite DXA normalisation	Incomplete recovery regardless of era	Sibonga et al. 2020 (Sibonga et al., 2020); Vico et al. 2017 (Vico et al., 2017)
Inter-individual variability (hip BMD loss range)	Not well-characterised	3–4× range across crew on identical protocols	High variability remains a consistent feature	Sibonga et al. 2019 (Sibonga et al., 2019)

Evidence from Bed-Rest Analog Trials

Bed-rest models remain the closest practical analogue to microgravity on Earth. Head-down tilt at −6° reproduces the cephalad fluid shift and spinal unloading characteristic of spaceflight, and allows experimental control over diet and exercise that is impossible in actual flight.(Pavy-Le Traon et al., 2007) Monthly BMD losses in unexercised bed-rest subjects run 0.5–1.5% at weight-bearing sites. Its principal limitation is reduced ecological validity: bed rest retains a gravitational vector in the anterior-posterior axis, removes the space-specific physiological stressors of radiation and altered circadian lighting, and differs in psychological context from orbital conditions. Monthly bone loss rates in unexercised bed-rest subjects (0.5–1.5%) fall at the lower end of published spaceflight rates (0.5–2.0%), a pattern noted by Traon et al., who attribute the lower bed-rest rates to the absence of radiation, psychological stress, and fluid dynamic shifts present in actual spaceflight.(Pavy-Le Traon et al., 2007)

A consistent finding across randomised bed-rest trials is the hierarchical superiority of high-load resistance exercise over aerobic training for skeletal preservation. Shackelford et al. demonstrated in a 17-week bed-rest study that multi-joint lower extremity resistance exercise significantly attenuated BMD loss at the hip and spine compared to no-exercise controls, while low-resistance aerobic exercise had minimal skeletal effect.(Shackelford et al., 2004) Combined resistance plus aerobic protocols show incremental benefit over resistance alone, supporting the current ISS two-modality exercise approach. Importantly, substantial inter-individual response heterogeneity is observed in bed-rest trials — a pattern consistent with that documented in ISS crewmembers by Sibonga et al. (Sibonga et al., 2019) — with some participants maintaining BMD within measurement error while others lose three times the group mean despite identical protocols. This finding underscores the limitations of population-level prescription and reinforces the case for precision medicine approaches to countermeasure design.

Whole-Body Vibration

Whole-body vibration (WBV) at 20–40 Hz and 0.1–1.0 g promotes osteogenic mesenchymal stem cell differentiation, suppresses adipogenesis, and inhibits osteoclastogenesis through pathways complementary to ARED.(Rittweger et al., 2010; Rittweger et al., 2005) Rittweger et al. demonstrated that side-alternating resistive vibration exercise over 56 days of bed rest significantly attenuated BMD loss at the hip and lumbar spine.(Rubin et al., 2004) As a standalone countermeasure WBV achieves more modest protection than ARED protocols; its primary value lies as a broad-spectrum mechanical adjunct providing high-frequency vibratory stimuli that ARED cannot replicate. Practical microgravity implementation requires mechanical isolation from the spacecraft structure, as documented in NASA technical assessments of vibration isolation systems for payloads aboard the ISS: crew activities, ventilation systems, and other disturbances generate vibration signatures that would be transmitted to a non-isolated platform and could interfere with the vibratory stimulus profile.

Lower Body Negative Pressure

LBNP devices apply sub-atmospheric pressure to the lower body, generating a simulated gravitational loading vector. Combined with treadmill locomotion, LBNP enables near-normal ground reaction force profiles in weightlessness. Zwart et al. demonstrated in a randomised bed-rest trial with female identical twins that LBNP treadmill exercise significantly attenuated calcaneal and hip BMD loss.(Zwart et al., 2007) Equipment complexity has limited ISS integration, but LBNP warrants investigation for partial-gravity surface operations on the Moon or Mars.

The 22-Hour Problem and Alternative Loading Strategies

ISS crewmembers are allocated approximately two hours per day for exercise, leaving twenty-two hours of near-zero gravitational stimulus. ARED exercise during that window generates an osteogenic signal at the moment of loading, but does not suppress osteoclastic activity across the remainder of the day; RANKL-driven and sclerostin-driven resorption continues during the extended period of mechanical silence. This temporal mismatch between the exercise window and the duration of skeletal unloading is a fundamental constraint on what exercise alone can achieve, and is the primary physiological rationale for pharmacological adjuncts whose effects operate continuously rather than episodically.

