

The Effects of Caloric Restriction and/or Intermittent Fasting on Bone Health

Connor A. Hernon^{1,2}, Abdullah Elsayed³, Raphael M. Vicente⁴, Ariane Zamarioli⁴, Melissa A. Kacena^{3,5,6}, Jonathan W. Lowery^{1,2,3,5,6}

¹Division of Biomedical Science, Marian University College of Osteopathic Medicine, Indianapolis, Indiana, USA

²Bone & Muscle Research Group, Marian University, Indianapolis, Indiana USA

³Department of Orthopaedic Surgery, Indiana University School of Medicine, Indiana, USA

⁴Department of Orthopaedics and Anaesthesiology, Ribeirão Preto Medical School, University of São Paulo, SP, Brazil

⁵Richard L. Roudebush VA Medical Center, IN, USA

⁶Indiana Center for Musculoskeletal Health, School of Medicine, Indiana University, Indianapolis, Indiana, USA

Article Info

Article Notes

Received: September 10, 2021

Accepted: December 31, 2021

*Correspondence:

Dr. Jonathan W. Lowery, PhD,
Marian University College of Osteopathic Medicine, 3200 Cold
Spring Rd, Indianapolis, Indiana, USA;
Email: jlowery@marian.edu

©2021 Lowery JW. This article is distributed under the terms of the Creative Commons Attribution 4.0 International License.

Keywords:

Intermittent Fasting
Caloric Restriction
Bone
Fracture
Osteoporosis

Abstract

This mini-review summarizes the available information regarding the impact of caloric restriction (CR) and/or intermittent fasting (IF) on bone health. CR and IF are dietary interventions used in rehabilitative healthcare for augmenting weight loss and also proposed for recovery of conditions such as stroke and heart failure. CR restricts the total number of calories rather than different food groups or periods of eating. In contrast, IF severely restricts caloric intake for a period of time followed by a period of ad libitum intake. Here, we discuss the available information regarding the impact of these rehabilitation diets on bone metabolism, highlighting areas of consistency and discrepancy and suggesting future areas of study to advance the understanding of CR and/or IF on bone health.

Introduction

Osteoporosis is a chronic condition characterized by low bone mass and places individuals at increased risk for fracture. Rehabilitation and lifestyle modifications that preserve and/or promote gains in bone mass include regular physical activity, resistance training and dietary modification such as increased protein intake, adequate intake of calcium and vitamin D, and supplementation with magnesium and, possibly, vitamin K¹⁻⁵. In contrast, numerous studies indicate that caloric restriction (CR) and/or intermittent fasting (IF), which have been proposed to augment rehabilitation for such conditions as stroke, cardiomyopathy, and heart failure⁶⁻⁹, may negatively impact bone health¹⁰⁻¹². Thus, it is important to clarify the impact of these diets on bone metabolism so that fracture risk is mitigated in the context of rehabilitative healthcare.

CR is a diet that restricts the total number of calories rather than different food groups or periods of eating¹³. The calorie limit is based upon a percentage of the recommended daily intake, which is calculated using the individual's basal metabolic rate. In contrast, IF severely restricts caloric intake for a period of time followed by a period of ad libitum intake¹⁴. The fasting period can be practiced in different ways such as fasting every other day, fasting for two to three days at a time, or even fasting during particular hours of each day (also referred to as time-restricted feeding). The effects of CR and/or IF on weight loss and other outcomes have been extensively

summarized elsewhere¹⁰⁻¹². However, not all of these effects are beneficial, as evidenced in the somewhat conflicting literature reporting on the impact that these diets have on bone metabolism. Here, we summarize this information, highlighting areas of consistency and discrepancy, and suggest future areas of study to advance the understanding of caloric restriction and/or intermittent fasting on bone health.

Bone Remodeling and Bone Health

Bone matrix is produced by cells called osteoblasts and resorbed by cells called osteoclasts. The balance of activity between these two cell populations determines bone mass and strength, which generally peaks in humans during early adulthood. When the actions of osteoblasts and osteoclasts are coupled, there is no net change in bone mass. However, when uncoupled in situations such as aging, the rate of bone resorption outpaces bone formation, leading to loss of bone mass. Low bone mass is a defining feature of osteoporosis and is a major risk factor for fracture [15], which places individuals at greater risk for disability and death. Thus, strategies aimed at building and/or preserving bone mass are of great clinical significance.

