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Article - Review

Additional Strategies to Heal a Fracture: The Impact of Lifestyle Modifications to Improve Bone Repair

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Suffering from a bone fracture can hinder a patient's ability to work and greatly diminish their quality of life. Depending on fracture characteristics, treatment options consist of non-operative and operative management. Regardless of intervention needed, the process of bone healing is multi-factorial. Therefore, patients who are interested in maximizing their functional recovery can make changes within their control to optimize the healing process. Changes as simple as adding beets and probiotics could have a significant impact on returning function earlier and alleviating pain sooner.

If physicians elevate their current recovery strategy advice, it may be possible to improve a patient's recovery and increase bone healing whilst minimizing adverse effects on quality of life. A clear set of guidelines related to diet, nutritional supplementation, sleep, and activity are essential tactics to minimize the time it takes for the patient to return to work or essential activities of daily living.

Dietary Considerations for Bone Healing

Depending on management, the bony healing process after a fracture consists of primary bone healing without callus formation through the cutting cone pathway or secondary bone healing which occurs through three stages: inflammation, callus formation, and bone remodeling.[1] The diet of our patients can either directly foster these processes or hinder them.

Initially, cells and cytokines are recruited to remove necrotic tissue, promote angiogenesis, and initiate bone repair. Angiogenesis refers to the formation of new blood vessels, which allows growth factors and immune cells access to the area of injury to supply the new bone. The vascular endothelial cells continue to proliferate and divide.[2] While anti-angiogenic diets have been researched as a method of tumor treatment to inhibit vascular development, pro-angiogenic foods may be beneficial for an individual to incorporate into his or her diet for improved fracture healing. For instance, dietary nitrites were associated with improved revascularization in patients with ischemia and can be found in leafy green vegetables like spinach and beets.[4]

Revascularization is important because bone repair requires oxygen and nutrients, which are provided by blood flow.[1] Oxygen is necessary for both the survival and proliferation of new cells. Mineral nutrients such as calcium, vitamin D, phosphorus, and magnesium are all required for the formation of new bone. Additionally, blood flow helps remove waste such as carbon dioxide and lactic acid from the area of injury, which reduces inflammation and promotes healing. As inflammation subsides, chondrogenesis and osteogenesis begin to heal the broken bone. The cartilage extracellular matrix provides strength and support as the bone heals. As the bone remodels into new bone, the bone marrow space is re-established and the previously increased vasculature regresses to the pre-trauma level.

Vitamins

To support new bone development, patients should prevent developing micronutrient deficiencies.[5] For example, vitamin D deficiency was found in 40-70% of elderly patients presenting with a fracture and is associated with an increased risk of non-union.[6] Vitamin D is necessary to support the absorption of calcium for callus formation. Vitamin D can be found in tuna, salmon, some mushrooms, and fortified cereals and plant milks.[7] Additionally, phosphate-restricted diets negatively impacted fracture healing due to decreased bone morphogenetic protein signaling-2 and a disrupted circadian cycle. Dietary sources of phosphates include yogurt, fish, eggs, nuts, and legumes.[8]

Vitamin C is necessary for chondrogenic and osteogenic differentiation of the mesenchymal stem cells, as well as collagen formation for bone healing.[5] A deficiency in Vitamin C delays callus and cartilage formation and increases the risk of impaired healing. A case study by Michelson, et al., demonstrated the importance of Vitamin C by describing a 25-year-old female with scurvy and a humerus fracture. After 6 months, radiology showed no evidence of healing. However, callus formation began soon after her vitamin C deficiency was addressed.[9] An estimated 40-80% of elderly patients with fractures are deficient in Vitamin C, but Vitamin C can easily be found in citrus fruits, green peppers, red peppers, strawberries, tomatoes, broccoli, brussels sprouts, turnip, and other leafy vegetables.[10]

