Sylvia R. Karasu M.D.
The Gravity of Weight

Melatonin and the Anguish of the Marrow

This hormone may have a role in the treatment of osteoporosis.

Posted September 24, 2022

KEY POINTS

- **Bone remodeling is a dynamic process that occurs throughout life and reflects a balance between bone resorption and bone formation.**
- **Osteopenia and osteoporosis, diagnosed by degrees of low bone mass and bone tissue deterioration, lead to substantial morbidity and mortality.**
- **Melatonin may minimize the adverse effects of microgravity on bone in astronauts during prolonged space flight.**

"Skeleton," 1956, by English artist John Bratby. Private Collection.

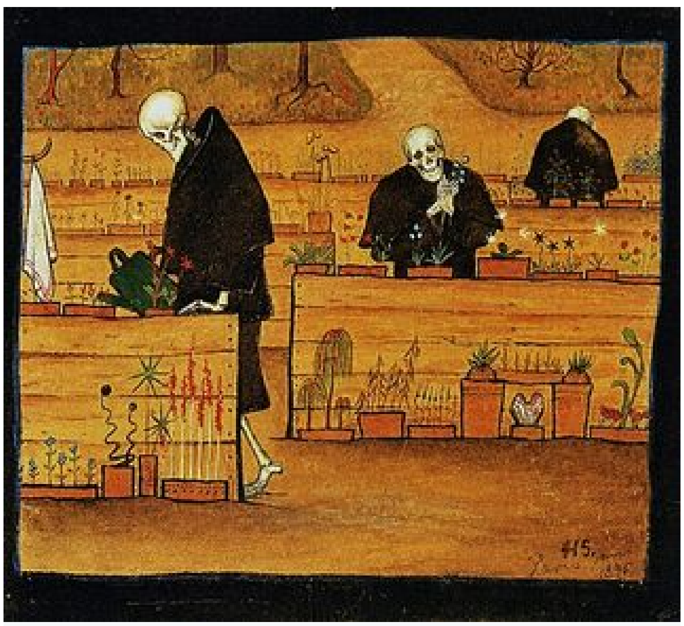
Source: Photo credit: Copyright, Estate of John Bratby. All rights reserved 2022/Bridgeman Images. Used with permission.

Many writers have waxed poetic about the fragility of our bones: Shakespeare wrote of “marrowless bones” (*Macbeth*) and “hollow bones” (*Measure for Measure)*, while T.S. Eliot wrote of “the anguish of the marrow, the ague of the skeleton” (*Whispers of Immortality*).

There is nothing poetic, though, about osteoporosis, "the most common metabolic disease of bone" (Sandyk et al., 1992).

Osteoporosis, with its "insidious loss of bone" (Sandyk et al.), is a progressive, chronic "systemic skeletal disease" (Liu et al., 2013.) It is characterized by degrees, first presenting as osteopenia of low bone mass and "microarchitectural deterioration" of bone tissue. Bones become fragile, with significant morbidity and mortality, particularly when hip and vertebral fractures result (Li et al., 2019.)

One in three women and one in five men over age 50 worldwide will develop an osteoporotic fracture within their lifetime (Munmum and Witt-Enderby, 2021.) Projections indicate that by 2030, without intervention, 64.3 million Americans will develop osteopenia and 11.9 million will have osteoporosis (Lu et al., 2021.)



"Garden of Death," by Finnish artist Hugo Simberg, 1896. Osteoporosis may result in considerable morbidity and even mortality in both men and women.

Source: Wikimedia Commons/Public Domain.

Bone-remodeling occurs throughout life and is a "dynamic process" reflecting a "fine balance" between osteoclast-mediated bone resorption and osteoblast-mediated bone formation. This process regulates calcium balance, heals overt fractures, and repairs minute cracks secondary to daily activity (Munmun and Witt-Enderby.) Bone metabolism, including the repair and remodeling of bone, is closely regulated by circadian rhythms (Lu et al.)

Genetics plays a role, but the process is also exquisitely sensitive to physiological changes in the body, including changes due to aging, exercise, immobilization, diet, vitamin deficiencies, smoking, excessive alcohol consumption, circadian misalignment, and medications like steroids (Malakoti et al., 2022.)