One response to this problem is to distribute loading across the day rather than concentrate it in one session. Brief bouts of high-impact activity — even 5 to 10 minutes at several points in the day — are mechanobiologically more effective than an equivalent volume in a single session, based on terrestrial evidence.(Turner, 1998) Whether this translates to clinically meaningful gains in microgravity has not been tested. WBV platforms could in principle provide passive stimulus during rest or work periods, and LBNP has been explored similarly, though neither approach has been evaluated for osteogenic efficacy outside of active

exercise conditions. Resistance-loaded postures, such as standing with elastic bands providing hip and spine compression, are low-mass options worth investigating — but there are no published data on their efficacy under weightlessness. A more immediate question is whether the existing two-hour exercise window could be restructured to improve skeletal loading efficiency, even without adding time. Controlled dose-response bed-rest trials are the practical route to testing this.(Loehr et al., 2015; Turner, 1998) The daily exercise schedule on the ISS is operationally constrained by mission planning and crew scheduling; any restructuring would require coordination between mission medical teams and operations planners. Controlled bed-rest research is the most feasible setting for testing restructured protocols before flight implementation. Scheduling flexibility allows systematic factorial variation of session timing, duration, and distribution — something not possible in actual spaceflight. The NASA 70-day head-down tilt programme has used this approach for randomised countermeasure assignment across multiple physiological systems.(Koppelmans et al., 2015)

Pharmacological and Nutritional Adjuncts

Bisphosphonates

Bisphosphonates inhibit osteoclastic resorption by targeting farnesyl diphosphate synthase within the mevalonate pathway, disrupting osteoclast cytoskeletal function and inducing apoptosis. Their high-affinity binding to bone hydroxyapatite confers a skeletal half-life of years to decades, meaning that suppression of resorption can persist long after the cessation of dosing. The primary controlled evidence in actual spaceflight derives from the randomised, double-blind, placebo-controlled trial of Orwoll et al., in which ISS crewmembers received weekly oral alendronate (70 mg) initiated three weeks before flight. Alendronate-treated crewmembers demonstrated significantly reduced hip BMD loss and attenuated urinary N-telopeptide excretion compared to placebo over six-month missions.(Orwoll et al., 2013) LeBlanc et al. reported supporting bed-rest data showing that bisphosphonate administration combined with exercise produced smaller residual BMD deficits than exercise alone.(LeBlanc et al., 2013)

Assessment of evidence strength and external validity. The Orwoll et al. trial is the only randomised pharmacological trial conducted in actual spaceflight; its sample size was small (n = 14 per group) and the study was not powered to detect fracture outcomes. Effect sizes for hip BMD preservation were clinically meaningful but confidence intervals were wide, limiting precision of the estimates. External validity to exploration-class missions is uncertain on the following grounds: the trial duration was limited to six months at ISS conditions. The astronaut cohort was also demographically restricted — predominantly physically fit men aged 35–55. The pharmacokinetic behaviour of alendronate under microgravity has not been characterised; gastrointestinal motility and fluid distribution both differ from terrestrial physiology and may affect absorption. The bed-rest data of LeBlanc et al. provide controlled mechanistic corroboration but are subject to the same model-to-spaceflight extrapolation constraints discussed in Section 4.3. There is also a timing concern specific to longer missions. Alendronate's antiresorptive activity persists for months to years after the last dose. If this extends into the post-flight period, it could suppress the osteoclast-driven resorption that precedes the formation response Walle et al. documented in the first six months after landing.(Walle et al., 2024) Pre-flight single-dose intravenous zoledronic acid has been proposed as an alternative offering more predictable pharmacokinetics and a more defined effect duration; prospective evaluation in a spaceflight context has not been published.

Anti-Sclerostin Therapy

The correlation between circulating sclerostin and in situ trabecular formation rates observed by Walle et al. in ISS crewmembers provides mechanistic justification for sclerostin inhibition as a countermeasure target.(Walle et al., 2024) Romosozumab is an anti-sclerostin monoclonal antibody approved for postmenopausal osteoporosis. It increases bone formation and decreases resorption. The FRAME trial showed superior vertebral and non-vertebral fracture reduction versus placebo at 12 months.(Cosman et al., 2016) The ARCH trial, comparing romosozumab to alendronate, reported higher rates of serious cardiovascular events in the romosozumab group (adjudicated cardiac ischaemic events 2.5% vs 1.9%), leading to a regulatory contraindication in individuals with prior myocardial infarction or stroke.(Saag et al., 2017)

