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Commentary

No pain, no gain: Will migraine therapies increase bone loss and impair fracture healing?

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While the modern cliché "no pain, no gain", is a commonly used exercise motto, earlier forms of this adage were related to work ethic. Over time, the meaning of this phrase has adapted – so too has our understanding of biology and medicine. In this issue of *EBioMedicine*, Appelt and colleagues [1] demonstrated that a neuropeptide, calcitonin gene-related peptide (CGRP), which is known to be involved in the pathogenesis of migraines (pain), is essential in fracture repair (gain). This begs the question whether the converse is also true. Whether recently FDA approved anti-migraine therapies (no pain), which block either CGRP or the CGRP receptor, may impair fracture healing (no gain). This important clinical question warrants examination, especially considering that women disproportionately suffer from both migraine and osteoporosis-related fractures.

Migraine is a neurological disease defined by recurrent unprovoked headaches lasting over four hours with one or more disabling symptoms including nausea, vomiting, dizziness, and extreme sensitivity to sound and light. More than 1 billion people suffer from migraines worldwide [2]. Migraine disproportionately affects women with 85% of chronic migraine sufferers being women. Approximately 1 in 4 women will experience migraine in their lives. Fluctuations in estrogen levels are associated with severe and frequent attacks, which may explain why migraine is most common between the ages of 18–44, and in women (perimenopause typically begins when women are in their 40's) [2].

CGRP levels significantly rise during migraine attacks, and injection of CGRP induces migraine-related symptoms [3]. Further CGRP, especially the α-isoform, is primarily thought to be involved in pain processes. Previous studies have suggested that CGRP-expressing dorsal root ganglia respond to noxious heat and mechanical stimuli [3]. Further, studies investigating genetic ablation of αCGRP demonstrated that αCGRP-expressing sensory neurons contribute to noxious heat perception and inflammation-induced thermal hyperalgesia but not to noxious mechanical stimuli or mechanical hyperalgesia [4]. Therefore, based on the large therapeutic need as well as the role of CGRP in pain and migraine, several companies pursued the development of inhibitors of CGRP or its receptor for the treatment of migraine. There are currently 6 FDA approved therapies including: Aimovig (erenumab-aooe), Ajovy (fremanezumab-vfrm), Emgality (galcanezumab-gnlm), Vyepti (eptinezumab-jjmr), Ubrelvy (ubrogepant), and Nurtec ODT (rimegepant sulfate) for acute and preventative treatment of migraine. Clinical trial results demonstrate migraine treatment efficacy with limited to no issues regarding tolerability and safety [5].

While there is a critical need for effective migraine treatments, as with all therapies, benefits and risks must be balanced. Although we are unaware of clinical studies examining the impact of use of these drugs on development of osteoporosis or complications following fracture, it is certainly reasonable to imagine these drugs, while helping with migraine, could have a significant side effect in terms of bone loss and impaired fracture healing.

As we recently reviewed [6], CGRP inhibits osteoclastogenesis and bone resorption, and αCGRP increases osteoblast proliferation and bone formation. Further, αCGRP global knockout mice (αCGRP$^{-/-}$ mice) were found to have reduced bone formation and low bone mass [7]. Thus, CGRP plays a critical role in regulating bone mass by both increasing bone formation and reducing bone resorption, leading to a net gain in bone mass. Unfortunately, the reduction of αCGRP results in low bone mass.

Herein lies a possible bone mass problem with use of migraine therapeutics that sequester or block αCGRP or the CGRP receptor. This problem is further exacerbated by the fact that women are predominantly affected by migraine and osteoporosis. Indeed, approximately 54 million of the U.S. population have osteoporosis and low bone mass and on average 1 in 2 women and 1 in 4 men over the age of 50 will suffer an osteoporotic fracture [8].

With regard to fracture and CGRP, as recently summarized [6], several investigators have shown CGRP expression at the fracture site and reported correlative findings. Prior to the studies reported in this issue of *EBioMedicine* by Appelt et al. [1] perhaps the best evidence

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for a role of CGRP in fracture repair was a report that intraperitoneal injection with CGRP inhibitor significantly impaired fracture healing in a rat model, as demonstrated by a significant reduction in mineralized callus with an increase in cartilage [9]. In the current study, Appelt et al. [1] first demonstrate that CGRP and its receptor, calcitonin receptor-like receptor (CRLR), are expressed during bone regeneration. They demonstrate profound impairment of bone regeneration (0.7 mm femoral osteotomy) in αCGRP$^{-/-}$ mice compared to wild-type controls. Indeed, they show 66.66% of αCGRP$^{-/-}$ mice display non-unions and 25% of αCGRP$^{-/-}$ mice display delayed unions. At the fracture site, they observed reductions in bone forming osteoblasts and bone resorbing osteoclasts, both of which are required for successful bone repair. Next, a series of mechanistic studies demonstrated that the phenotype observed in αCGRP$^{-/-}$ mice is not cell-autonomous, but rather is due to the lack of secreted αCGRP to function in normal fracture repair. Fracture callus tissue was then subjected to transcriptomic analyses and 170 genes differed significantly in αCGRP$^{-/-}$ mice compared to wild-type controls. As may be expected in a fracture model, many of the identified genes were known regulators of skeletal homeostasis and bone regeneration. Finally, to determine whether the differentially regulated genes observed in fracture repair were altered due to the interaction of αCGRP with its receptor, CRLR, bone marrow cells were treated with recombinant αCGRP or olcegepant (CRLR antagonist), and many of the genes which were identified in genome wide analyses were significantly increased with αCGRP treatment and decreased with olcegepant treatment. Overall, the findings of Appelt, et al. [1] compellingly demonstrate the important role of secreted αCGRP in fracture repair.

With the growing body of evidence demonstrating the important role of αCGRP in successful fracture repair and the regulation of bone mass, long-term consequences of CGRP antagonists, especially on bone mass and fracture healing in women, must be considered. This then begs the question whether use of CGRP/CGRP receptor targeted therapies to reduce migraine pain will also increase our risk of developing osteoporosis and/ or preclude fracture healing. Understanding these possible consequences will require additional clinical investigations.

Declaration of Competing Interest

The authors declare no conflict of interest.

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