Adequate intake of vitamin K and vitamin A facilitates calcium absorption, direction, and utilization for the bone healing process.[11] Current research suggests that post-trauma, calcium used for bone callus formation is derived from the skeleton, which is independent of dietary calcium. In contrast, dietary calcium appears to be utilized more frequently during the late stages of post-fracture recovery. Although there is still room for research on how vitamins specifically benefit bone healing after a

fracture, Vitamin K2, a regulator of bone resorption, may help bone recovery by stabilizing bone metabolism.[12]

Alcohol and Smoking

The current general recommendations for alcohol consumption for women are 1 drink per day and 2 drinks per day for men (due to the differences in alcohol metabolism).[13] However, when healing from a fracture, alcohol increases the chance of nonunion by significantly inhibiting normal fracture callus formation due to several proposed mechanisms. Alcohol appears to inhibit mesenchymal stem cells (MSCs) at the site of the fracture injury, which give rise to osteoblasts and chondrocytes necessary for callus formation.[14] Alcohol can also reduce blood supply to the fracture site, impeding the delivery of vital nutrients and oxygen to the healing bone tissue. Additionally, it weakens the immune system, making it harder for the body to fight off infection and inflammation, both of which can delay the healing process.

Supporting this, Chakkalakal, et al., demonstrated reduced fracture callus bone strength, stiffness, and rigidity in animals that received 36% of calories from alcohol for 6 weeks before and 6 weeks after a surgically administered fibula fracture in rats.[15] Interestingly, those that became abstinent after the injury have normal fracture callus bio mechanical properties. This suggests that even those who consume alcohol regularly prior to their fracture could experience the healing benefits of removing alcohol from their diet while recovering.

Nicotine smoking is also a well-documented factor that slows bone healing and increases the risk for non-union.[16] Hoogendorn, et al., even found a 40% increased time to union and chance of non-union when compared with non-smokers.[17] Refraining from smoking may be a much more difficult change compared to the other suggestions noted in this article. However, an earlier recovery could be a motivating factor as ex-smokers can experience bone healing benefits upon quitting.

Probiotics

The gut-bone axis refers to the bi-directional relationship of the digestive tract and bone health. The gut's microbiome plays an important role in the absorption and metabolism of nutrients such as calcium and vitamin D19. The gut also produces hormones and other signaling molecules that can affect bone cells and bone remodeling. For example, the hormone leptin, which is produced in the gut and fat cells, can regulate bone mass by affecting the activity of osteoblasts and osteoclasts. Comparatively, osteocalcin, a protein produced by osteoblasts, has been shown to affect the composition of the gut microbiome and improve glucose metabolism.

Therefore, probiotics may be a beneficial addition to a patient's post-trauma diet. Howard, et al., identified significant change in the microbiome of the gut after only 72 hours of a trauma.[20] Studying the impact of probiotic treatment on elderly patients with distal radius fracture, Lei, et al., designed a randomized double-blind, placebo-controlled study.[21] At the end of month 6, the group consuming probiotic treatment and the placebo group both experienced similar end results in pain improvement and the ability to perform functional activities of daily living. Fascinatingly, however, the group that consumed the probiotics experienced much faster pain improvement and recovery to perform functional activities of daily living when compared to the placebo group during the first 4 months of the study. Therefore, supplementing with probiotics may alleviate pain sooner and return to normal function earlier.

Nutrient	Female RDA	Male RDA
Vitamins		
Vitamin C (mg/day)	75	90
Vitamin D (μg/day)		
19–70 years	15	15
>70 years	20	20
Vitamin E (mg/day)	15	15
Minerals		
Calcium (mg/day)		
19 to 50 years	1,000	1,000
51–70 years	1,200	1,000
>70 years	1,200	1,200
Copper (μg/day)	900	900
Phosphorus	700	700
Zinc (mg/day)	8	11
Iron (mg/day)		
19–50 years	18	8
>50 years	8	8
Macronutrients		
Protein (g/day)	46	56