The most common clinical measure of bone mass is dual-energy X-ray absorptiometry (DXA), which determines areal bone mineral density. It is important to note that DXA provides only a snapshot of bone mass whereas other techniques, such as measurement of serum markers, provide greater detail about dynamic changes in skeletal physiology. The most clinically-validated markers for bone formation or bone resorption are Procollagen type-1 N-terminal propeptide (P1NP) and C-terminal telopeptide of type 1 collagen (CTX), respectively, hereafter referred to as “bone turnover markers”¹⁶. These factors inform about the activity of osteoblasts and osteoclasts, which themselves are regulated by numerous systemic and local regulators such as leptin, parathyroid hormone (PTH), calcitriol, calcitonin, growth hormone (GH), insulin-like growth factor 1 (IGF-1), glucocorticoids, thyroid hormones, estrogens, androgens, transforming growth factor (TGF)-beta, and cytokines^{17,18}. Below, we highlight some of these factors that are particularly germane to the study of caloric restriction and/or intermittent fasting.

Caloric Restriction and Bone Health

In this section, we discuss the existing studies examining the impact of caloric restriction on bone health with an emphasis on molecular markers of bone remodeling. Studies in this area vary widely in the 1) specific caloric restriction employed, 2) duration of dietary restriction, and 3) species (or strain) studied.

Hamrick et al. studied the effects of increasing caloric restriction with time on bone health in mice [19]. The mice

received a 10% restriction beginning at fourteen weeks of age, a 25% restriction at fifteen weeks of age, and a final 40% restriction at sixteen weeks of age continuing until twenty-four weeks of age. This resulted in varied responses by anatomical location and between cortical versus trabecular bone. Compared to mice fed ad libitum, calorie-restricted mice displayed decreased femoral and vertebral cortical thickness whereas trabecular bone in both locations was unchanged (femora) or increased (vertebrae). Importantly, calorie-restricted mice had reduced femoral fracture strength. These changes were associated with a decrease in both serum leptin and IGF-1 in response to caloric restriction. These results are generally consistent with Delvin et al., who studied the effects of 30% caloric restriction in mice from three weeks of age to twelve weeks of age²⁰. Compared to mice fed ad libitum, calorie-restricted mice displayed impaired skeletal growth resulting in smaller body size and low bone mass. These changes were associated with reduced bone formation rate with increased bone resorption rate and decreased levels of serum leptin and IGF-1. This is consistent with the work of Shien et al, who subjected obese rats to 35% caloric restriction for four months, resulting in decreased bone mineral density and lower leptin and IGF-1 along with changes in several other serum markers²¹. It is important to note that these findings differ somewhat from those observed in rats subjected to 30% caloric restriction from three weeks of age to seven weeks of age, which resulted in similar bone strength relative to body weight and increased trabecular bone volume in the lumbar spine compared to control²². That said, two studies in adult rats subjected to 30% or 40% caloric restriction indicates that the β -adrenoreceptor signaling plays a role in the response to energy restriction, with β -adrenergic blockade attenuating bone loss and preserving serum leptin levels following prolonged calorie restriction^{23,24}.

Interestingly, one study using mice and rats suggests that the effects of prolonged caloric restriction on bone mass appear impacted by age, with chronic caloric restriction preventing age-related bone loss. It is unclear if this finding is due to the prolonged nature of this intervention or if short duration caloric restriction in aged mice or rats impacts bone health²⁴. Indeed, twenty years of 30% caloric restriction in rhesus macaques – initiated between eight and fourteen years of age – led to only modest changes in bone volume related to smaller body mass with variable responses in serum markers of bone turnover²⁵.