Melatonin is a hormone produced at night by the pineal gland in the brain. As we age, melatonin levels fall. It has been suggested that declines in these levels, with accompanying declines in the “bone-protective” hormones such as estrogen, testosterone, and progesterone, as seen with aging, may contribute to an imbalance in the remodeling of bone and even the progressive loss of bone. With changes in hormonal levels, women after menopause are particularly vulnerable to developing osteopenia and ultimately full-blown osteoporosis (Munmum and Witt-Enderby.)

Further, growing evidence suggests that inflammation and oxidative stress contribute to osteoporosis and its imbalance between bone formation and resorption (Guan et al., 2022.) As an anti-inflammatory and “free radical scavenger,” melatonin may be therapeutic in preventing bone loss (Amstrup et al., 2013; Munmum & Witt-Enderby.)

It has even been suggested that plasma melatonin levels around menopause could be used as a "marker of potential susceptibility" for the development of osteoporosis after menopause or even as "prophylaxis" to treat women at risk (Sandyk et al.)

Netsuke figure of a crouching skeleton. Japanese, 19th century. Images of skeletons appear throughout art, including miniature carved figurines. Metropolitan Museum of Art, NYC.

Source: Photo credit: Album. Alamy Stock Photo. Used with permission.

Researchers, for example, found melatonin levels in postmenopausal women with osteoporosis were significantly lower than in young women with normal bone mass and suggested that melatonin levels could serve as an "auxiliary diagnostic index" for osteoporosis (Cao et al., 2022.)

For a review of this extraordinary natural hormone, which can inhibit inflammation and tumor production and have cardiovascular, immunological, and neurological benefits (Guan et al.; Lu et al.), see my previous post.

To date, there is no effective therapy that reverses osteoporosis: the medications developed can inhibit further bone deterioration and inhibit bone resorption, but most fail to result in "extensive" new bone formation and fail to reverse bone loss that has occurred (Sánchez-Barcelò et al., 2010; Li et al.)

Further, some medications, such as bisphosphonates, have untoward side effects, including osteonecrosis of the jaw, and require expensive, prolonged use (Ikegame et al., 2019.) As a result, there is often poor patient compliance and an imperative need to develop better therapies (Cao et al.)

"Skeletons Warming Themselves," by English artist James Ensor, 1889. Melatonin may have a role in both preventing and treating osteoporosis.

Source: Wikimedia Commons/Public Domain.

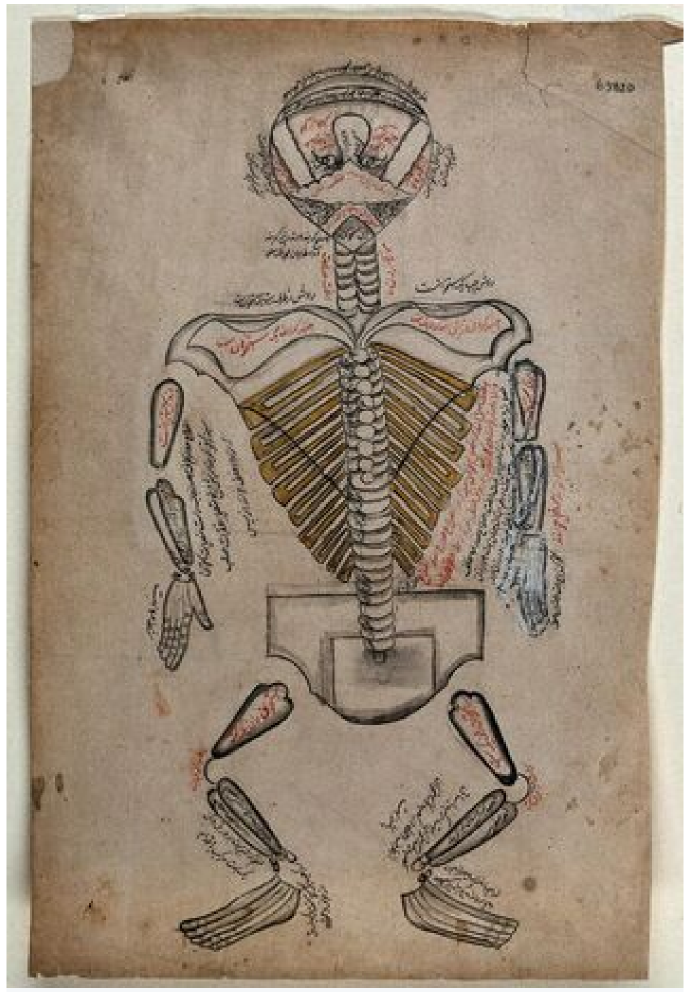
Melatonin, though, with its excellent safety profile, may not only prevent bone loss but may have a role in maintaining "bone homeostasis" (López-Muñoz et al., 2022; Li et al.) Further, it may have "strong effects" locally since it is not only produced in the pineal gland but in many other tissues, including the bone marrow itself (Li et al.) In other words, could melatonin be used as a "novel" means of increasing bone mass? (Cardinali et al., 2003.)

