

Do Hibernating Mammals Lose Bone Mass?

A Review of Disuse Osteoporosis and Mammalian Torpor

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1 Introduction

Age-related osteoporosis affects tens of millions of individuals worldwide. Estimations of disease prevalence are scarce for the developing world (Handa, Kalla, & Maalouf, 2008), but range in developed countries from 1% to 8% in men and 9% to 38% in women above 50 years of age (Wade, Strader, Fitzpatrick, Anthony, & O'Malley, 2014). Understanding the biological mechanisms underlying the condition is an important long-term pursuit of public health research.

Osteoporosis can also result from reduced mechanical loading on bones, classified separately from age-related bone loss as disuse osteoporosis. The response of bone to mechanical stimuli, altering its mass and morphology to meet the load-bearing stressors demanded of it, has been long recognized as Wolff's Law (Wolff, 1986), usually modeled as a dual feedback loop between bone stressors and bone deposition or loss (Ruff, Holt, & Trinkaus, 2006). Heightened risk of bone fracture is well-documented amongst patients following long-term hospitalization for stroke (Kanis, Oden, & Johnell, 2001; Wei, Lyu, Huo, & Su, 2018) or spinal cord injury (Wang, Chen, DeVivo, & Huang, 2001). Astronauts' exposure to weightlessness results in drastic and rapid bone density loss (Holick, 1998; LeBlanc et al., 2000), which has been replicated in mice (Aguirre et al., 2009) and rats (Garber, McDowell, & Hutton, 2000).

Despite humans' and rats' experience of disuse osteoporosis, sedentary lifestyles which would in humans contribute to significant bone loss – for instance, hibernation – are found in multiple mammalian taxa including Rodentia (Daan, Barnes, & Strijkstra, 1991; Mzilikazi, Madikiza, Oelkrug, & Baxter, 2012), Carnivora (Tøien et al., 2011), and Primates (Dausmann, Glos, Ganzhorn, & Heldmaier, 2004). The length of time many of these mammals spend in hibernation is enough to cause extreme bone degradation in many non-hibernating animals. How these species' regular torpor affects their bone growth and resorption can give novel insights into medicine both terrestrial and in space.

2 Central Questions in Forming Connections between Torpor and Osteoporosis

Understanding the relationship between torpor and osteoporosis requires investigation of three central questions:

1. *What physiological mechanisms underlie disuse osteoporosis?* Bone density is a complex physiological system mediated by multiple processes in different parts of the body. Teasing out which mechanisms

are responsible for disuse osteoporosis in particular is necessary to understand how hibernation plays a role in its mediation.

2. *Do all hibernating animals share an evolutionary history?* Hibernation occurs in many families of mammals. If hibernation is an ancestral trait, then its absence in separate taxa may be linked to development of disuse osteoporosis in multiple groups independently; conversely, if hibernation is a derived trait in its separate taxa, then the prevention of disuse osteoporosis may have developed independently.
3. *Do hibernating animals experience disuse osteoporosis?* If hibernating animals do not experience a loss of bone density despite long-term sedentary practice, it can provide insights into how bone is formed and density regulated in all mammals.

2.1 Physiology of Disuse Osteoporosis

Disuse osteoporosis, despite having structural similarity to that associated with aging, is notable for its rapid onset. Cessation of bone stress induces bone loss at ten times the rate of that occurring in post-menopausal osteopenia (Bloomfield, 2010), indicating a different mechanism or combination of mechanisms inducing the condition.

In humans, disuse osteoporosis occurs most commonly in bed rest patients immobilized by a medical condition. However, the population most well-suited as models for the phenomenon is astronauts, whose dual status as government-employed scientists and test subjects provides a wealth of information on their experience. Along with the various other medical conditions associated with microgravity, this spaceflight osteopenia presents a significant health risk to astronauts. Recent estimations of bone density loss in low-Earth orbit find astronauts lose on average 1% of bone mass per month, especially concentrated in the long bones (Lang et al., 2004).