Studies on the impact of caloric restriction in human subjects have produced inconsistent findings. For instance, Riedt et al. studied the effects of caloric restriction on obese premenopausal females subjected to a caloric deficit of approximately 30-40% with calcium supplementation for six months. Although leading to weight loss, this

intervention did not impact bone mineral density or serum bone turnover markers²⁶. This is generally consistent with a study involving 25% caloric restriction in overweight individuals that showed no change in bone mineral density, though this study reported changes in certain bone turnover markers²⁷. In contrast, Villareal et al. reported that prolonged 35% caloric restriction for an average of 6.8 ± 5.2 years leads to reduced bone mineral density²⁸. Notably, individuals on a high protein diet plus caloric restriction experience less bone loss than caloric restriction alone²⁹, suggesting that the amount of bone loss during caloric restriction may be mitigated by specifically increasing protein intake.

Intermittent Fasting and Bone Health

In this section, we discuss the relatively limited data examining the impact of intermittent fasting on bone health. As with caloric restriction, studies vary with regard to the duration and/or pattern of fasting, which creates difficulty in drawing generalizable conclusions. For instance, Clayton et al. examined how fasting for twenty-four hours affects bone turnover markers in humans during the re-feeding period and found no impact on bone turnover markers between fasting and control subjects³⁰. This is generally consistent with Barnosky et al. in which they compared six months of alternate-day fasting compared to caloric restriction on bone metabolism in obese adults. The intermittent fasting group was subjected to alternate-day fasting where the participants received 25% calories one day followed by 125% the next. The calorie-restricted group had a 35% energy restriction. Bone mineral density and bone turnover markers were unchanged in either group compared to individuals on the control diet³¹. In contrast, Bahijri et al. examined the effects of intermittent fasting on bone markers during the Muslim holiday of Ramadan in which observers fast from sunrise until sunset and found decreased evening PTH levels after two weeks of IF. This study did not include an assessment of bone mineral density and it is unclear if this effect is due to caloric restriction, sleep disturbance, or other factors such as alteration in mineral intake with evening serum calcium significantly higher during Ramadan³².

Limitations and need for Future Research

The focus of this mini-review was to examine the available data regarding the impact of caloric restriction and/or intermittent fasting on bone health. Significant discrepancies exist within this literature, especially with regard to the length of intervention, degree of restriction, etc. A relatively small sample size is an additional limitation, particularly for the human subject trials. This underscores the need for future work to replicate previous study designs and provide independent corroboration of findings in diverse patient populations. That said, it is

generally consistent across species and multiple studies that caloric restriction negatively influences bone mass; at present, it appears that intermittent fasting may not. It is important to note, however, that bone mass is only one aspect of fracture risk and measurements of fracture rate, bone strength, and bone quality are generally lacking in the studies detailed here. This presents a significant gap in our current knowledge about the long-term impact of caloric restriction and/or intermittent fasting on bone health. Furthermore, we are unaware of any published data about the impact of these diets on fracture healing itself, which is clinically significant since individuals practicing caloric restriction and/or intermittent fasting may experience fracture related to trauma or fragility. Future study is required to address this important limitation of the current literature.

Methods

A search of PubMed was conducted with the phrases “intermittent fasting and bone,” “intermittent fasting and skeleton not bone,” “caloric restriction and bone,” and “caloric restriction and skeleton not bone,” resulting in 285 articles. These articles were screened by CH and AE for relevance to the topic, eliminating 186 publications. The remaining 99 were screened for inclusion in the article based on meeting both of the following criteria: 1) the intervention(s) involved intermittent fasting and/or caloric restrictions and 2) the outcome measures were bone mineral density and/or bone turnover markers. This resulted in the inclusion of the thirteen articles referenced in the above sections “Caloric restriction and bone health” and “Intermittent fasting and bone health.”

Acknowledgements

Intramural funds for the publication of this work were provided to JWL by Marian University.

Conflict of Interest

The authors declare no conflicts of interest.