Table 1. Adult Recommended Dietary Allowances (RDA) for Nutrients Related to Fracture.
Reproduced from Roberts, J.L. and Drissi, H. (2020), Advances and Promises of Nutritional Influences on Natural Bone Repair. J. Orthop. Res., 38: 695-707. https://doi.org/10.1002/jor.2452

Fact or Myth? Drink Milk

Due to the association of calcium with both milk and bone, a common notion for healing bone is to drink milk. While calcium is a significant part of bone composition, research is ongoing whether dairy is the best source of calcium for health and to what extent increasing intake of dairy post-fracture improves fracture healing. For example, a review by Tai, et al., of dietary calcium intake on bone mineral density (BMD) found it can produce a small increase in BMD but was limited in its progression and not associated with lower fracture risk.[22] Further, Michaelsson, et al., found high milk intake (more than

3 glasses per day) was associated with higher fracture and mortality risk for both men and women in Sweden. The study suggested the increased risk of mortality and fracture could be explained by the increased D-galactose content of milk, leading to elevated biomarkers for oxidative stress and inflammation (Interleukin 6).[23] Meanwhile, this same study found that yogurts and cheese, which contain lower D-galactose content, were associated with lower rates of mortality and fracture risk. However, calcium deficiency may not significantly impact bone fracture healing after the injury occurred.[5]

If dairy is consumed for dietary calcium, yogurts or cheeses would be a better choice than milk. Dr. Derek Donegan, M.D., MBA, a Professor of Orthopaedic Surgery at the University of Pennsylvania recognizes nutritional drawbacks in the diet of his patients, stating "dietary sources are important, but the bioavailability of key nutrients are variable. I often recommend supplementation in addition to dietary changes to fully optimize my patients nutrient profile." Therefore, calcium supplements should also be considered over milk.

Fact of Myth? Take NSAIDs for the Pain

Nonsteroidal anti-inflammatory drugs (NSAIDs) are also a common recovery strategy for a bone fracture management. However, NSAIDs have an inhibitory effect on the cyclooxygenase enzyme activity that is needed for bone healing. Research is inconclusive as to whether this translates to clinical medicine and impairs the healing process for bone fractures. Al Farii, et al., found that patients on NSAIDs for over 4 weeks after a fracture were at higher risk for nonunion, while less than 2 weeks of NSAID use was not associated with impaired fracture healing.[24] However, the use of indomethacin specifically was significantly associated with an increased risk of nonunion of the bone.

Although research is inconclusive, pain maintenance is an indisputable and essential aspect of patient care that should be considered carefully. Regarding his use of NSAIDs in managing fractures, Dr. Donegan noted that "while animal studies in both spine fusions and femur fractures have demonstrated an increased nonunion rate with the use of NSAIDs, this has not translated into the clinical realm. Most clinical studies demonstrate a benign effect of NSAIDs on fracture healing. Additionally, due to our current concerns about opioid use and the "Opioid Crisis," the use of non-opioid medications, such as NSAIDs, to help manage patient's pain after an acute fracture is an important part of the treatment algorithm. Clinical studies have actually demonstrated that the nonunion rate in patients healing from fractures using opioids versus NSAIDs is the same. Therefore, except for very select situations, NSAIDs are a cornerstone to my multi-modal approach to treating patients after an acute fracture." As such, pain relievers may be a necessity for many patients and should be balanced with the individual patient's recovery goals.

Fact or Myth? Limit activity and Rest

Rest should not be mistaken for inactivity. Mechanical stimulation can stimulate the bone repair pathways of inflammation, proliferation, and remodeling.[25] While physical therapy is commonly prescribed after a fracture to return strength to the affected area, non-weight-bearing movement and activity of the area may improve the bone repair process as well. Pursuant to Wolff's law, if a bone is subjected to increased stress, it will respond by increasing its density and strength, making it better able to withstand the loads placed upon it.[26] Dr. Donegan's goals for fracture healing is "to allow return to function as soon as possible." He states that "this is often a guiding tenet for operative versus non-operative management. In that regard, for non-articular fractures, once the bone is stable, weight bearing is initiated to take advantage of Wolff's law and enhance fracture healing."