Disuse osteoporosis traditionally presents as excess resorption of bone, which has been disputed over whether via extended resorption time (Bain & Rubin, 1990) or increase in abundance of osteoclasts relative to osteoblasts (Weinreb, Rodan, & Thompson, 1989). Following this resorption, bones lose structural integrity and mechanical properties (Li et al., 2005), resulting in significantly weaker bone (McGee-Lawrence, Carey, & Donahue, 2008). Not all bone is equally susceptible to degradation – trabeculae have been shown to decrease in mass at a rate approximately fivefold that of cortical bone (Lang et al., 2004), which has been attributed to the greater surface area of trabecular bone for osteoclast function (McGee-Lawrence, Carey, & Donahue, 2008).

While the usual recommendation to prevent bone loss is to increase weight-bearing activity (Kohrt, Bloomfield, Little, Nelson, & Yingling, 2004), there is some evidence to suggest there is more at play in disuse osteopenia than a lack of bodyweight resistance. Even astronauts keeping to the current proscribed ISS exercise regimen – 2-3 hours of resistance training per day and wearing clothing inducing passive resistance – is insufficient at reducing spaceflight osteopenia (LeBlanc et al., 2000). Attempts to address this dichotomy have been highly varied and the subject of much academic debate. Scholars disagree over which mechanical stimulus most adequately explains Wolff's Law, whether fluid flow, strain rate, magnitude, or distribution, or loading frequency (Patel, Judex, Rubin, & Rubin, 2020).

In analyzing the impact of mechanical forces on bone cellular structure, researchers have used whole-body vibration as a proxy for the gravitational and muscle forces experienced in non-sedentary life (de Zepetnek, Giangregorio, & Craven, 2009). Whole-body vibration has been found to be strongly associated with incidence of industrial injury, especially lower-back pain (Cardinale & Pope, 2003); however, Rubin, Sommerfeldt, Judex, and Qun (2001) argue that at low magnitudes, vibration can be osteogenic to the point of doubling the rate of bone growth. With such a wide gulf between the magnitude of its harms and benefits, the medical community remains apprehensive about vibration as an osteoporosis therapy (Wysocki, Butler, Shamliyan, & Kane, 2011) especially considering the high variability in commercially-available devices (Muir, Kiel, & Rubin, 2013), but it remains a novel way to understand bone loading.

Other researchers have looked towards the fluid pooling associated with immobility as a causative agent, regardless of weight-bearing (Bloomfield, 2010). Within ten minutes of unloading, rats' hindlimbs rapidly lose blood flow and cephalic fluid volume, which becomes only further pronounced after 28 days (Colleran et al., 2000). In turkeys, immobilization leading to significant bone loss has been mitigated by artificially

increasing fluid volume and pressure (Qin, Kaplan, Saldanha, & Rubin, 2003). Given this, Bloomfield (2006, 2010) has proposed interstitial fluid pressure as the main predictive and diagnostic tool for understanding disuse osteoporosis.

2.2 Evolution and Physiology of Hibernation

Mammals are not the only class that practice hibernation – many species of birds have been observed in a torpid state in both the wild and induced conditions, but the physiology of their hibernation is not well understood (Lyman, 1982). Regardless, it provides evidence for regular torpor as a widespread and evolutionarily old trait. Geiser (2008) has argued for three separate events in which chordates evolved torpor: a plesiomorphic evolution early in the development of both marsupials and birds, and once as a derived trait in placental mammals. Kikuchi and Vanneste (2010) used the probable environmental conditions following the K-Pg asteroid impact to argue for the mass extinction as a selection event in favor of hibernating mammals. Rapid change in atmospheric O₃ concentration at the K-Pg boundary is proposed as the leading cause of mammalian extinction, where only torpid mammals were able to reduce their exposure to safe levels. Lovegrove (2012) used a maximum likelihood phylogeny to trace the history of mammalian hibernation beyond the K-Pg boundary to the split between marsupials and placental mammals 144 mya, finding a ML of 0.58 for torpor at the root of the tree.

