

Review

Allergy and the bone: unexpected relationships

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Objective: To examine the relationships between allergy and bone metabolism as represented by the effects of antihistamines and leukotriene modifiers on bone resorption and formation.

Data Sources: The major databases MEDLINE and Scopus were searched using the keywords *bone metabolism, bone resorption, bone formation, antihistamines, h1 antagonist, leukotriene antagonist, and leukotriene modifier*.

Study Selection: The studies were independently evaluated by all the coauthors, who judged their pertinence to this review.

Results: Two of the most intriguing aspects in the field are the possible effects of leukotriene modifiers on fracture repair and the hypothesized role of antihistamines in contrasting osteoporosis. Another rapidly expanding field of research is that related to the immune-modulating effects of vitamin D because serum levels of vitamin D have been shown to correlate with pulmonary function, asthma onset, and the development of allergic diseases.

Conclusion: Although unexpected, data are now available suggesting a strict connection among allergy, its treatments, and bone metabolism.

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INTRODUCTION

Both allergic and bone diseases share a high prevalence in the general population. In fact, musculoskeletal conditions are the most common causes of severe long-term pain and physical disability, affecting hundreds of millions of people around the world. At any one time, 30% of adults are affected by joint pain, swelling, or limitation of movement.¹ Similarly, more than 20% of the general population has allergic diseases, mainly, allergic rhinitis and asthma.²

Up to a few years ago, the only clinical link between these 2 groups of diseases was the possible negative effects on bone metabolism of long-term corticosteroids, which are commonly used in allergic patients, mainly in the inhaled formulation. More recently, other relevant relationships between bone metabolism and allergic disorders or atopy (and their treatment) have been identified. One of the most important and now well-recognized links between bone metabolism and allergy is represented by vitamin D, but this is not the subject of the current review. Other recently discovered links between allergy and bone metabolism are represented by the effects of antihistamines and leukotriene modifiers (LTMs) on bone resorption and formation. The aim of the present review is to examine those 2 relationships in the light of the

most recent literature. The major databases MEDLINE and Scopus were searched. The studies were independently evaluated by all the coauthors, who judged their pertinence to this review.

EFFECTS ON BONE METABOLISM OF TREATMENTS USED FOR ALLERGIC DISEASES

Corticosteroids

Obstructive lung diseases, including asthma, represent one of the most common indications for the use of corticosteroids, which are administered either by inhalation or via systemic routes.³ The lung disease most commonly associated with long-term corticosteroid treatments is certainly asthma, either allergic or nonallergic. This fact has been clearly confirmed by the data of the General Practice Research Database of England and Wales, which evaluated the first oral corticosteroid prescription from 1992 to 1997.³ However, in asthma, systemic corticosteroids are used intermittently, and only 9% of the patients prescribed corticosteroids are still undergoing treatment 1 year after the first prescription and 6% after 2 years. On the contrary, in patients with rheumatologic diseases, as well as inflammatory bowel diseases, corticosteroids are often used for long periods, with 29% of them being treated for up to 1 year and 19% for 2 years or more.³

The risk of osteoporotic fractures is strictly dependent on the dose and the duration of corticosteroid therapy (particularly in men and postmenopausal women), whereas it appears to be poorly related to bone mineral density (BMD).⁴ It has also been observed that the risk of fractures significantly increases within 3 months of corticosteroid treatment and decreases soon after treatment withdrawal.⁵ This finding in-

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dicates that even relatively short treatment courses are associated with an increased fracture risk, even among patients with a normal BMD. The underlying disease also plays a relevant role. For instance, rheumatoid arthritis and other rheumatic diseases amplify the corticosteroid-related risk of fractures at both the spine and the hip, whereas pulmonary diseases do not appear to increase the risk of fractures.⁵

