REVIEW OPEN ACCESS

Gravity: An Essential Factor in Skeletal Health and Bone Homeostasis

Saviya Kashif[1], Khansa Kashif[2]

[1]*College of Molecular Medicine, Ziauddin University, Karachi, Pakistan*

[2]*Department of Physical Therapy, Iqra University, Karachi, Pakistan*

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Abstract

Gravity contributes significantly to bone integrity and bone health. If gravity is absent or reduced, resulting in massive loss of bone density and structural impairment, like astronauts, who lose much of their bone mass and structure, when they are in space. Human bones are highly responsive to mechanical loading, which is controlled mainly by gravitational forces. This review aimed to show the physiological, cellular, and molecular mechanisms through which gravity influences bone remodeling. It focuses attention on how mechanical loading and weight-bearing activities contribute to maintaining bone mass and the prevention of osteoporosis. The role of osteocytes as mechanosensors, the impact of microgravity on gene expression, and epigenetic modifications linked to skeletal deterioration are also discussed. This narrative review addresses some of the implications of prolonged weightlessness, potential measures for bone loss in space, and opportunities for insights into osteoporosis prevention and treatment on Earth. This narrative review was conducted by examining peer-reviewed literature from databases including PubMed and Google Scholar, using keywords such as 'gravity,' 'bone health,' 'osteoporosis,' and 'epigenetics.' Relevant studies were selected based on their contribution to understanding the physiological impact of gravity on skeletal integrity. It provides recommendations for emerging research into artificial gravity, whole-body vibration therapy, and medicines designed to preserve skeletal health. The contribution of gravity in bone physiology to preventing and treating bone disease is critical for developing strategies to prevent bone deterioration in both space travelers and persons with long-term sedentary lifestyles and conditions of musculoskeletal disorders. Understanding the role of microgravity experiments can contribute to understanding techniques for the prevention and treatment of osteoporosis on Earth.

Keywords: Gravity, bone remodeling, microgravity, osteocytes, osteoporosis, mechanotransduction, skeletal adaptation, artificial gravity, bone loss, epigenetics.

1. INTRODUCTION

Bone is a constantly growing system of tissues that can grow and remodel itself; this remodeling activity is controlled by mechanical loading and gravity [1]. When gravity is lowered (lower than normal), such as after prolonged bed rest or spaceflight, bone density decreases (and thus fracture risk increases) [2]. Mechanical forces also directly affect osteocytes, osteoblasts, and osteoclasts [3]. These cell types direct and coordinate the complex process of creating and resorbing bone, and disruption of this balance results in profound skeletal consequences, including osteoporosis, increased bone fragility, and poor structural integrity [4].

Mechanotransduction (the ability of bone cells to convert mechanical signals into biochemical responses) is fundamental to bony homeostasis [5]. The effect of mechanical loading from gravity on mechanically abundant bone neurons has been characterized by the activation of various intracellular signaling pathways important for bone metabolism, including the Wnt/catenin pathway, the RANKL/OPG signaling

*Address correspondence to this author at the College of Molecular Medicine, Ziauddin University, Karachi, Pakistan; E-mail: saviya.kashif@zu.edu.pk

pathway, and sclerostin-mediated osteogenesis [6]. Mechanotransduction studies offer insights into how the effects of prolonged microgravity on bone homeostasis can be understood [7].

As human space exploration extends beyond Earth's orbit, the problem of skeletal degeneration in astronauts is increasing in importance [8]. Also, the ground-based application of research from spaceflight may benefit people with osteoporosis, age-related bone loss, or immobilization-induced skeletal degeneration. The review assessed the essential role of gravity in maintaining bone homeostasis, its consequences and the current and future interventions to counter bone loss.

2. DISCUSSION

Bone remodeling occurs when osteoclasts resorb bone and osteoblasts subsequently deposit bone [9]. Gravity serves as a mechanical stimulus that promotes osteoblast activity and reduces excessive osteoclast activity [10]. Engaging in weight-bearing activities, such as walking and resistance exercise, can help to maintain bone mass since bone mass is maintained when covering strain to the skeletal system causes a stimulus to stimulate osteoblast activity [11].

2.1. The Role of Gravity in Bone Remodeling

Gravity plays a crucial role in skeletal health and bone homeostasis by influencing bone formation, maintenance, remodeling, and mechanical loading [10]. Table **1** provides a summary of the effect of gravity on bone health. In normal gravity, bone formation is supported by increased activity in osteoblasts and balanced resorption of bones, which helps keep mass stable; microgravity, on the other hand, reduces the differentiation of osteoblasts and increases the activity of osteoclasts, resulting in bone loss and greater porosity.