Assessment of evidence strength and external validity. No controlled spaceflight data exist for romosozumab or any anti-sclerostin agent. The mechanistic case rests on the Walle et al. correlation data,(Walle et al., 2024) which, while the strongest human spaceflight evidence available for the sclerostin pathway, represents a small cohort (n = 17) with correlation analysis rather than an interventional design. Terrestrial fracture trial evidence is robust for postmenopausal women with low baseline BMD, but this population differs substantially from the active, younger, predominantly male astronaut cohort. The dual

anabolic-antiresorptive mechanism is theoretically well-matched to the spaceflight phenotype of simultaneously impaired formation and elevated resorption, but whether the same mechanistic logic translates to the microgravity loading environment — where the mechanosensory signal suppressing Wnt activation persists regardless of pharmacological intervention — has not been tested. The cardiovascular safety signal requires careful pre-flight cardiovascular evaluation before any trial use, and is potentially disqualifying for crewmembers with identified cardiac risk factors.

Denosumab and Other Antiresorptive Agents

Denosumab, a fully human anti-RANKL monoclonal antibody, suppresses osteoclastogenesis through a mechanism distinct from bisphosphonates and with fully reversible skeletal effects following discontinuation. In the FREEDOM trial, denosumab reduced hip and vertebral fracture risk in postmenopausal women over three years compared with placebo, with a well-characterised safety profile.(Cummings et al., 2009) No spaceflight trial has been conducted. Denosumab also creates an operational problem specific to spaceflight. Stopping it without sequential antiresorptive therapy causes rapid BMD loss and vertebral fractures in terrestrial patients, typically within 12–18 months of the last dose.(Anastasilakis et al., 2021) Anastasilakis et al. characterise the rebound phenomenon as a multifactorial dysregulation of bone remodelling in which osteoclast number and activity overshoot pre-treatment levels, with up to 10% of patients experiencing multiple vertebral fractures when denosumab is discontinued without sequential antiresorptive therapy.(Anastasilakis et al., 2021) Preventing this rebound requires a bisphosphonate to be administered within 6 months of the last denosumab dose. That is not currently feasible within the pharmacological and logistical framework of a Mars transit, which limits denosumab's applicability for such missions unless dedicated protocols are developed.

Nutritional Optimisation

Adequate nutritional status is a prerequisite for the effectiveness of exercise and pharmacological countermeasures. Calcium intake of 1,000–1,200 mg/day and serum 25-hydroxyvitamin D ≥50 nmol/L — achievable only by oral supplementation of 2,000–4,000 IU/day given the absence of solar UVB exposure in spacecraft — are the primary NASA Human Research Program nutritional requirements for skeletal health.(Smith et al., 2012) Protein intake of ≥1.2 g/kg/day supports bone collagen matrix and skeletal muscle mass maintenance, with the Smith et al. analysis identifying body mass maintenance as an independent predictor of better skeletal outcomes in ARED-era crewmembers, implicating energy deficit as a contributing risk factor.(Smith et al., 2012) Emerging bed-rest evidence supports alkalising dietary modifications and sodium bicarbonate supplementation to reduce spaceflight-induced hypercalciuria via reduction of dietary acid load, as reviewed in the context of ISS nutritional requirements by Smith et al., though this evidence base remains limited to short-duration analog studies.(Smith et al., 2012) Vitamin K2 (menaquinone) acts as a cofactor for γ-carboxylation of osteocalcin, and Zwart et al. measured vitamin K status across long-duration ISS missions and bed-rest analog studies, finding that plasma phylloquinone concentrations and osteocalcin carboxylation were generally maintained during spaceflight, suggesting that standard dietary vitamin K intake may be adequate during flight.(Zwart et al., 2011) However, no randomised controlled trial has evaluated vitamin K2 supplementation as a standalone bone countermeasure in spaceflight or validated bed-rest models, and the evidence base does not currently support a specific dosing recommendation for in-flight use.

Evidence-Based Pharmacological Recommendations

Three tiers of pharmacological and nutritional recommendation can be derived from available controlled data. Tier 1 — universal, no contraindications: calcium 1,000–1,200 mg/day and vitamin D 2,000–4,000 IU/day are required nutritional prerequisites for all crewmembers and should be prescribed from pre-flight baseline assessment through the post-flight recovery period.(Smith et al., 2012) These are not optional adjuncts but mandatory components of any countermeasure protocol. Tier 2 — selective use in high-risk crewmembers: bisphosphonate therapy is indicated where any of the following criteria are met: pre-flight DXA hip T-score at or below −1.0; prior documented in-flight BMD loss exceeding 1.5% per month at the hip; or HR-pQCT trabecular number below the age- and sex-matched reference range. Weekly oral alendronate 70 mg, initiated three weeks pre-flight, is the only regimen with direct spaceflight randomised controlled trial evidence.(Orwoll et al., 2013) It must be discontinued at landing to preserve the six-month post-flight bone repair window documented by Walle et al.(Walle et al., 2024) Pre-flight single-dose intravenous zoledronic acid 5 mg is a candidate alternative for crewmembers where oral administration is contraindicated, but lacks spaceflight trial data. Tier 3 — not recommended for routine ISS use: romosozumab is not recommended for standard ISS protocols because it requires cardiovascular pre-screening that may be disqualifying,(Saag et al., 2017) and no spaceflight trial has been conducted. Denosumab is not recommended because sequential