The route of administration is obviously another important factor.^{6,7} The bioavailability of oral corticosteroid is very high, and an exponential increase in fracture risk is observed for daily doses greater than 5 mg of prednisone-equivalents.⁸ The same dose given as an inhaled formulation is less harmful.⁸ The potential of inhaled corticosteroids to induce adverse effects on the bone is dependent not only on the dose and duration but also on the systemic bioavailability, which depends in turn on the absorption and the first-pass metabolism.^{7,9} The bioavailability varies among the different molecules, ranging from approximately 80% for budesonide to less than 5% for fluticasone and mometasone, whereas the bioavailability of ciclesonide is virtually zero. Many studies¹⁰⁻²⁰ have evaluated the effects of inhaled corticosteroids on BMD, often reporting conflicting results (Table 1) but consistently showing that some effect of inhaled corticosteroids on bone density can be demonstrated using sensitive markers of bone metabolism. One meta-analysis²¹ and some narrative reviews^{7,22} concluded that inhaled corticosteroids cause a dose-related reduction in BMD, and some large cross-sectional studies²² found a dose-related increase in fractures in people taking inhaled corticosteroids compared with controls. Nasal sprays are generally considered less harmful than inhaled corticosteroids^{8,9} also because the dose administered is lower.

Surprisingly, most epidemiologic data on fracture risk during corticosteroid therapy are based on observational, retrospective studies, which are generally poorly controlled. Currently, the best available data are derived from placebo arms of randomized clinical trials for the treatment of corticosteroid-induced osteoporosis.^{4,5}

LTMs and Bone Fracture Healing

The normal process of bone fracture healing can be divided into 4 phases. Immediately after a fracture the main features

are a localized tissue hypoxia and the hematoma formation. The early repair phase is characterized by an inflammatory response, with cell recruitment to the fracture site. In the regenerative phase, the fracture is bridged with new bone. Cells that migrated to or proliferated in the fracture callus differentiate into chondrocytes and osteoblasts during endochondrally formed woven bone. This type of bone spans the fracture site and is then remodeled into mature lamellar bone to restore the mechanical integrity of the bone.^{23,24} The early phase may be critical for the ultimate success of fracture healing. Several studies²⁴ have shown increased levels or increased gene expression of proinflammatory cytokines, mitogenic growth factors, and cell-differentiating growth factors within the early fracture callus. When a fracture occurs, the extravasation and subsequent differentiation of the monocyte are dependent on environmental factors that include a number of inflammatory stimuli. These factors promote an inflammatory macrophage phenotype that can direct local inflammatory processes by abundant tumor necrosis factor α production. The exposure of monocytic cells to the RANKL produced by osteoblastic cells and T lymphocytes promotes osteoclastogenesis and bone resorption. The local production of morphogenetic proteins, such as transforming growth factor β 1 and bone morphogenic protein 2, promote wound healing and bone regeneration.²⁵ Recently, it has been shown that fracture healing is impaired in mice lacking a functional cyclooxygenase 2 (COX-2) gene and the COX-2 enzyme that is critical for normal inflammation.^{24,26,27}

Apparently, fracture repair depends on the metabolic activation of arachidonic acid locally released by the tissue destruction associated with fracture. Arachidonic acid is activated to prostaglandins by COX-2. Nonsteroidal anti-inflammatory drugs inhibit COX-2 function and therefore can affect the fracture healing process, especially if administered during the early phases.²⁴ This role of COX-2 in the formation of new bone is empirically exploited for the prevention of ectopic calcifications after the surgical intervention for hip arthroprosthesis by administering nonsteroidal anti-inflammatory drugs²⁸ or COX-2 inhibitors²⁹ soon after the surgical intervention. The local formation of leukotrienes (LTs) plays an opposite role in the process of fracture repair. Arachidonic acid can be metabolized also by 5-lipoxygenase (5-LO).