Although the physiological function of torpor may be evolutionarily old, its practice in individual species shows marked diversity and adaptability. Dausmann, Nowack, Kobbe, and Mzilikazi (2012) argue that the differences in hibernation between three heterothermic strepsirrhine species derive not from physiological changes but from evolutionary and reproductive strategy. Torpor, while most known in the context of overwintering, also has lesser-explored physiological and fitness functions. Torpor can provide benefits in times of resource disadvantage, postponing nutrient and water needs until more favorable periods. Furthermore, individual species utilize hibernation for lesser-understood functions such as female sperm storage and migratory fat buildup (Geiser & Brigham, 2012). Another hibernation mechanism more analogous to that of bone deposition may be the management of the immune system. Like osteons, immune cells are dispersed throughout the body, created in marrow, and are heavily dependent on serum composition. During hibernation, leukocyte count drops by 90%, adaptive immunity is drastically depressed, and antibody production slows (Bouma et al., 2012).

2.3 Torpor and Osteoporosis

Research into mammalian hibernation has found some evidence for bone loss in small mammals. Decline in bone mass has been identified in bats (Krook, Wimsatt, Whalen, MacIntyre, & Nunez, 1977), hamsters (Steinberg, Singh, & Mitchell, 1981), and ground squirrels (McGee-Lawrence et al., 2011). Krook et al. (1977) explain this phenomenon as “obviously, the maintenance of calcium levels compatible with survival” (p. 271); however, the majority of these studies have been primarily observational and are thus limited in explanatory potential (McGee-Lawrence, Carey, & Donahue, 2008). Complicating this is the observation that while bats’ bones decrease in mass during hibernation, they remain until late in the hibernation period denser than in the summer (Bruce & Wiebers, 1970), potentially implying that bone is built up in preparation for overwintering as is done with fat stores. More recent quantitative work on hibernating ground squirrels has identified trabecular microstructural bone loss, but without any corresponding loss in cortical bone strength or macrostructure (McGee-Lawrence et al., 2011). It is hypothesized that these animals have an as-yet-unidentified biological mechanism to maintain bone strength for future use while simultaneously using trabecular bone as mineral storage for metabolism.

Bears’ bones, in contrast, have long been understood to maintain mass throughout hibernation. While past theories involved the idea of bone degradation followed by rapid bone formation after leaving hibernation (McGee-Lawrence, Carey, & Donahue, 2008), *in vivo* studies have found balanced levels of resorption and formation in hibernating bears (McGee-Lawrence, Maki, et al., 2008), suggesting a physiological adaptation to hibernation. Blood serum measurements in polar bears indicate that bone formation may be accelerated during hibernation, although methodological limitations preclude detailed data (McGee-Lawrence, Carey, & Donahue, 2008). Furthermore, serum measurements are unable to assess localized differences in bone degradation, which is important in researching disuse osteoporosis as long bones are more susceptible than

are other bones (Lang et al., 2004). Trabecular bone, which in humans is the most affected by disuse, showed no difference between bears killed just before or after hibernation (Parady, Wohl, Ukrainetz, & Sawers, 2004), lending credence to the theory that bears are able to maintain bone throughout hibernation rather than rebuild in the spring and summer.

3 Discussion

Sampling bones of killed animals before and after hibernation, while able to show whether they experience disuse osteoporosis, fails to indicate by what mechanism this is mediated. Hibernation involves a number of physiological behaviors that are of interest in considering bone loss. To increase body temperature and stave off hypothermia, both bears (Lin, Egeland, Schertenleib, Nelson, & Robbins, 2004; Tøien et al., 2011) and smaller mammals (Daan et al., 1991; Geiser, 2004) are known to shiver on a regular periodic basis. Following the hypothesis of low-magnitude vibration, hibernating animals' shivering practices may be a mechanism to stimulate bone growth and maintenance despite disuse. In contrast, McGee-Lawrence, Carey, and Donahue (2008) propose a number of neuronal and hormonal mechanisms that may mediate osteon activity via leptin, parathyroid hormone, or norepinephrine. However, these associations are at best correlative with no verifiable biological pathway.