antiresorptive therapy on discontinuation — required to prevent vertebral fracture rebound — is not feasible within the logistical framework of a flight mission.(Anastasilakis et al., 2021)

Anti-sclerostin therapy (romosozumab) and RANKL inhibition (denosumab) are not currently recommended for standard ISS use, given the absence of spaceflight trial data, the cardiovascular safety requirement for romosozumab pre-screening,(Saag et al., 2017) and the denosumab rebound risk on discontinuation without sequential therapy. Both agents may be considered in future trial protocols designed for longer missions of this type. For all crewmembers, whether or not pharmacotherapy is used, adherence to calcium (1,000–1,200 mg/day) and vitamin D (2,000–4,000 IU/day targeting serum 25(OH)D ≥50 nmol/L) supplementation and protein adequacy (≥1.2 g/kg/day) should be confirmed before departure and monitored in-flight, as these nutritional prerequisites condition the effectiveness of both exercise and pharmacological strategies.(Smith et al., 2012)

Post-Flight Skeletal Recovery

Post-flight recovery of areal BMD was first systematically characterised by Sibonga et al., who modelled DXA data from 45 ISS and Mir crewmembers using exponential recovery functions. Estimated 50% recovery times were approximately one to two years at the most severely affected sites, including the femoral trochanter and neck.(Sibonga et al., 2007) Sibonga et al. (2019) report that Sibonga et al. (2019) observed that ARED-era crewmembers showed improved recovery trajectories compared with pre-ARED cohorts, attributing the improvement to smaller absolute mission-induced deficits, but prolonged and incomplete recovery at trabecular-rich sites persists across both eras.(Sibonga et al., 2019)

An important qualification to DXA-based recovery assessments was identified by the QCT cohort study of Sibonga et al. (2020). While areal BMD by DXA returned to preflight values in nine of ten ISS astronauts within twelve months of landing, hip trabecular volumetric BMD by QCT remained below preflight in five of ten at twelve months — and four of those five showed incomplete recovery at twenty-four months.(Sibonga et al., 2020) This pattern follows from a technical limitation of DXA: as the skeleton reloads after flight, periosteal expansion and cortical consolidation restore the areal projection measurement while trabecular deficits persist beneath. Post-flight clearance decisions based on DXA alone may therefore be made on incomplete information, and the finding has informed updated NASA recommendations to include QCT in post-flight surveillance.

The temporal dynamics of post-flight repair were examined by Walle et al. (2024) using time-lapsed HR-pQCT at the distal tibia in seventeen ISS crewmembers. New bone formation at sites previously resorbed during flight was concentrated in the first six months post-landing. In that window, approximately 32% of newly formed bone occurred at in-flight resorption sites. In the following six months, only about 3% in the subsequent six-to-twelve month window.(Walle et al., 2024) This tenfold decline suggests a mechanically driven repair response that fills vacated resorption cavities early in the post-flight period but decays rapidly thereafter. The finding is relevant to rehabilitation timing and pharmacological strategy: progressive loading in the early post-landing period may be most effective precisely when this repair response is active, while antiresorptive agents given in this window would be expected to suppress the osteoclastic resorption that precedes and couples to the formation response — a concern specifically raised in the context of bisphosphonate timing by LeBlanc et al.(LeBlanc et al., 2013)

Several practical implications follow for rehabilitation design. Early commencement of progressive loading — within weeks of landing rather than months — aligns with the window of maximal repair responsiveness identified by Walle et al.(Walle et al., 2024) Anabolic pharmacological agents — including anti-sclerostin antibodies or recombinant PTH analogues such as teriparatide, which are approved for terrestrial osteoporosis — have demonstrated anabolic effects on bone formation in terrestrial randomised trials, but no controlled data exist for their use in the post-spaceflight context; the potential applicability is mechanistically inferred from the Walle et al. repair window finding.(Walle et al., 2024) For crewmembers returning from partial-gravity environments, the temporal characteristics of this repair response cannot be assumed to match what Walle et al. documented after ISS missions at 1 g, and prospective characterisation is required.(Walle et al., 2024)