Table 1. Summary of the Studies Investigating the Effects of Inhaled Corticosteroids on Bone Density

Source	No. of Patients	Drug	Dose, μ g	Follow-up, mo	Bone density
Altintas et al ¹⁸ (2005)	60 Children	BUD/FP	400/250	19	Normal
Ishizuka et al ¹³ (2002)	128 Adults	FP	200-400	12	Reduced
Egan et al ¹¹ (1999)	33 Adults	BDP/FP	2000/1000	24	Normal
Griffiths et al ¹⁷ (2004)	81 Children	FP	>1000	6	Normal
Hughes et al ¹⁰ (1999)	59 Adults	BUD/FP	500/800	12	Normal
Kemp et al ¹⁶ (2004)	160 Adults	FP	440	24	Normal
Medici et al ¹⁴ (2002)	69 Adults	BDP/FP	1500/750	12	Normal
Roux et al ¹⁵ (2003)	174 Children	FP	200	24	Normal
Wong et al ¹² (2000)	196 Adults	BDP/FP	800/500	6	Reduced

Abbreviations: BDP, beclomethasone dipropionate; BUD, budesonide; FP, fluticasone propionate.

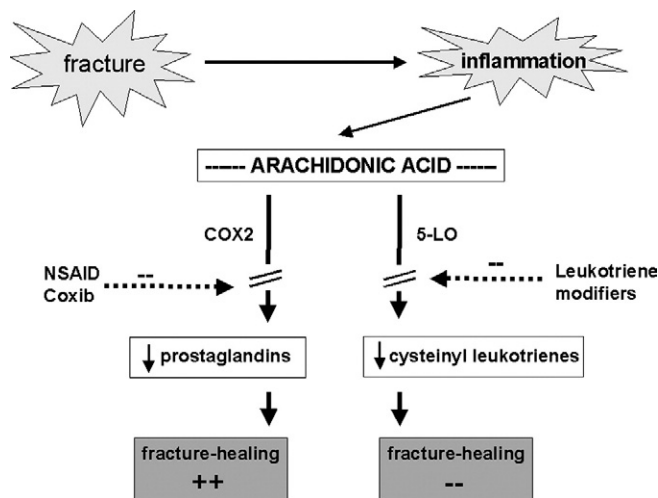


Figure 1. Arachidonic acid metabolites and fracture. Arachidonic acid locally released after a fracture is activated to prostaglandins by cyclooxygenase 2 (COX-2) and to leukotrienes by 5-lipoxygenase (5-LO). Prostaglandins play a key role in fracture repair; thus, nonsteroidal anti-inflammatory drugs (NSAIDs) can impair fracture healing. On the contrary, cysteinyl leukotrienes seem to act as negative regulators of mesenchymal stem cell differentiation; thus, leukotriene modifiers may promote fracture repair.

5-LO functions for the LT family as COX does in the prostaglandin family and, acting in concert with 5-LO-activating protein, catalyzes the conversion of arachidonic acid in 2 major groups of LTs. These 2 groups consist of LTB₄ and the cysteinyl leukotrienes (CysLTs) LTC₄, LTD₄, LTE₄, and LTF₄. The CysLTs seem to act as negative regulators of mesenchymal stem cell differentiation. In vitro studies of human mesenchymal cells showed enhanced cellular differentiation in the presence of pranlukast, a specific CysLT₁ receptor antagonist,³⁰ highlighting the potential inhibitory effect of the CysLT₁ pathway on mesenchymal cell differentiation and the possible promoted fracture repair via CysLT₁ receptor inhibition (Fig 1). In an in vivo animal model of fracture repair, the outcome of treatment with montelukast sodium and zileuton on events leading to skeletal regeneration was evaluated.³¹ Zileuton is a 5-LO inhibitor that broadly blocks LT synthesis, whereas montelukast sodium is a specific CysLT₁ receptor antagonist. One study³¹ showed that treatment with both these drugs results in an enhanced chondroid phase and faster transition to bone formation, leading to a larger callous size and a faster transition to bone formation with enhanced fracture repair. These findings, although still confined to animal models, highlight the role of the CysLT₁ receptor as a negative regulator of chondrocyte activity. This should encourage the investigation of the usefulness of these medications in humans as possible enhancing fracture-healing therapy.