3.1 Areas for Future Study

Hibernation being a trait ancestral to mammals implies that the development of disuse osteoporosis may be an evolutionarily recent trait, appearing after the loss of hibernation in an ancestral lineage. As many of the non-hibernating mammals are also those in lineages with larger brains, Heldstab, Isler, and van Schaik (2018) propose hibernation as a constraint on brain size evolution, using the expensive brain hypothesis. Adapting this research to examine whether brain size evolution is also connected to the physiological mechanisms underlying disuse osteoporosis could prove promising.

Even if hibernating mammals do have physiological mechanisms to prevent osteoporosis from disuse, as there is clear evidence for in some species, it is still notable that the animals are still operating at an energy deficit. During hibernation, many animals excrete waste from their metabolic processes, which contains calcium and other nutrients used to build and maintain bone (McGee-Lawrence, Carey, & Donahue, 2008). In humans, decrease in BMI within healthy boundaries has no correlated effect on bone strength (Kelley et al., 2018), but this is in a species that continues to consume food and nutrients during weight loss. Hibernating animals' metabolic processes, however slowed, is not similarly supplemented with an intake of calories or nutrients. How mammals that excrete waste products during hibernation can maintain bone structure is a potential area of further research.

One unexplored area of research is whether hibernating animals experience disuse osteopenia even outside of the torpid state. Nearly all limb-immobilization studies have been performed on animals who do not hibernate, such as laboratory rats (Weinreb et al., 1989) and dogs (Li et al., 2005). Performing such experiments on bears presents many methodological difficulties, but could enlighten theories of how disuse osteoporosis is prevented. Crucially, whether they experience disuse osteoporosis outside of a state of torpor grants clues as to whether such a process is exclusive to the special metabolic state experienced during hibernation or whether it evolved as a separate process.

References

- Aguirre, J. I., Plotkin, L. I., Stewart, S. A., Weinstein, R. S., Parfitt, A. M., Manolagas, S. C., & Bellido, T. (2009). Osteocyte apoptosis is induced by weightlessness in mice and precedes osteoclast recruitment and bone loss. *Journal of Bone and Mineral Research*, *21*(4), 605–615. doi:10.1359/jbmr.060107
- Bain, S. D., & Rubin, C. T. (1990). Metabolic modulation of disuse osteopenia: Endocrine-dependent site specificity of bone remodeling. *Journal of Bone and Mineral Research*, *5*(10), 1069–1075. doi:10.1002/jbmr.5650051011
- Bloomfield, S. A. (2006). Does altered blood flow to bone in microgravity impact on mechanotransduction? *Journal of Musculoskeletal and Neuronal Interactions*, *6*(4), 324–326.