Evidence from research in cell models, animal models, and even human clinical trials has accumulated that melatonin may have an "anti-osteoporosis" role (Li et al.) and even "holds the potential to be a standalone anti-osteoporosis therapy" (Zhao et al., 2022.)

In one animal study, melatonin increased bone mass in normal, peri-menopausal, and postmenopausal rats whose bone mass had decreased after researchers had removed their ovaries (Guan et al.)

In another animal model, melatonin also led to increased bone mass and was able "to reverse completely" the "architectural deterioration and functional defects" in the bones of mice made osteoporotic secondary to menopause (Sharan et al., 2017.)

Clinical studies in postmenopausal women with osteopenia have found that treatment with melatonin for a year increased bone mineral density in a dose-dependent fashion and suggested that melatonin has the "potential" to be a treatment for osteoporosis (Li et al.; Malakoti et al.)



A skeleton. Watercolor drawing by a Persian artist. 19th century, part of the "Alexandrian series."

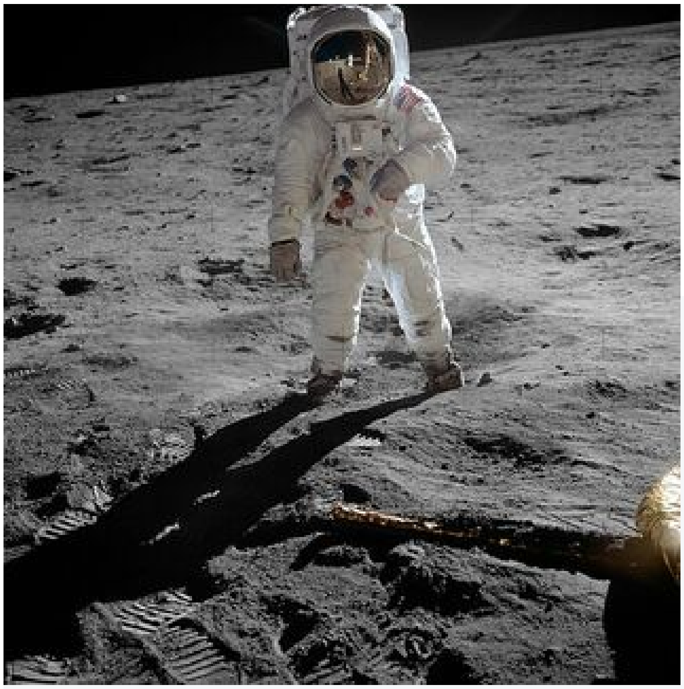
Source: Wellcome Trust Collection. Licensed under Creative Commons/Public Domain.

A major limitation, though, is that evidence is still lacking in establishing protocols for the use of melatonin: specific dosage, duration, and timing regimens for clinical efficacy remain largely unknown (Malakoti et al.)

One exciting potential use of melatonin is in preventing bone loss and the negative effects on bone metabolism induced by weightlessness and "microgravity" during space flights (Malakoti et al.; Ikegame et al.) The precise mechanisms for bone loss under these conditions are unknown and remain "one of the key challenges" for astronauts. By increasing calcitonin secretion, melatonin inhibits osteoclastic activity that microgravity conditions stimulate (Ikegame et al.)