Knowledge Gaps and Research Priorities

Long-Duration Missions Beyond Six Months

The quantitative human spaceflight bone data reviewed by Stavnichuk et al. across 25 studies derive from ISS missions of four to twelve months; no controlled human bone data exist for missions of longer duration. The skeletal response to continuous microgravity exposure extending to twenty-four to thirty months — as would occur during a Mars transit — is entirely uncharacterised in any human dataset. Stavnichuk et al. note that existing data do not permit characterisation of skeletal responses beyond twelve-month missions, and the temporal pattern of bone loss over longer durations — including whether loss rates attenuate, plateau, or continue linearly — remains unknown in humans and requires prospective study with standardised QCT and HR-pQCT imaging outcomes. For mission planning purposes, the conservative assumption of persistent losses at ARED-era rates is appropriate until contradicted by prospective data.(Stavnichuk et al., 2020; Smith et al., 2012; Sibonga et al., 2019) On that basis, a simple linear extrapolation from ARED-era monthly hip loss rates of approximately 0.5–0.6% per month(Smith et al., 2012; Sibonga et al., 2019) would project cumulative proximal femur BMD deficits of 12–18% after a 24-month Mars transit — a calculation that, while illustrative of the potential magnitude, assumes constant loss rates and has not been empirically tested in missions of that duration.

Partial-Gravity Environments: Moon and Mars

Lunar gravity (approximately 0.16 g) and Martian gravity (approximately 0.38 g) represent skeletal loading environments for which virtually no direct human bone data exist. It remains unclear whether partial gravity provides enough mechanical stimulation to prevent progressive bone loss, or whether it merely slows the rate compared with near-zero gravity. No controlled human data exist to answer this. Animal studies using centrifuge-based partial gravity simulation have suggested a possible threshold effect, with some skeletal compartments showing attenuated loss at fractional gravity levels, but as Stavnichuk et al. note, these findings cannot be reliably extrapolated to humans over extended durations.(Stavnichuk et al., 2020) Defining the minimum effective gravitational loading dose for bone preservation, characterising the skeletal response to partial gravity transitions, and determining whether ARED-equivalent exercise in 0.38 g provides adequate protection are among the highest-priority physiological research objectives for the Artemis and Gateway programmes — objectives for which no published human data currently exist.

Personalised Countermeasure Applications

The threefold to fourfold inter-individual range in monthly hip BMD loss observed across crewmembers on nominally identical ARED protocols is not merely a statistical observation — it has direct implications for mission safety and countermeasure design. Population-level protocols that are adequate for the median responder may be substantially inadequate for the highest-risk individuals, who accumulate mission-induced deficits far exceeding group means while appearing to receive the same intervention. Stratifying crewmembers by pre-flight risk and adjusting countermeasure intensity accordingly would address this variability.

Pre-flight assessment of individual risk is the starting point for any personalised approach. Candidate stratification inputs include: DXA-derived areal BMD and T-score at the hip and spine; HR-pQCT-derived trabecular microarchitectural parameters (trabecular number, thickness, and separation at the distal tibia); pre-flight biochemical markers including baseline sclerostin and P1NP, which Gabel et al. demonstrated are predictive of in-flight bone loss magnitude;(Gabel et al., 2022) and genomic variants in SOST, VDR, ESR1, and COL1A1, which have been associated with differential bone density and mechanosensitivity in terrestrial population studies, as reviewed by Zwart et al.(Gabel et al., 2022) No validated pre-flight risk stratification tool exists for spaceflight. Gabel et al. showed that pre-flight biomarker profiles predicted in-flight bone loss,(Gabel et al., 2022) and Orwoll et al. identified individual risk stratification as a priority need without defining a validated stratification algorithm.(Orwoll et al., 2013) Developing such a tool from existing ISS cohort data — which includes pre-flight DXA, HR-pQCT where available, and biomarker profiles — is a concrete, achievable near-term research objective that does not require new data collection.