Beyond weight-bearing exercises for a stable bone, Dr. Donegan also stated "in regard to articular fractures, initiation of range of motion of the joint involved is critical for healing of the articular fracture and ultimate long term outcome of that joint." Prior research demonstrates that bone repair at a fracture site is stimulated by mechanical movement[25]. One potential explanation for improved fracture repair is that increased mechanical stimulation during the proliferation and the remodeling phase increases vascularization and chondrogenesis to the fracture site[27].

Additionally, sleep has a biochemical impact on bone recovery. While research is limited, current studies suggest that abnormal sleep patterns increase fracture risk.[28] One explanation is that bone resorption is regulated by a person's circadian clock.[29] Further, a lack of sleep will increase cortisol levels and inflammation, which impair bone recovery. Specific guidelines for post-fracture sleep are still being researched, but general optimal sleep recommendations for adults include 7-9 hours of sleep per night, regular bedtime and wake-up times, limitation of noise where you sleep, avoidance of nicotine and alcohol, and avoidance of caffeine 6 hours before sleep.[30,31,32]

Patients trust their physician to care for them, and it is important for physicians to have the ability to provide patients information and a plan that can materially aid in the patient's recovery. Patients can control a piece of their recovery pathway by ensuring adequate and regular sleep, maintaining movement and activity, and temporarily modifying their diet to include foods that support angiogenesis,

callus formation, and bone remodeling. The standard of care for a bone fracture should incorporate these types of specific diet modifications, as well as specific sleep and activity guidance, to support healing and new bone growth.