Further, melatonin may be used in conjunction with bone graft materials to stimulate the regeneration of bone and even to protect bone from radiation as well as from vascular damage due to fractures (Lu et al.)

Though more clinical trials are warranted, melatonin provides hope for diagnosing and treating the "anguish of the marrow."



Buzz Aldrin's walk on the moon, July 21, 1969. Apollo 11 Mission Commander Neil Armstrong took the photo. Conditions of microgravity lead to decreased bone density. Treating astronauts with melatonin holds promise.

Source: Wikimedia Commons/Public Domain.

References

Amstrup AK et al. Melatonin and the skeleton. *Osteoporosis International* 24(12): 2919-27.Article 851663, 2013.

Cao L et al. Melatonin mediates osteoblast proliferation through STIM1/ORAL1 pathway. *Frontiers in Pharmacology* 13. Article 851663 (8 pages), 2022.

Cardinali et al. Melatonin effects on bone: experimental facts and clinical perspectives. *Journal of Pineal Research* 34(2): 81-87, 2003.

Eliot TS. *Whispers of Immortality.* In: *Poems* (Alfred A. Knopf, 1920): https://www.poetryfoundation.org/poems/52563/whispers-of-immortality. Retrieved: 9/19/22.

Guan H et al. Melatonin increases bone mass in normal, perimenopausal, and postmenopausal osteoporotic rats via the promotion of osteogenesis. *Journal of Translational Medicine* 20(1): 132 (15 pages), 2022.

Ikegame M et al. Melatonin is a potential drug for the prevention of bone loss during space flight. *Journal of Pineal Research* 67(3): e12594 (13 pages), 2019.

Li T et al. Melatonin: another avenue for treating osteoporosis? *Journal of Pineal Research* 66(2): e12548 (12 pages), 2019.

Liu J; F. Huang; Hong-Wen H. Melatonin effects on hard tissues: bone and tooth. *International Journal of Molecular Sciences* 14(5): 10063-74, 2013.

López-Muñoz et al. Editorial: therapeutic advances in melatonin research. *Frontiers in Pharmacology* 13: article 947117 (2 pages), 2022.

Lu X et al. Insight into the roles of melatonin in bone tissue and bone-related diseases (review). *International Journal of Molecular Sciences* 47(5): 82 (19 pages), 2021.

Malakoti F et al. The role of melatonin in bone regeneration: a review of involved signaling pathways. *Biochimie* (Article-in-press) (15 pages), 2022.

Munmum F; Witt-Enderby P. Melatonin effects on bone: implications for use as a therapy for managing bone loss. *Journal of Pineal Research* 71(1): e12749. (24 pages), 2021.

Sánchez-Barceló EJ et al. Scientific basis for the potential use of melatonin in bone diseases: osteoporosis and adolescent idiopathic scoliosis. *Journal of Osteoporosis:* 830231 (10 pages). 2010.

Sandyk R et al. Is postmenopausal osteoporosis related to pineal gland functions? *International Journal of Neuroscience* 62(3-4): 215-225, 1992.

Shakespeare W. *Measure for Measure* I, ii, 54. In: *The Oxford Shakespeare: The Complete Works* (Compact Edition). Stanley Wells et al, Editors: Oxford: Clarendon Press, 1998, p. 792.

Shakespeare W. *The Tragedy of Macbeth* III, iv, 94. In: *The Oxford Shakespeare: The Complete Works* (Compact Edition). Stanley Wells et al, Editors: Oxford: Clarendon Press, 1998, p. 988.

Sharan et al. Regulation of bone mass through pineal-derived melatonin-MT2 receptor pathway. *Journal of Pineal Research* 63(2): e12423, 2017.

Zhao Y et al. Assessment of the therapeutic potential of melatonin for the treatment of osteoporosis through a narrative review of its signaling and preclinical and clinical studies. *Frontiers in Pharmacology* 13: article 866625 (15 pages),2022.

About the Author

Sylvia R. Karasu, M.D., is a clinical professor of psychiatry at Weill Cornell Medical College and the senior author of *The Gravity of Weight.*

Online: my own website