Table 1: Effects of gravity on bone health.

Normal Gravity	Microgravity
Increased osteoblast activity	Reduced osteoblast differentiation
Balanced bone resorption	Increased osteoclast activity
Bone mass maintained	Bone loss, increased porosity

2.2. Mechanotransduction Pathways

Mechanical loading *via* gravity activates mechanoreceptors located on osteocytes, which will then stimulate the release of signaling molecules, such as prostaglandins, nitric oxide, and ATP, which maintain and modulate osteoblastic activity [12].

2.3. Impact on Bone Cells

Osteocytes are the key mechanosensors, which are able to sense strain and communicate with osteoblasts and osteoclasts to modulate whole bone mass. Absence of gravity will lead to reduced connectivity in osteocytes, leading to impairments in modulating bone remodeling [13].

2.4. Gene Expression and Epigenetic Changes

Research indicates that mechanical unloading can change the expression of bone-related genes, including RUNX2 and SOST [14, 15]. Moreover, epigenetic changes can also occur, such as DNA methylation and histone modifications, which contribute to skeletal adaptation in microgravity [16].

2.5. Effects of Microgravity on Bone Health

2.5.1. Bone Loss in Spaceflight

Studies on astronauts show that prolonged exposure to microgravity leads to rapid bone loss, particularly in weight-bearing bones like the femur and spine. The reduction in mechanical loading results in increased bone resorption and decreased bone formation [17, 18].

2.5.2. Changes in Bone Microarchitecture

When exposed to microgravity, trabecular bone thins, and cortical bone porosity increases, predisposing these structures to fracture. Changes in collagen matrix content also negatively affect and worsen the structural stability of bone [19].

2.6. Molecular and Cellular Mechanisms

Altered mechanical stress in microgravity influences multiple signaling pathways, such as reduced Wnt/β-catenin signaling, increased RANKL/OPG ratio, and altered expression of sclerostin, which leads to an imbalance in bone remodeling [1, 4]. Furthermore, bone loss is accelerated by the alterations in osteoblast-osteoclast coupling and disruption of the cytokine network seen during spaceflight studies [20].

Table **2** outlines how microgravity influences certain bone cell activity. Increased apoptosis and insensitivity to mechanical cues in osteocytes translate to lower bone mass. Diminished osteoblastic activity and greater sclerostin concentrations lead to lower bone formation.

Increased bone resorption is associated with more active osteoclasts owing to elevated RANKL.

Table 2: Cellular effects of microgravity on osteocytes, osteoblasts, and osteoclasts.

Effect of Microgravity on Bone Cells	Cellular Response	Outcome
Osteocytes	Increased apoptosis, reduced mechano-sensation	Decreased bone mass
Osteoblasts	Suppressed differentiation, increased sclerostin	Reduced bone formation
Osteoclasts	Upregulated RANKL, increased activity	Increased bone resorption

2.7. Epigenetic Regulation of Bone in Altered Gravity

Emerging research suggests epigenetic changes may have an impact on the skeletal adaptation to reduced gravity by altering the expression of genes regulating osteoblasts and osteoclasts. Epigenetic changes differ from genetic mutations, as epigenetic alterations can be reversed to help mitigate bone loss in astronauts, as well as in individuals with osteopenia/osteoporosis [21]. There are 3 main avenues of epigenetic regulation (DNA methylation, histone modifications, and microRNA "miRNA" regulation) that likely contribute to the altered bone remodeling associated with microgravity [22, 23].

2.8. DNA Methylation and Osteogenic Gene Suppression

DNA methylation involves the addition of methyl groups to cytosine residues within CpG islands, leading to gene silencing or activation depending on the target genes [24]. In microgravity, studies have shown that hypermethylation of Wnt pathway genes results in the suppression of osteoblast differentiation and reduced bone formation [25]. The Wnt/β-catenin signaling pathway is crucial for osteogenesis, and its downregulation leads to decreased bone mass [26]. Conversely, hypomethylation of RANKL (Receptor Activator of Nuclear Factor Kappa-B Ligand) genes increases osteoclast activity, thereby accelerating bone resorption [27]. Additionally, epigenome-wide association studies have identified differentially methylated regions (DMRs) in skeletal stem cells exposed to simulated microgravity, which may explain the long-term effects of spaceflight on bone health [28].