REFERENCES

1. L. Claes, S. Recknagel, and A. Ignatius, "Fracture healing under healthy and inflammatory conditions," Nature Reviews Rheumatology, vol. 8, no. 3, pp. 133–143, 2012. https://www.nature.com/articles/nrrheum.2012.1
2. Pan, D., Gong, X., Wang, X., & Li, M. (2021). Role of Active Components of Medicinal Food in the Regulation of Angiogenesis. Frontiers in pharmacology, 11, 594050. https://doi.org/10.3389/fphar.2020.594050
3. Medina, M. Á., & Quesada, A. R. (2014). Dietary proteins and angiogenesis. Nutrients, 6(1), 371–381. https://doi.org/10.3390/nu6010371
4. Rammos, C., Luedike, P., Hendgen-Cotta, U., & Rassaf, T. (2015). Potential of dietary nitrate in angiogenesis. World journal of cardiology, 7(10), 652–657. https://doi.org/10.4330/wjc.v7.i10.652
5. Roberts, J.L. and Drissi, H. (2020), Advances and Promises of Nutritional Influences on Natural Bone Repair. J. Orthop. Res., 38: 695-707. https://doi.org/10.1002/jor.24527
6. Sprague S, Petrisor B, Scott T, et al. 2016. What is the role of vitamin D supplementation in acute fracture patients? A systematic review and meta-analysis of the prevalence of hypovitaminosis D and supplementation efficacy. J Orthop Trauma 30:53–63.
7. National Institutes of Health Office of Dietary Supplements. (2022). Vitamin D fact sheet for health professionals. https://ods.od.nih.gov/factsheets/VitaminD-HealthProfessional/.
8. National Institutes of Health Office of Dietary Supplements. (2022). Phosphorus fact sheet for health professionals. https://ods.od.nih.gov/factsheets/Phosphorus-HealthProfessional/.
9. Michelson J, Cohen A. 1988. Incidence and treatment of fractures in thalassemia. J Orthop Trauma 2:29–32.
10. Chambial, S., Dwivedi, S., Shukla, K. K., John, P. J., & Sharma, P. (2013). Vitamin C in disease prevention and cure: an overview. Indian journal of clinical biochemistry : IJCB, 28(4), 314–328. https://doi.org/10.1007/s12291-013-0375-3
11. Shuid AN, Mohamad S, Mohamed N, et al. Effects of calcium supplements on fracture healing in a rat osteoporotic model. J Orthop Res 2010;28:1651–1656. https://doi.org/10.1002/jor.21180
12. Iwamoto, J., Seki, A., Sato, Y., Matsumoto, H., Tadeda, T., & Yeh, J. K. (2010). Vitamin K2 promotes bone healing in a rat femoral osteotomy model with or without glucocorticoid treatment. *Calcified tissue international*, *86*(3), 234–241. https://doi.org/10.1007/s00223-010-9333-8
13. Greaves, L., Poole, N., & Brabete, A. C. (2022). Sex, Gender, and Alcohol Use: Implications for Women and Low-Risk Drinking Guidelines. *International Journal of Environmental Research and Public Health*, 19(8), 4523. https://doi.org/10.3390/ijerph19084523
14. Eby, J. M., Sharieh, F., & Callaci, J. J. (2020). Impact of Alcohol on Bone Health, Homeostasis and Fracture repair. *Current Pathobiology Reports*, 8(3), 75–86. https://doi.org/10.1007/s40139-020-00209-7
15. Dennis A. Chakkalakal, Jerzy R. Novak, Edward D. Fritz, Teresa. J. Mollner, Daniel L. McVicker, Kevin L. Garvin, Michael H. McGuire, Terrence M. Donohue. Inhibition of bone repair in a rat model for chronic and excessive alcohol consumption. *Alcohol*, Volume 36, Issue 3, 2005, Pages 201-214. https://doi.org/10.1016/j.alcohol.2005.08.001.
16. Patel, R. A., Wilson, R. F., Patel, P. A., & Palmer, R. M. (2013). The effect of smoking on bone healing: A systematic review. *Bone & joint research*, 2(6), 102–111. https://doi.org/10.1302/2046-3758.26.2000142
17. Hoogendoorn, J. M., & van der Werken, C. (2002). Ongunstige effecten van roken op de genezing van gecompliceerde tibiafracturen [The adverse effects of smoking on healing of open tibial fractures]. *Nederlands tijdschrift voor geneeskunde*, *146*(35), 1640–1644. https://pubmed.ncbi.nlm.nih.gov/12233160/
18. Castillo, R. C., Bosse, M. J., MacKenzie, E. J., Patterson, B. M., & LEAP Study Group (2005). Impact of smoking on fracture healing and risk of complications in limb-threatening open tibia fractures. *Journal of orthopaedic trauma*, *19*(3), 151–157. https://doi.org/10.1097/00005131-200503000-00001