References

1. Scaturro D, Vitagliani F, Terrana P, Tomasello S, Camarda L, Letizia Mauro G: Does the association of therapeutic exercise and supplementation with sucrosomial magnesium improve posture and balance and prevent the risk of new falls? *Aging Clin Exp Res* 2021.
2. Capozzi A, Scambia G, Lello S: Calcium, vitamin D, vitamin K2, and magnesium supplementation and skeletal health. *Maturitas* 2020, 140: 55-63.
3. Bielemann RM, Martinez-Mesa J, Gigante DP: Physical activity during life course and bone mass: a systematic review of methods and findings from cohort studies with young adults. *BMC Musculoskelet Disord* 2013, 14:77.
4. Tenforde AS, Sayres LC, Sainani KL, Fredericson M: Evaluating the relationship of calcium and vitamin D in the prevention of stress fracture injuries in the young athlete: a review of the literature. *PM R* 2010, 2(10): 945-949.

5. Weaver AA, Houston DK, Shapses SA, Lyles MF, Henderson RM, Beavers DP, Baker AC, Beavers KM: Effect of a hypocaloric, nutritionally complete, higher-protein meal plan on bone density and quality in older adults with obesity: a randomized trial. *Am J Clin Nutr* 2019, 109(2):478-486.
6. Ciobanu O, Elena Sandu R, Tudor Balseanu A, Zavaleanu A, Gresita A, Petcu EB, Uzoni A, Popa-Wagner A: Caloric restriction stabilizes body weight and accelerates behavioral recovery in aged rats after focal ischemia. *Aging Cell* 2017, 16(6):1394-1403.
7. Sandesara PB, Sperling LS: Caloric Restriction as a Therapeutic Approach to Heart Failure: Can Less Be More in (Mice) and Men? *Circ Heart Fail* 2018, 11(3):e004930.
8. de Lucia C, Gambino G, Petraglia L, Elia A, Komici K, Femminella GD, D'Amico ML, Formisano R, Borghetti G, Liccardo D et al: Long-Term Caloric Restriction Improves Cardiac Function, Remodeling, Adrenergic Responsiveness, and Sympathetic Innervation in a Model of Postischemic Heart Failure. *Circ Heart Fail* 2018, 11(3):e004153.
9. Waldman M, Cohen K, Yadin D, Nudelman V, Gorfil D, Laniado-Schwartzman M, Kornwoski R, Aravot D, Abraham NG, Arad M et al: Regulation of diabetic cardiomyopathy by caloric restriction is mediated by intracellular signaling pathways involving 'SIRT1 and PGC-1alpha'. *Cardiovasc Diabetol* 2018, 17(1):111.
10. Halpern B, Mendes TB: Intermittent fasting for obesity and related disorders: unveiling myths, facts, and presumptions. *Arch Endocrinol Metab* 2021.
11. Dorling JL, Martin CK, Redman LM: Calorie restriction for enhanced longevity: The role of novel dietary strategies in the present obesogenic environment. *Ageing Res Rev* 2020, 64:101038.
12. Pifferi F, Aujard F: Caloric restriction, longevity and aging: Recent contributions from human and non-human primate studies. *Prog Neuropsychopharmacol Biol Psychiatry* 2019, 95:109702.
13. Redman LM, Ravussin E: Caloric restriction in humans: impact on physiological, psychological, and behavioral outcomes. *Antioxid Redox Signal* 2011, 14(2):275-287.
14. Rynders CA, Thomas EA, Zaman A, Pan Z, Catenacci VA, Melanson EL: Effectiveness of Intermittent Fasting and Time-Restricted Feeding Compared to Continuous Energy Restriction for Weight Loss. *Nutrients* 2019, 11(10).
15. Ayub N, Faraj M, Ghatan S, Reijers JAA, Napoli N, Oei L: The Treatment Gap in Osteoporosis. *J Clin Med* 2021, 10(13).
16. Greenblatt MB, Tsai JN, Wein MN: Bone Turnover Markers in the Diagnosis and Monitoring of Metabolic Bone Disease. *Clin Chem* 2017, 63(2):464-474.
17. Hadjidakis DJ, Androulakis, II: Bone remodeling. *Ann N Y Acad Sci* 2006, 1092:385-396.