In practice, stratification might work across three levels. Crewmembers identified as low-risk on pre-flight assessment (above-average trabecular density, normal biochemical markers, no high-risk genomic variants) could continue standard ARED protocols with close in-mission biomarker monitoring. Intermediate-risk crewmembers could receive augmented protocols — potentially including additional ARED sessions, structured supplementary brief loading bouts as described in Section 4.6, and WBV adjuncts — with QCT surveillance at six months post-flight in addition to the standard twelve-month DXA. Crewmembers in the high-risk category — pre-flight T-score approaching −1.0, low HR-pQCT trabecular number, elevated baseline sclerostin, or relevant genomic variants — may be candidates for bisphosphonate consideration. Post-flight

rehabilitation timing should take into account the six-month repair window data from Walle et al.(Walle et al., 2024; Orwoll et al., 2013)

Another option is to use in-mission biomarker data to adjust the protocol as the mission progresses. Standardised in-flight serum CTX and P1NP assays have been performed in previous ISS biosampling programmes, including those reported by Gabel et al. and Smith et al., demonstrating feasibility.(Smith et al., 2012; Gabel et al., 2022) If performed at one and three months into a mission, crewmembers showing above-expected resorption marker elevation or below-expected formation marker maintenance could be identified for protocol intensification — a responsive rather than purely predictive model of personalised countermeasure delivery. What is still missing is agreement on what threshold should trigger a change — for example, how far above preflight baseline a 30-day CTX value needs to be before action is taken. Sibonga et al. proposed QCT-based triggers for post-flight pharmacological intervention but did not define in-mission biomarker thresholds.(Sibonga et al., 2020) No published NASA or international space agency guidance currently specifies marker values that warrant in-mission protocol modification.

Sex Differences in Skeletal Response

Most spaceflight bone studies have been conducted in male crewmembers. This reflects the historical composition of the astronaut corps rather than any scientific rationale. As female representation increases, emerging analyses suggest sex-related differences in skeletal response and recovery trajectories consistent with established terrestrial differences in bone microarchitecture, hormonal regulation, and mechanical loading response between men and women.(Gabel et al., 2022) Female crewmembers may face additional skeletal risk factors: lower baseline trabecular bone microstructural reserve at the hip and distal tibia, hormonal fluctuations associated with contraceptive use in spaceflight, and potential oestrogen deficiency-related acceleration of bone loss in perimenopausal crewmembers on later-career long-duration missions. Adequately powered prospective studies stratified by sex — explicitly accounting for hormonal contraceptive type, menstrual cycle status, and menopausal stage — are required to establish whether current ARED protocols are equivalently protective across sexes and to characterise sex-specific countermeasure requirements.

Exercise Prescription Optimisation

Despite ARED's central role in ISS countermeasures, its prescription parameters — loading intensity, exercise selection, sets and repetitions, weekly frequency, session duration, and periodisation structure — have not been formally optimised through controlled dose-response experimentation. Key questions include: what is the minimum effective loading dose required for adequate skeletal protection within operational scheduling constraints? Do periodisation strategies — progressive overload cycles, exercise rotation, planned deload periods — improve long-term skeletal adaptations over the static protocol currently employed? Does the temporal ordering of resistance and aerobic exercise within a session influence osteogenic signalling, as suggested by concurrent training research in terrestrial populations? Controlled bed-rest factorial trials systematically varying these prescription parameters are the most practically achievable path to answering these questions and could directly inform updated ISS exercise prescriptions ahead of lunar and Mars mission planning; the NASA bed-rest programme and the ongoing MABL-B investigation aboard the ISS confirm that the research infrastructure for such controlled studies is operational.(Koppelmans et al., 2015)

Imaging and Biomarker Standardisation

The absence of standardised post-flight imaging protocols across space agencies limits longitudinal data comparability and statistical power of pooled analyses. QCT should be a required adjunct to DXA in post-flight bone surveillance, with absence of trabecular volumetric BMD recovery at two years constituting a trigger for specialist review.(Sibonga et al., 2020) HR-pQCT should be incorporated as a standard outcome in future ISS research cohorts. Circulating biomarkers — sclerostin, DKK1, CTX, and P1NP — monitored at standardised mission timepoints could serve as countermeasure monitoring tools and pharmacological intervention triggers. Formal agreement between NASA, ESA, JAXA, and Roscosmos on common imaging modalities, acquisition protocols, and biomarker panels would substantially enhance the statistical power of the collective ISS bone dataset.

Prioritised Research Agenda

The preceding sections identify multiple knowledge gaps. The following priority ranking is based on three practical criteria: proximity to a current mission decision; feasibility with existing infrastructure; and the size of the safety gap addressed.

The most immediate needs are those achievable with existing infrastructure. Standardising QCT alongside DXA in post-flight surveillance across agencies requires protocol agreement rather than new technology. Developing a pre-flight risk stratification tool from existing ISS cohort data is an analytical project

requiring no new data collection. Over a 2–5 year horizon, the bed-rest programme can address ARED dose-response optimisation, WBV as an adjunct, and a pilot trial of IV zoledronic acid. Longer-term priorities — adequately powered sex-stratified ISS cohort studies, partial-gravity analogue experiments, and the first controlled anti-sclerostin spaceflight trial — require infrastructure and resources not currently in place.

