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Lessons from Space: Microgravity-Induced Bone Loss and Osteoporosis

Santhosh Kumar T N, Chaithanya Nambiar

Department of Orthopedics ESIC PGIMSR MC & Model Hospital, Rajainagar, Bengaluru

Corresponding Author: Santhosh Kumar T N, *ESIC PGIMSR MC & Model Hospital, Rajainagar, Bengaluru.*

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Osteoporosis is a chronic skeletal disorder characterised by reduced bone mass and microarchitectural deterioration, ultimately increasing susceptibility to fragility fractures and long-term morbidity (1). A major challenge in osteoporosis research is its slow and progressive nature; clinically meaningful bone loss often develops over decades, making longitudinal mechanistic studies and rapid therapeutic evaluation difficult (2). Conventional terrestrial models—including ovariectomised animals, ageing models, and dietary manipulations—successfully reproduce selected hormonal or metabolic aspects of osteoporosis but often fail to capture the full complexity of mechanically driven bone remodelling dysfunction (3). In this context, microgravity environments, encountered during spaceflight or replicated through ground-based unloading models, have emerged as powerful experimental systems that induce rapid and reproducible skeletal deterioration, thereby offering an accelerated window into bone loss mechanisms (4,5).

Microgravity-induced bone loss occurs at a striking rate of approximately 1–2% per month in weight-bearing skeletal regions such as the femur, tibia, and lumbar spine, far exceeding the pace observed in age-related or post-menopausal osteoporosis on Earth (4,6). This rapid deterioration enables the observation of early molecular and cellular events that are otherwise difficult to capture in traditional models. Importantly, ground-based analogues such as hindlimb unloading in rodents and prolonged bed rest in humans reproduce many of these skeletal outcomes, including trabecular thinning, reduced bone mineral density, compromised mechanical strength, and altered bone architecture within weeks (5,7). However, despite their widespread use, existing terrestrial models often inadequately replicate the profound mechanical unloading that is central to skeletal homeostasis, underscoring the unique translational value of microgravity research (8).

A shared hallmark between microgravity-induced bone loss and terrestrial osteoporosis is the disruption of balanced bone remodelling. Under normal gravitational conditions, mechanical loading stimulates osteoblast differentiation and function through mechanotransduction pathways that translate physical forces into biochemical signals (9). In microgravity, the absence of mechanical strain suppresses osteoblast activity while promoting osteoclast-mediated bone resorption, resulting in a net loss of bone mass (4,10). While this imbalance parallels the remodelling defects observed in post-menopausal osteoporosis—where estrogen deficiency drives increased osteoclastogenesis—the underlying initiating factors differ, highlighting both convergence and divergence between these conditions (1,11). Microgravity therefore represents a complementary, rather than identical, model of osteoporotic bone loss.

At the mechanistic level, emerging evidence implicates disruption of key mechanosensory systems, including integrins, primary cilia, and mechanosensitive ion channels such as Piezo1, in microgravity-induced skeletal deterioration (9,12). These mechanosensors play critical roles in detecting mechanical load and activating downstream signalling cascades essential for osteogenesis. Their impaired activation under unloading conditions contributes to suppression of Wnt/β-catenin signalling, reduced osteoblast differentiation, and enhanced osteoclast activity (10,13). Concurrent dysregulation of the RANK/RANKL/OPG axis has been consistently reported, favouring osteoclast maturation and bone resorption (11,14). In addition, increased oxidative stress, altered calcium metabolism, and fluid redistribution further modulate skeletal responses in microgravity, features that do not fully mirror terrestrial osteoporosis and warrant cautious interpretation (6,15).

Despite substantial advances, important gaps remain. Not all studies report uniform alterations across mechanotransduction pathways, and the temporal hierarchy linking mechanical unloading to irreversible skeletal deterioration remains incompletely understood (8,12). Moreover, the extent to which early microgravity-induced molecular changes predict long-term osteoporotic outcomes on Earth has yet to be fully clarified. Addressing these limitations is essential for strengthening the translational relevance of microgravity-based skeletal research.

Against this background, the present studies should seek to investigate specific molecular mechanisms governing bone remodelling dysregulation under microgravity-simulated conditions. By focusing on specific pathway/biomarker/model, the studies should be carried out aimng to bridge existing mechanistic gaps and to identify unloading-responsive targets with relevance to terrestrial osteoporosis, thereby extending microgravity research from descriptive parallels toward hypothesis-driven translational insight.

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