Antihistamines and Osteoporosis

Histamine plays a crucial role in the pathogenesis of allergic diseases, and histamine receptor antagonists are widely used

to relieve the symptoms of these conditions. The role of histamine for bone health has been suggested by a number of studies in mastocytosis and also by animal studies.³² Excess histamine accelerates bone resorption and, in patients with systemic mastocytosis, where proliferating mast cells continuously release histamine, osteoporosis is a frequent finding (Table 2).³³⁻³⁷ In ovariectomized rats the block of histamine uptake by histamine₁ (H₁) and histamine₂ (H₂) receptor antagonists is associated with decreased osteoclast activity and bone resorption.^{38,39} In a mouse model of histamine deficiency, an increased production of osteoclast differentiation factor and receptor activator of nuclear factor κ B ligand was found, but this was not associated with osteoclast overactivity possibly for the costimulatory role of histamine on nuclear factor κ B production.⁴⁰ Histamine acts directly on osteoclasts, osteoclast precursors, and osteoblasts, promoting osteoclastogenesis through autocrine and paracrine mechanisms.⁴¹ All these findings suggest that histamine modulates osteoclastic bone resorption and that by blocking histamine receptors osteoclastogenesis might be hampered (Fig 2). In an observational study, the rate of prevalent low-energy fractures in untreated pollen allergic patients was found to be almost 3-fold higher than in nonallergic women matched for age, body mass index, and menopausal age. It was also found that antihistamine users had fewer nontraumatic fractures compared with nonusers.⁴² The authors speculated on the possible protective role of the H₁-receptor, compensating for both the negative effect of pollen allergy and the adverse effect of inhaled corticosteroid treatment on bone fracture risk. In the Third National Health and Nutrition Examination Survey study, in adults 60 years and older, the use of H₁- or H₂-receptor antagonists was associated with higher femoral BMD values as measured by dual-energy x-ray absorptiometry than in nonusers.⁴³ On the contrary, those taking H₂-antihistamines had lower BMD than nonusers.⁴³ It can be speculated that antacid medications decrease calcium absorption, and in fact an increased risk of fractures was seen also with proton pump inhibitors (adjusted odds ratio, 1.6-2.5).⁴⁴ Nonetheless, proton pump inhibitors also interfere with osteoclastic metabolism, and their effect on calcium absorption at the usual doses is considered negligible.

Some preliminary data suggest a protective role of histamine receptor antagonists with some inconsistent findings for H₂-receptor antagonists. Additional studies are definitely

Table 2. Occurrence of Osteoporosis in Patients With Mastocytosis

Source	No. (%) of patients with osteoporosis/No. of patients with mastocytosis
Travis et al ³³ (1988)	16/58 (27.6)
Johansson et al ³⁴ (1996)	7/16 (43.8)
Theoharides et al ³⁵ (2002)	6/23 (26.1)
Kushnir-Sukhov et al ³⁶ (2006)	3/21 (14.3)
Barete et al ³⁷ (2010)	23/75 (30.7)