- Bloomfield, S. A. (2010). Disuse osteopenia. *Curent Osteoporosis Reports*, 8(2), 91–97. doi:10.1007/s11914-010-0013-4
- Bouma, H. R., Strijkstra, A. M., Talaie, F., Henning, R. H., Carey, H. V., & Kroese, F. G. M. (2012). The hibernating immune system. In T. Ruf, C. Beiber, W. Arnold, & E. Millesi (Eds.), *Living in a seasonal world: Thermoregulatory and metabolic adaptations* (Chap. 23, pp. 259–270). doi:10.1007/978-3-642-28678-0_23
- Bruce, D. S., & Wiebers, J. E. (1970). Calcium and phosphate levels in bats (*Myotis lucifugus*) as a function of season and activity. *Experientia*, 26(6), 625–627. doi:10.1007/BF01898726
- Cardinale, M., & Pope, M. H. (2003). The effects of whole body vibration on humans: Dangerous or advantageous? *Acta Physiologica Hungarica*, 90(3), 195–206. doi:10.1556/APhysiol.90.2003.3.2
- Colleran, P. N., Wilkerson, M. K., Bloomfield, S. A., Suva, L. J., Turner, R. T., & Delp, M. D. (2000). Alterations in skeletal perfusion with simulated microgravity: A possible mechanism for bone remodeling. *Journal of Applied Physiology*, 89(3), 1046–1054. doi:10.1152/jappl.2000.89.3.1046
- Daan, S., Barnes, B. M., & Strijkstra, A. M. (1991). Warming up for sleep? – ground squirrels sleep during arousals from hibernation. *Neuroscience Letters*, 128(2), 265–268. doi:10.1016/0304-3940(91)90276-Y
- Dausmann, K. H., Glos, J., Ganzhorn, J. U., & Heldmaier, G. (2004). Hibernation in a tropical primate. *Nature*, 429, 825–826. doi:10.1038/429825a
- Dausmann, K. H., Nowack, J., Kobbe, S., & Mzilikazi, N. (2012). Afrotropical heterothermy: A continuum of possibilities. In T. Ruf, C. Beiber, W. Arnold, & E. Millesi (Eds.), *Living in a seasonal world: Thermoregulatory and metabolic adaptations* (Chap. 2, pp. 13–27). doi:10.1007/978-3-642-28678-0_2
- de Zepetnek, J. O. T., Giangregorio, L. M., & Craven, B. C. (2009). Whole-body vibration as potential intervention for people with low bone mineral density and osteoporosis: A review. *Journal of Rehabilitation Research & Development*, 46(4), 429–542. doi:10.1682/jrrd.2008.09.0136
- Garber, M. A., McDowell, D. L., & Hutton, W. C. (2000). Bone loss during simulated weightlessness: A biomechanical and mineralization study in the rat model. *Aviation, Space, and Environmental Medicine*, 71(6), 586–592.
- Geiser, F. (2004). Metabolic rate and body temperature reduction during hibernation and daily torpor. *Annual Review of Physiology*, 66, 239–274. doi:10.1146/annurev.physiol.66.032102.115105
- Geiser, F. (2008). Ontogeny and phylogeny of endothermy and torpor in mammals and birds. *Comparative Biochemistry and Physiology Part A: Molecular & Integrative Physiology*, 150(2), 176–180. doi:10.1016/j.cbpa.2007.02.041
- Geiser, F., & Brigham, R. M. (2012). The other functions of torpor. In T. Ruf, C. Beiber, W. Arnold, & E. Millesi (Eds.), *Living in a seasonal world: Thermoregulatory and metabolic adaptations* (Chap. 10, pp. 109–121). doi:10.1007/978-3-642-28678-0_10
- Handa, R., Kalla, A. A., & Maalouf, G. (2008). Osteoporosis in developing countries. *Best Practice & Research Clinical Rheumatology*, 22(4), 693–708. doi:10.1016/j.berh.2008.04.002
- Heldstab, S. A., Isler, K., & van Schaik, C. P. (2018). Hibernation constrains brain size evolution in mammals. *Journal of Evolutionary Biology*, 31(10), 1582–1588. doi:10.1111/jeb.13353
- Holick, M. F. (1998). Perspective on the impact of weightlessness on calcium and bone metabolism. *Bone*, 22(5), 105S–111S. doi:10.1016/S8756-3282(98)00014-3
- Kanis, J., Oden, A., & Johnell, O. (2001). Acute and long-term increase in fracture risk after hospitalization for stroke. *Stroke*, 32(3), 702–706. doi:10.1161/01.STR.32.3.702
- Kelley, J. C., Stettler-Davis, N., Leonard, M. B., Hill, D., Wrotniak, B. H., Shults, J., . . . Zemel, B. S. (2018). Effects of a randomized weight loss intervention trial in obese adolescents on tibia and radius bone geometry and volumetric density. *Journal of Bone and Mineral Research*, 33(1), 42–53. doi:10.1002/jbmr.3288
- Kikuchi, R., & Vanneste, M. (2010). A theoretical exercise in the modeling of ground-level ozone resulting from the K–T asteroid impact: Its possible link with the extinction selectivity of terrestrial vertebrates. *Palaeogeography, Palaeoclimatology, Palaeoecology*, 288(1-4), 14–23. doi:10.1016/j.palaeo.2010.01.027
- Kohrt, W. M., Bloomfield, S. A., Little, K. D., Nelson, M. E., & Yingling, V. R. (2004). Physical activity and bone health. *Medicine & Science in Sports & Exercise*, 36(11), 1985–1996. doi:10.1249/01.MSS.0000142662.21767.58
- Krook, L., Wimsatt, W. A., Whalen, J. P., MacIntyre, I., & Nunez, E. A. (1977). Calcitonin and hibernation bone loss in the bat (*Myotis lucifugus*). *The Cornell Veterinarian*, 67, 265–271.