Box 1. Best-Evidence Countermeasure Recommendations for ISS-Duration Missions

Exercise (foundational, highest evidence):

ARED-based resistance: 3–6 sessions/week; squat, deadlift, heel raise at ≥70% 1RM. (Smith et al., 2012; Sibonga et al., 2019)

Combined aerobic: daily treadmill running and cycle ergometry as complement.

Nutrition (required foundation):

Calcium: 1,000–1,200 mg/day. Vitamin D: 2,000–4,000 IU/day; target 25(OH)D ≥50 nmol/L. (Smith et al., 2012)

Protein: ≥1.2 g/kg/day; maintain body mass and energy balance.

Pre-flight: Optimise baseline BMD and vitamin D; use HR-pQCT where available for risk stratification.

Post-flight (critical window): Commence progressive loading within 6 months of landing. (Walle et al., 2024)

QCT surveillance at 1 and 2 years; absence of trabecular recovery at 2 years triggers review. (Sibonga et al., 2020)

Investigational / high-risk (specialist supervision required):

Bisphosphonates: controlled spaceflight evidence exists. (Orwoll et al., 2013; LeBlanc et al., 2013)

WBV as ARED adjunct.

Romosozumab: strong mechanistic rationale; no spaceflight trial; cardiac pre-screening required. (Saag et al., 2017)

Note: Research-context recommendations only — not clinical prescriptions.

Discussion

ARED-based resistance exercise has reduced bone loss relative to aerobic-only protocols,(Smith et al., 2012; Sibonga et al., 2019) and the mechanobiological rationale for why it should work is solid. What is less satisfying is that proximal femur deficits persist, and QCT and HR-pQCT continue to document trabecular losses that DXA misses entirely. The protection is partial. One limitation that is easy to understate: astronauts exercise for roughly two hours a day. The remaining twenty-two hours are spent in near-zero gravity, with osteoclastic activity continuing through RANKL-driven and sclerostin-driven pathways that a single daily exercise bout does not switch off. That gap is a core reason pharmacological approaches have been explored.

Individual responses to ARED protocols vary considerably — monthly hip BMD losses range threefold to fourfold across crewmembers on nominally identical regimens. This variability has practical consequences. First, group-level effect estimates will understate the skeletal deficit experienced by the most susceptible individuals. Second, the existence of crewmembers who show minimal loss under current protocols confirms that the mechanobiological principle underpinning ARED is sound; the variability is more likely attributable to differences in adherence, loading technique, energy balance, or genetic susceptibility than to a fundamental failure of the intervention concept.

Bed-rest analog data are the best controlled evidence available — but extrapolation to spaceflight has real limits. Head-down tilt retains a gravitational vector, normal atmospheric pressure, and a psychological context that differs substantially from orbit. Unexercised bed-rest subjects lose bone at 0.5–1.5% per month, consistently less than spaceflight rates of 0.5–2.0%. Traon et al. attribute the gap to physiological stressors beyond mechanical unloading alone.(Pavy-Le Traon et al., 2007) The hierarchy of countermeasure modalities seen in bed-rest trials is arguably transferable to spaceflight; absolute effect sizes are not.

The pharmacological evidence base is narrow — arguably too narrow to support strong recommendations. The Orwoll et al. bisphosphonate trial is the only randomised spaceflight pharmacological trial conducted to date;(Orwoll et al., 2013) its small sample (n = 14 per group), absence of fracture endpoints, and wide confidence intervals limit the precision of its efficacy estimates. A further concern involves the long skeletal half-life of alendronate. Persistent antiresorptive activity during the early post-flight period could interfere with the targeted repair response described by Walle et al.,(Walle et al., 2024) and this remains an

unresolved consideration for its use across all crewmembers. The mechanistic justification for anti-sclerostin therapy rests on the Walle et al. correlation data alone;(Walle et al., 2024) no interventional spaceflight trial has been conducted, and the ARCH trial cardiovascular signal(Saag et al., 2017) requires pre-screening that may be disqualifying for some crewmembers. For missions of 24 months or more, linear extrapolation from ARED-era hip loss rates of 0.5–0.6% per month(Smith et al., 2012; Sibonga et al., 2019) projects proximal femur BMD deficits of 12–18% — a range derived from six-month data applied to untested durations and therefore a lower-bound estimate subject to revision. The absence of human skeletal data for Martian partial gravity (0.38 g), combined with the vertebral fracture risk demonstrated by Burkhart et al.,(Burkhart et al., 2020) means that no evidence-based countermeasure standard exists for missions of this length and type.