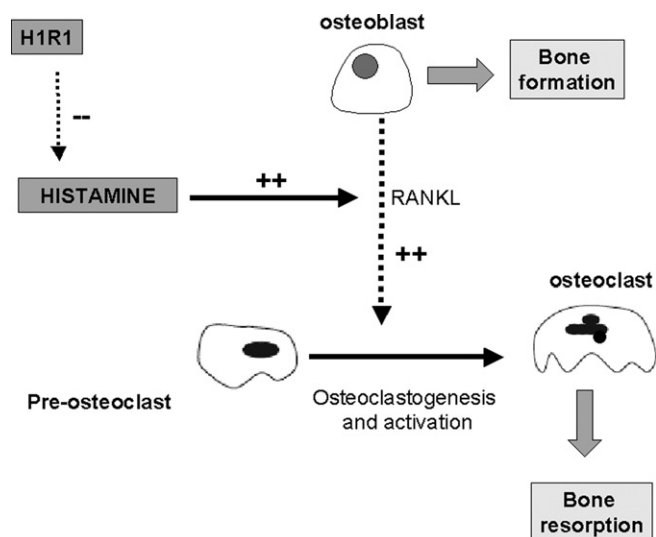


Figure 2. Histamine, antihistamines, and bone. Histamine seems to increase bone resorption and osteoclastogenesis by increasing the expression of RANKL in osteoblasts and bone marrow stromal cells. On the contrary, histamine blockade by histamine₁ receptor (H1R1) antagonists might protect against osteoporosis.

warranted to shed light on the relationship between histamine receptor antagonists and bone health.

CONCLUSION

Not only is the clinical link between allergic and bone diseases represented by the negative effects on bone metabolism of long-term corticosteroids, but also other drugs used in allergic diseases appear to have an effect on bone. LTM are likely to improve fracture healing, and antihistamines might have a positive effect on bone mass. These findings are based on animal models or observational studies; interventional studies in human are warranted. The activity of some drugs on both bone metabolism and allergic diseases supports a close interaction between immune and skeletal systems. The realization of the intricate nature of this interaction has been supported by the fact that a number of cell surface receptors, cytokines, and signaling pathways serve a critical role in both the immune and skeletal systems. This gave rise to the development of a new discipline called osteoimmunology. Finally, it must be remembered that another important link between bone metabolism and allergy is represented by vitamin D, which seems to play a key role in immune regulation⁴⁵ and is strictly linked to the development of asthma and atopy.