2.9. Histone Modifications and Bone Loss

Histone modifications, such as acetylation, methylation, and phosphorylation, alter chromatin accessibility and influence gene expression [29]. In microgravity, reduced H3K27 acetylation has been linked to impaired osteoblast differentiation, as this modification is associated with active transcription of osteogenic genes [22]. Additionally, increased H3K9 methylation, a marker of transcriptional repression, has been found to silence genes essential for bone formation, further contributing to osteoporosis-like symptoms in astronauts [30]. These histone modifications suggest that microgravity induces a shift toward a bone-resorptive state by altering chromatin dynamics, ultimately favoring osteoclastogenesis while suppressing osteoblast activity [31].

2.10. MicroRNA (miRNA) Dysregulation

miRNAs are small non-coding RNAs that post-transcriptionally regulate gene expression by targeting messenger RNA (mRNA) for degradation or translational inhibition. Microgravity conditions have been shown to upregulate miR-214, which directly inhibits osteoblast function by suppressing ATF4, a transcription factor critical for bone matrix formation [32]. In contrast, downregulation of miR-21, a miRNA known to promote osteoblast proliferation and differentiation, further exacerbates bone loss. The altered miRNA expression profile observed in spaceflight suggests a shift in cellular signaling networks that suppress bone formation and enhance resorption [33]. Moreover, circulating exosomal miRNAs have been identified as potential biomarkers for bone loss in astronauts, providing insight into how space-induced epigenetic changes may translate to clinical applications on Earth [34].

2.11. Strategies to Decrease Bone Loss

2.11.1. Resistance Exercise and Mechanical Loading

To counteract bone loss, exercise regimens such as high-impact exercise and resistance training have been utilized in space [35]. The Advanced Resistive Exercise Device (ARED) is an exercise device that mimics weight-bearing training while in microgravity. Research suggests that multi-modal training, with endurance, resistance, and high-impact loading, produces the most beneficial effects [35].

2.11.2. Pharmacological Treatment

Bisphosphonates, selective estrogen receptor modulators (SERMs), and possible use of sclerostin inhibitors are being investigated to prevent bone loss for astronauts as

well as individuals at risk for osteoporosis [36]. New research is also investigating the potential for anabolic agents, such as parathyroid hormone analogs, to be utilized [37].

2.11.3. Artificial Gravity and Vibration

Centrifugation and whole-body vibration are potential methods to effect gravity loading, thereby allowing for an intervention to maintain bone health. Animal testing indicates that intermittent artificial gravity loading may enhance osteogenic activity, while whole-body vibration has shown promise to maintain bone mass in the osteogenic process via increased proliferation of osteoblasts and decreased activity of osteoclasts [38].

2.11.4. Nutritional Strategies

Adequate intake of calcium and vitamin D continues to be important for bone health. Recent studies are also evaluating omega-3 fatty acids, protein supplementation, and vitamin K as possible agents of promoting bone anabolism in microgravity [39, 40]. This narrative review provides a broad insight into the impact of gravity on bone health; however, it is not a systematic review. The absence of predefined inclusion criteria, uniform study quality assessment, and quantitative pooling hampers the arbitrability of the results among the studies. Consequently, the findings were more speculative and interpretative, and additional systematic reviews or meta-analyses are needed to confirm and expand upon these findings.

CONCLUSION

Gravity is necessary for healthy bones, primarily owing to the mechanical stimulation of bone-forming cells and the inhibition of bone resorption. The effect of microgravity on bone health documented in astronauts reinforces the importance of gravitational loading in sustaining bone health. Ongoing research regarding exercise, pharmacology, and simultaneous artificial gravity studies is necessary to advance countermeasures to help counteract the effects of microgravity, as well as susceptibility to fractures and osteoporosis/osteopenia on Earth. Future studies should attempt to optimize the efficacy of these strategies and interventions to best protect both astronaut and terrestrial bone health. In addition to exercise and pharmacology, continued research regarding epigenetic changes, as well as gene therapy approaches, holds promise in determining innovative therapeutic interventions for mitigating bone loss with microgravity and aging.

LIST OF ABBREVIATIONS

ARED: Advanced Resistive Exercise Device

OPG: Osteoprotegerin

RANKL: Receptor Activator of Nuclear Factor Kappa-B Ligand

SERMs: Selective Estrogen Receptor Modulators

Wnt: Wingless-Related Integration Site

SOST: Sclerostin

RUNX2: Runt-Related Transcription Factor 2

OPG: Osteoprotegerin Gene

CONFLICT OF INTEREST

The authors declare there is no conflict of interest.

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AUTHOR CONTRIBUTIONS

All authors contributed equally.

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