

VITAMIN D AND BONE HEALING

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Bone healing is an intricate process that relies on many cellular and molecular components. Healing traditionally occurs in four phases: the inflammatory phase, soft callus formation, hard callus formation, and remodeling phase. Each of these phases requires the presence of a variety of compounds, growth factors and signaling molecules. (1, 2). If one component is missing or present in insufficient quantity, healing may be compromised.

Vitamin D is a fat-soluble molecule that has several forms, including 25-hydroxyvitamin D (storage form) and 1,25-dihydroxyvitamin D (active form) (2). Although variation exists, most define a normal Vitamin D level as 32-100 ng/ml. Mild and severe deficiencies have been established as 15-32 ng/ml and <15 ng/ml, respectively (2). Deficiencies may be linked to several factors including time of year, geographic location, sex, and other medical comorbidities. Vitamin D deficiency is a common contributor to fracture, especially in the older patient population (3). Deficiency may also lead to hypocalcemia, osteoporosis, osteomalacia, rickets, and secondary hyperparathyroidism (3). Of particular importance to this review, deficiency has also been linked to fracture nonunion.

Vitamin D is critical to the fracture healing pathway. It is most known for its contribution to overall mineralization of bone and maintenance of bone integrity. It also plays a role in calcium homeostasis (1, 2). Given the above listed functions, it would seem that Vitamin D would be primarily involved in hard callus and remodeling phases, however, it may have many functions at the cellular level, which impact the initial stages of healing as well. While mixed results have been shown as to the effects of Vitamin D on interleukins, tumor necrosis factor, and transforming growth factor, studies have shown positive effects in terms of enhanced expression of vascular endothelial growth factor, platelet derived growth factor, and bone morphogenetic protein 3 (1). The implications of this include angiogenesis and an increase in mesenchymal stem cell and osteoblast activity. Soft callus formation relies on the presence of growth factors that may be influenced by Vitamin D and, although unclear, it may promote endochondral bone formation (1). Vitamin D is responsible for differentiation of osteoblasts and may stimulate collagen type one production during the hard callus stage. Finally, during remodeling, Vitamin D plays a part in osteoclastogenesis (1).

Many studies have looked at the serum and intra-osseous concentrations of Vitamin D during the healing process. In a 2013 study by Briggs et al, serum levels were found to drop by 21% over a six-week period following fracture (4). In the initial stages of fracture healing, Vitamin D receptors are present on callus bone formation (5). Animal and human models have demonstrated decreased serum concentrations of Vitamin D following fracture (6). Although inconclusive, this could be related to the presence of Vitamin D receptors on callus bone formation. In a study by Ettehad et al, total serum levels of Vitamin D in patients with lower extremity fracture were found to be decreased with progression through the healing process, with the drop being most significant during the first week of healing (7). This may be a result of greater osteoblast activity and a greater rate of bone production during this window of time. A conclusion could be made from these results that supplementation instituted early on in the healing process may prove beneficial to the patient; however, further investigation is required.

Additional studies have focused on Vitamin D deficiency and the impact on bone healing. Approximately 1 billion people worldwide and 25% of people in the US are Vitamin D deficient (3). Bogunovic et al reported an overall prevalence of 40% Vitamin D deficiency in orthopedic patients (5). This study also noted increased prevalence of deficiency in patients who were male, those with darker skin tones, and those who had sustained a trauma or sports-related injury (5). Brinker et al performed a study in 2007 that showed that 68% of patients with a fracture nonunion were Vitamin D deficient. They postulated that the deficiency was linked to the increased levels in alkaline phosphatase and parathyroid hormone and decreased calcium levels, factors which have been shown to negatively affect bone healing (8). In a prospective case-control study by Smith et al in 2014, the authors examined prevalence of Vitamin D deficiency in patients with low energy fracture of the foot and ankle. Forty-seven percent of patients were found to have Vitamin D below the recommended level. Vitamin D deficiency has been associated with patients who have comorbidities including smoking and obesity, among others (3).

Effects of Vitamin D supplementation on healing have also been a focus of research. In rat studies, a clear relationship

has been shown between deficiency and fracture healing. Those who were deficient showed decreased healing relative to those with adequate levels (1). Findings such as decreased ability to withstand torsion, delayed union, weaker bone, decreased callus formation, and poor mineralization were also noted in rats with Vitamin D deficiency (1). Thus a conclusion could be made that Vitamin D supplementation would promote stronger callus formation, superior biomechanical properties of bone, and decreased rates of delayed/nonunion. However, further studies are required in a human model to determine whether these conclusions can be applied.

Supplementation has been strongly advocated in the elderly population for both fall and fracture prevention. There are several guidelines that recommend at least 800 IU Vitamin D per day for fracture prevention (2). This patient demographic has largely been the focus of supplementation studies and overall a paucity of literature exists focusing on a human model. Several studies have shown significant fracture reduction in Vitamin D supplementation patients compared to those not receiving therapy. If Vitamin D appears to help prevent fracture by affecting integrity of bone, a conclusion could be drawn that it would help with the healing process (9). Vitamin D toxicity is rare and therefore supplementation, as long as prescribed by a qualified medical professional, can only stand to benefit the patient when appropriate (9). The Endocrine Society Clinical Practice Guideline recommends that all deficient adults be given 50,000 IU once a week for eight weeks or 6000 IU per day to achieve a level above 30ng/ml and then be transitioned to a maintenance dose of 1500-2000 IU per day (10).

While the exact impact Vitamin D has on the process of fracture healing remains unclear, there does appear to be a benefit to Vitamin D supplementation during the healing process. Based on the literature available, it would be advisable to check Vitamin D levels in patients who present with risk factors associated with deficiency. It may also be prudent to check levels in patients who have undergone open reduction and internal fixation following sustained trauma, those who are scheduled for reconstructive type

surgeries where a substantial amount of bone healing will be taking place, and in patients exhibiting signs of delayed or nonunion. Future studies may yield results that promote screening for Vitamin D deficiency on a routine basis preoperatively for all patients. If a patient is found to be deficient, supplementation can be instituted to promote better outcomes in bone healing. However, more research needs to be conducted to evaluate at what Vitamin D levels optimum healing occurs, when supplementation should be implemented, and to what extent (7). It is also worth investigating various medical comorbidities and their impact on Vitamin D levels. This topic is a growing area of interest and one that is deserving of further attention to better elucidate the role that Vitamin D plays in our practice.

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