18. Gao Y, Patil S, Jia J: The Development of Molecular Biology of Osteoporosis. *Int J Mol Sci* 2021, 22(15).
19. Hamrick MW, Ding KH, Ponnala S, Ferrari SL, Isaacs CM: Caloric restriction decreases cortical bone mass but spares trabecular bone in the mouse skeleton: implications for the regulation of bone mass by body weight. *J Bone Miner Res* 2008, 23(6):870-878.
20. Devlin MJ, Cloutier AM, Thomas NA, Panus DA, Lotinun S, Pinz I, Baron R, Rosen CJ, Bouxsein ML: Caloric restriction leads to high marrow adiposity and low bone mass in growing mice. *J Bone Miner Res* 2010, 25(9):2078-2088.
21. Shen CL, Zhu W, Gao W, Wang S, Chen L, Chyu MC: Energy-restricted diet benefits body composition but degrades bone integrity in middle-aged obese female rats. *Nutr Res* 2013, 33(8):668-676.
22. Joshi RN, Safadi FF, Barbe MF, Del Carpio-Cano F, Popoff SN, Yingling VR: Different effects on bone strength and cell differentiation in pre pubertal caloric restriction versus hypothalamic suppression. *Bone* 2011, 49(4):810-818.
23. Baek K, Bloomfield SA: Blocking beta-adrenergic signaling attenuates reductions in circulating leptin, cancellous bone mass, and marrow adiposity seen with dietary energy restriction. *J Appl Physiol* (1985) 2012, 113(11):1792-1801.
24. Tatsumi S, Ito M, Asaba Y, Tsutsumi K, Ikeda K: Life-long caloric restriction reveals biphasic and dimorphic effects on bone metabolism in rodents. *Endocrinology* 2008, 149(2):634-641.
25. Colman RJ, Beasley TM, Allison DB, Weindruch R: Skeletal effects of long-term caloric restriction in rhesus monkeys. *Age (Dordr)* 2012, 34(5):1133-1143.
26. Riedt CS, Schlüssel Y, von Thun N, Ambia-Sobhan H, Stahl T, Field MP, Sherrill RM, Shapses SA: Premenopausal overweight women do not lose bone during moderate weight loss with adequate or higher calcium intake. *Am J Clin Nutr* 2007, 85(4):972-980.
27. Redman LM, Rood J, Anton SD, Champagne C, Smith SR, Ravussin E, Pennington Comprehensive Assessment of Long-Term Effects of Reducing Intake of Energy Research T: Calorie restriction and bone health in young, overweight individuals. *Arch Intern Med* 2008, 168(17):1859-1866.
28. Villareal DT, Kotyk JJ, Armamento-Villareal RC, Kenguva V, Seaman P, Shahar A, Wald MJ, Kleerekoper M, Fontana L: Reduced bone mineral density is not associated with significantly reduced bone quality in men and women practicing long-term calorie restriction with adequate nutrition. *Aging Cell* 2011, 10(1):96-102.
29. Sukumar D, Ambia-Sobhan H, Zurfluh R, Schlüssel Y, Stahl TJ, Gordon CL, Shapses SA: Areal and volumetric bone mineral density and geometry at two levels of protein intake during caloric restriction: a randomized, controlled trial. *J Bone Miner Res* 2011, 26(6):1339-1348.
30. Clayton DJ, James LJ, Sale C, Templeman I, Betts JA, Varley I: Severely restricting energy intake for 24 h does not affect markers of bone metabolism at rest or in response to re-feeding. *Eur J Nutr* 2020, 59(8):3527-3535.
31. Barnosky A, Kroeger CM, Trepanowski JF, Klempel MC, Bhutani S, Hoddy KK, Gabel K, Shapses SA, Varady KA: Effect of alternate day fasting on markers of bone metabolism: An exploratory analysis of a 6-month randomized controlled trial. *Nutr Healthy Aging* 2017, 4(3):255-263.
32. Bahjiri SM, Ajabnoor GM, Borai A, Al-Aama JY, Chrousos GP: Effect of Ramadan fasting in Saudi Arabia on serum bone profile and immunoglobulins. *Ther Adv Endocrinol Metab* 2015, 6(5):223-232.