19. He, Y., & Chen, Y. (2022). The potential mechanism of the microbiota-gut-bone axis in osteoporosis: a review. *Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA*, *33*(12), 2495–2506. https://doi.org/10.1007/s00198-022-06557-x
20. Howard, B. M., Kornblith, L. Z., Christie, S. A., Conroy, A. S., Nelson, M. F., Campion, E. M., Callcut, R. A., Calfee, C. S., Lamere, B. J., Fadrosh, D. W., Lynch, S., & Cohen, M. J. (2017). Characterizing the gut microbiome in trauma: significant changes in microbial diversity occur early after severe injury. *Trauma surgery & acute care open*, *2*(1), e000108. https://doi.org/10.1136/tsaco-2017-000108
21. Lei, M., Hua, L. M., & Wang, D. W. (2016). The effect of probiotic treatment on elderly patients with distal radius fracture: a prospective double-blind, placebo-controlled randomised clinical trial. *Beneficial microbes*, *7*(5), 631–637. https://doi.org/10.3920/BM2016.0067
22. Tai V, Leung W, Grey A, Reid I R, Bolland M J. Calcium intake and bone mineral density: systematic review and meta-analysis BMJ 2015;351:h4183 doi:10.1136/bmj.h4183
23. Michaelsson K, Wolk A, Langenskiold S, Basu S, Warensjo Lemming E, Melhus H et al. Milk intake and risk of mortality and fractures in women and men: cohort studies BMJ 2014;349:g6015 doi:10.1136/bmj.g6015
24. Al Farii, H., Farahdel, L., Frazer, A., Salimi, A., & Bernstein, M. (2021). The effect of NSAIDs on postfracture bone healing: a meta-analysis of randomized controlled trials. OTA international : the open access journal of orthopaedic trauma, 4(2), e092. https://doi.org/10.1097/OI9.0000000000000092
25. Song L. (2022). Effects of Exercise or Mechanical Stimulation on Bone Development and Bone Repair. Stem cells international, 2022, 5372229. https://doi.org/10.1155/2022/5372229
26. Teichtahl, A. J., Wluka, A. E., Wijethilake, P., Wang, Y., Ghasem-Zadeh, A., & Cicuttini, F. M. (2015). Wolff's law in action: a mechanism for early knee osteoarthritis. Arthritis research & therapy, 17(1), 207. https://doi.org/10.1186/s13075-015-0738-7
27. H. Matsuzaki, G. R. Wohl, D. V. Novack, J. A. Lynch, and M. J. Silva, "Damaging fatigue loading stimulates increases in periosteal vascularity at sites of bone formation in the rat ulna," Calcified Tissue International, vol. 80, no. 6, pp. 391–399, 2007; E. A. Smith-Adaline, S. K. Volkman, M. A. Ignelzi, J. Slade, S. Platte, and S. A. Goldstein, "Mechanical environment alters tissue formation patterns during fracture repair," Journal of Orthopaedic Research, vol. 22, no. 5, pp. 1079–1085, 2004. Ho.
28. Swanson C. M. (2021). Sleep disruptions and bone health: what do we know so far?. Current opinion in endocrinology, diabetes, and obesity, 28(4), 348–353. https://doi.org/10.1097/MED.0000000000000639
29. Takarada, T., Xu, C., Ochi, H., Nakazato, R., Yamada, D., Nakamura, S., Kodama, A., Shimba, S., Mieda, M., Fukasawa, K., Ozaki, K., Iezaki, T., Fujikawa, K., Yoneda, Y., Numano, R., Hida, A., Tei, H., Takeda, S., & Hinoi, E. (2017). Bone Resorption Is Regulated by Circadian Clock in Osteoblasts. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research, 32(4), 872–881. https://doi.org/10.1002/jbmr.3053
30. Drake, C., Roehrs, T., Shambroom, J., & Roth, T. (2013). Caffeine effects on sleep taken 0, 3, or 6 hours before going to bed. Journal of clinical sleep medicine : JCSM : official publication of

the American Academy of Sleep Medicine, 9(11), 1195–1200. https://doi.org/10.5664/jcsm.3170
31. Hirshkowitz, M., Whiton, K., Albert, S. M., Alessi, C., Bruni, O., DonCarlos, L., Hazen, N., Herman, J., Adams Hillard, P. J., Katz, E. S., Kheirandish-Gozal, L., Neubauer, D. N., O'Donnell, A. E., Ohayon, M., Peever, J., Rawding, R., Sachdeva, R. C., Setters, B., Vitiello, M. V., & Ware, J. C. (2015). National Sleep Foundation's updated sleep duration recommendations: final report. *Sleep health*, *1*(4), 233–243. https://doi.org/10.1016/j.sleh.2015.10.004
32. Irish, L. A., Kline, C. E., Gunn, H. E., Buysse, D. J., & Hall, M. H. (2015). The role of sleep hygiene in promoting public health: A review of empirical evidence. *Sleep medicine reviews*, *22*, 23–36. https://doi.org/10.1016/j.smrv.2014.10.001