- Lang, T., LeBlanc, A., Evans, H., Lu, Y., Genant, H., & Yu, A. (2004). Cortical and trabecular bone mineral loss from the spine and hip in long-duration spaceflight. *Journal of Bone and Mineral Research*, *19*(6), 1006–1012. doi:10.1359/JBMR.040307
- LeBlanc, A., Schneider, V., Shackelford, L., West, S., Oganov, V., Bakulin, A., & Voronin, L. (2000). Bone mineral and lean tnumber loss after long duration space flight. *Journal of Musculoskeletal & Neuronal Interactions*, *1*(2), 157–160.
- Li, C. Y., Price, C., Delisser, K., Nasser, P., Laudier, D., Clement, M., . . . Schaffler, M. B. (2005). Long-term disuse osteoporosis seems less sensitive to biophosphonate treatment than other osteoporosis. *Journal of Bone and Mineral Research*, *20*(1), 117–124. doi:10.1359/JBMR.041010
- Lin, D. C., Egeland, L. A., Schertenleib, K. W., Nelson, O. L., & Robbins, C. T. (2004). Intermittent muscle activation in grizzly bears during hibernation: A strategy to prevent muscle atrophy? Society for Neuroscience Annual Meeting Program, San Diego: Society for Neuroscience.
- Lovegrove, B. G. (2012). A single origin of heterothermy in mammals. In T. Ruf, C. Beiber, W. Arnold, & E. Millesi (Eds.), *Living in a seasonal world: Thermoregulatory and metabolic adaptations* (Chap. 1, pp. 3–11). doi:10.1007/978-3-642-28678-0_1
- Lyman, C. P. (1982). Who is who among the hibernators. In C. P. Lyman, J. S. Willis, A. Malan, & L. C. H. Wang (Eds.), *Hibernation and torpor in mammals and birds* (pp. 12–36). New York: Academic Press.
- McGee-Lawrence, M. E., Carey, H. V., & Donahue, S. W. (2008). Mammalian hibernation as a model of disuse osteoporosis: The effects of physical inactivity on bone metabolism, structure, and strength. *Comparative and Evolutionary Physiology*, *295*(6), R199–R2014. doi:10.1152/ajpregu.90648.2008
- McGee-Lawrence, M. E., Maki, A. J., Johnson, S. E., Nelson, O. L., Robbins, C. T., & Donahue, S. W. (2008). Decreased bone turnover with balanced resorption and formation prevent cortical bone loss during disuse (hibernation) in grizzly bears (*Ursus arctos horribilis*). *Bone*, *42*(2), 396–404. doi:10.1016/j.bone.2007.10.010
- McGee-Lawrence, M. E., Stoll, D. M., Mantila, E. R., Fahrner, B. K., Carey, H. V., & Donahue, S. W. (2011). Thirteen-lined ground squirrels (*Ictidomys tridecemlineatus*) show microstructural bone loss during hibernation but preserve bone macrostructural geometry and strength. *Journal of Experimental Biology*, *214*(8), 1240–1247. doi:10.1242/jeb053520
- Muir, J., Kiel, D. P., & Rubin, C. T. (2013). Safety and severity of accelerations delivered from whole body vibration exercise devices to standing adults. *Journal of Science and Medicine in Sport*, *16*(6), 526–531. doi:10.1016/j.jsams.2013.01.004
- Mzilikazi, N., Madikiza, Z., Oelkrug, R., & Baxter, R. M. (2012). Hibernation in free-ranging African woodland dormice, *Graphiurus murinus*. In T. Ruf, C. Bieber, W. Arnold, & E. Millesi (Eds.), *Living in a seasonal world: Thermoregulatory and metabolic adaptations* (Chap. 4, pp. 41–50). doi:10.1007/978-3-642-28678-0_4
- Pardy, C. K., Wohl, G. R., Ukrainetz, P. J., & Sawers, A. (2004). Maintenance of bone mass and architecture in denning black bears (*Ursus americanus*). *Journal of Zoology*, *263*(4), 359–364. doi:10.1017/S0952836904005412
- Patel, V. S., Judex, S., Rubin, J., & Rubin, C. T. (2020). Mechanisms of exercise effects on bone quantity and quality. In J. P. Bilezikian, T. J. Martin, T. L. Clemens, & C. J. Rosen (Eds.), *Principles of bone biology* (4th, Chap. 76, pp. 1759–1784). doi:10.1016/B978-0-12-814841-9.00076-2
- Qin, Y.-X., Kaplan, T., Saldanha, A., & Rubin, C. (2003). Fluid pressure gradients, arising from oscillations in intramedullary pressure, is correlated with the formation of bone and inhibition of intracortical porosity. *Journal of Biomechanics*, *36*(10), 1427–1437. doi:10.1016/S0021-9290(03)00127-1
- Rubin, C. T., Sommerfeldt, D. W., Judex, S., & Qun, Y.-X. (2001). Inhibition of osteopenia by low magnitude, high-frequency mechanical stimuli. *Drug Discovery Today*, *6*(16), 848–858. doi:10.1016/S1359-6446(01)01872-4
- Ruff, C., Holt, B., & Trinkaus, E. (2006). Who’s afraid of the big bad Wolff? “Wolff’s law” and bone functional adaptation. *American Journal of Physical Anthropology*, *129*(4), 484–498. doi:10.1002/ajpa.20371
- Steinberg, B., Singh, I. J., & Mitchell, O. G. (1981). The effects of cold-stress, hibernation, and prolonged inactivity on bone dynamics in the golden hamster, *Mesocricetus auratus*. *Journal of Morphology*, *167*(1), 43–51. doi:10.1002/jmor.1051670105