Implications for Sport Science and Athletic Training

It is worth noting how much of the theoretical foundation for spaceflight exercise countermeasures comes from sport science. Turner's rules — that bone responds to high-magnitude strain, novel loading patterns, and accommodates to repeated stimulation — emerged from in vivo loading experiments.(Turner, 1998) They are now the mechanistic basis for both athletic resistance training and ARED prescription. The spaceflight results also mirror what sport scientists have long observed: impact and resistance athletes consistently have greater bone density at weight-bearing sites than endurance athletes, for the same mechanobiological reasons.(Turner, 1998)

Periodisation concepts from athletic training may offer a useful framework for thinking about ARED prescription optimisation, though this has not yet been formally tested. In strength and conditioning, progressive overload — systematic increases in loading magnitude, volume, and exercise variation over a training cycle — prevents accommodation and sustains long-term skeletal adaptation. The current ISS ARED protocol employs a relatively static prescription across six-month missions, with no planned variation in loading pattern or intensity progression. Applying periodised models used in high-performance athletic preparation could sustain osteogenic stimulation across longer missions where accommodation to a fixed protocol reduces efficacy — an application directly testable in bed-rest analog trials using study designs standard in sport science.(Koppelmans et al., 2015)

The concept of brief high-impact loading used in sport injury prevention and osteoporosis management in recreational athletes also has direct relevance to the supplementary loading strategies reviewed in Section 4. Research in sport science has demonstrated that as few as 10 high-impact loading cycles per day produce detectable site-specific bone formation responses in postmenopausal women, showing that short, strategically timed bouts contribute measurably to skeletal adaptation without requiring extended exercise time.(Rubin & Lanyon, 1984) Translating this to the spaceflight context — where daily exercise time is limited — suggests that brief supplementary loading bouts around ARED sessions could add meaningful osteogenic stimulus, a hypothesis directly amenable to testing in controlled bed-rest research. There is more overlap between spaceflight bone research and sport science than is currently reflected in the collaboration between these fields.

Conclusions

ARED works, but incompletely. Bone loss rates are lower than the aerobic-only era,(Smith et al., 2012; Sibonga et al., 2019) but deficits remain — especially at the proximal femur and in the trabecular compartment. A proportion of crewmembers show incomplete recovery at two years even after DXA values have normalised.(Vico et al., 2017; Walle et al., 2024; Sibonga et al., 2020) The discordance between DXA and QCT recovery trajectories identified by Sibonga et al.(Sibonga et al., 2020) is a clinically relevant finding that supports incorporation of QCT into post-flight surveillance as a standard rather than optional component. The time-limited nature of post-flight site-specific bone repair described by Walle et al.(Walle et al., 2024) indicates that the early post-landing period represents a window of particular importance for rehabilitation intensity and pharmacological timing.

The pharmacological evidence, though limited, is sufficient to support some degree of differentiation in recommendations. Calcium 1,000–1,200 mg/day and vitamin D 2,000–4,000 IU/day are indicated for all crewmembers.(Smith et al., 2012) For those meeting high-risk criteria — hip T-score at or below −1.0, prior in-flight loss above 1.5%/month, or low HR-pQCT trabecular number — weekly oral alendronate 70 mg may be considered from three weeks pre-flight. It should be discontinued at landing to avoid interfering with the post-flight repair window.(Walle et al., 2024; Orwoll et al., 2013) The evidence base for this is a single small trial. Romosozumab and denosumab are not recommended for routine ISS use on current evidence: romosozumab requires cardiovascular pre-screening(Saag et al., 2017) and denosumab requires operationally unachievable sequential therapy on discontinuation.(Anastasilakis et al., 2021)

For missions beyond twelve months, including Mars transits of 24–30 months, the honest answer is that we do not know whether current protocols are adequate. Six-month ISS data cannot be linearly extrapolated to those durations, and skeletal responses to partial-gravity environments after prolonged microgravity have never been measured in humans. Priority research needs include: dose-response optimisation of ARED prescription parameters through controlled bed-rest factorial trials; standardisation of QCT alongside DXA in post-flight surveillance protocols; prospective controlled trials of anti-sclerostin pharmacotherapy; characterisation of skeletal responses to lunar and Martian partial gravity; and adequately powered studies stratified by sex. Progress on these questions is needed before evidence-based countermeasure guidance can be developed for the exploration missions currently in planning.

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