- Tøien, Ø., Blake, J., Edgar, D. M., Grahn, D. A., Heller, H. C., & Barnes, B. M. (2011). Hibernation in black bears: Independence of metabolic suppression from body temperature. *Science*, *331*(6019), 906–909. doi:10.1126/science.1199435
- Wade, S. W., Strader, C., Fitzpatrick, L. A., Anthony, M. S., & O'Malley, C. D. (2014). Estimating prevalence of osteoporosis: Examples from industrialized countries. *Archives of Osteoporosis*, *9*, 182. doi:10.1007/s11657-014-0182-3
- Wang, C.-M., Chen, Y., DeVivo, M. J., & Huang, C.-T. (2001). Epidemiology of extraspinal fractures associated with acute spinal cord injury. *Spinal Cord*, *39*, 589–594. doi:10.1038/sj.sc.3101216
- Wei, M., Lyu, H., Huo, K., & Su, H. (2018). Impact of bone fracture on ischemic stroke recovery. *International Journal of Molecular Sciences*, *19*(5), 1533. doi:10.3390/ijms19051533
- Weinreb, M., Rodan, G. A., & Thompson, D. D. (1989). Osteopenia in the immobilized rat hind limb is associated with increased bone resorption and decreased bone formation. *Bone*, *10*(3), 187–194. doi:10.1016/8756-3282(89)90052-5
- Wolff, J. (1986). *The law of bone remodeling* (P. Maquet & R. Furlong, Trans.). doi:10.1007/978-3-642-71031-5
- Wysocki, A., Butler, M., Shamliyan, T., & Kane, R. L. (2011). Whole-body vibration therapy for osteoporosis: State of the science. *Annals of Internal Medicine*, *155*(10), 680–686. doi:10.7326/0003-4819-155-10-201111150-00006