REFERENCES

1. Woolf AD, Pfleger B. Burden of major musculoskeletal conditions. *Bull World Health Organ.* 2003;81:646–656.
2. Galassi C, De Sario M, Biggeri A, et al. Changes in prevalence of asthma and allergies in children and adolescents in Italy: 1994–2002. *Pediatrics.* 2006;117:34–42.
3. Van Staa TP, Leufkens HG, Abenham L, Begaud B, Zhang B, Cooper C. Use of oral corticosteroids in the United Kingdom. *Q J Med.* 2000; 93:105–11.
4. Adami S, Righetti D, Frigo A. L'osteoporosi cortisonica. *Reumatismo.* 2000;52:77–85.
5. Van Staa TP, Leufkens HG, Abenham L, Zhang B. Use of corticosteroid and risk of fractures: June 2000. *J Bone Miner Res.* 2005;20: 1487–1494.
6. Weldon D. The effects of corticosteroids on bone growth and density. *Ann Allergy Asthma Immunol.* 2009;103:3–11.
7. Weldon D. The effects of corticosteroids on bone: osteonecrosis (avascular necrosis of the bone). *Ann Allergy Asthma Immunol.* 2009;103: 91–98.
8. Vestergaard P, Reijnmark L. Fracture risk associated with systemical and topical corticosteroids. *J Intern Med.* 2005;257:374–384.
9. Passalacqua G, Albano M, Canonica GW, et al. Inhaled and nasal corticosteroids: safety aspects. *Allergy.* 2000;55:16–33.
10. Hughes JA, Conry GB, Male SM. One year prospective open study on the effect of high dose inhaled steroids, fluticasone propionate and budesonide on bone markers and bone mineral density. *Thorax.* 1999; 54:223–229.
11. Egan JJ, Maden C, Kalra S, Adams JE, Eastell R, Woodcock AA. A randomized, double blind study comparing the effects of beclomethasone and fluticasone on bone density over two years. *Eur Respir J.* 1999;13:1267–1275.
12. Wong CA, Walsh LJ, Smith CJP, et al. Inhaled corticosteroids use and bone mineral density in patients with asthma. *Lancet.* 2000;355: 1399–1403.
13. Ishizuka T, Yoshii A, Hisada T, et al. Effects of fluticasone propionate on bone mineral density in patients with persistent bronchial asthma. *Intern Med.* 2002;41:798–804.
14. Medici TC, Grabsky E, Hacky M, et al. Effect on one year treatment with inhaled fluticasone propionate and beclomethasone dipropionate on bone density and bone metabolism: a randomized parallel group study in adult asthmatic subjects. *Thorax.* 2002;55:375–382.
15. Roux C, Kolt S, Desfougeres JL, Minimi P, Bidat E. Long term safety of fluticasone propionate and nedocromil sodium on bone in children with asthma. *Pediatrics.* 2003;111:706–713.
16. Kemp JP, Osur S, Shrewsbury SB, et al. Potential effects of fluticasone propionate on bone mineral density in patients with asthma: a 2-year randomized, double blind, placebo controlled trial. *Mayo Clin Proc.* 2004;79:458–466.
17. Griffiths AL, Sim D, Strauss B, Rodda C, Armstrong D, Freezer N. Effect of high dose of fluticasone propionate on bone density and metabolism in children with asthma. *Pediatr Pulmonol.* 2004;37:116–121.
18. Altintas DU, Kakarok GB, Can S, Yilmaz M, Kendirli SG. The effects of long term use of inhaled corticosteroids on linear growth, adrenal function and bone mineral density in children. *Allergol Immunopathol.* 2005;33:204–209.
19. Hubbard RB, Smith CJ, Smeeth L, et al. Inhaled corticosteroids and hip fracture: a population-based case-control study. *Am J Respir Crit Care Med.* 2002;166:1563–1566.
20. Suissa S, Baltzan M, Kremer R, Ernst P. Inhaled and nasal corticosteroid use and the risk of fracture. *Am J Respir Crit Care Med.* 2004;169: 83–88.
21. Richy F, Bousquet J, Erlich GE, et al. Inhaled corticosteroid effect on bone in asthmatic and COPD patients: a quantitative systematic review. *Osteopor Int.* 2003;14:179–190.
22. Mortimer KJ, Harrison TW, Tattersfield AE. Effects of inhaled corticosteroids on bone. *Ann Allergy Asthma Immunol.* 2005;9:15–21.
23. Schindeler A, Liu R, Little DG. The contribution of different cell lineages to bone repair: exploring a role for muscle stem cells. *Differentiation.* 2009;77:12–18.
24. Simon AM, Manigrasso MB, O'Connor JP. Cyclo-oxygenase 2 function is essential for bone fracture healing. *J Bone Miner Res.* 2002;17: 963–976.
25. Champagne CM, Takebe J, Offenbacher S, Cooper LF. Macrophage cell lines produce osteoinductive signals that include bone morphogenetic protein-2. *Bone.* 2002;30:26–31.
26. Zhang X, Schwarz EM, Young DA, Puzas JE, Rosier RN, O'Keefe RJ. Cyclooxygenase-2 regulates mesenchymal cell differentiation into the

- osteoblast lineage and is critically involved in bone repair. *J Clin Invest.* 2002;109:1405–1415.
27. Naik AA, Xie C, Zuscik MJ, et al. Reduced COX-2 expression in aged mice is associated with impaired fracture healing. *J Bone Miner Res.* 2009;24:251–264.
 28. Fransen M, Neal B. Non-steroidal anti-inflammatory drugs for preventing heterotopic bone formation after hip arthroplasty. *Cochrane Database Syst Rev.* 2004;(3):CD001160.
 29. Macfarlane RJ, Ng BH, Gamie Z, et al. Pharmacological treatment of heterotopic ossification following hip and acetabular surgery. *Expert Opin Pharmacother.* 2008;9:767–786.
 30. Akino K, Minoda T, Mori N, Hirano A, Imaizumi T, Akita S. Attenuation of cysteinyl-leukotrienes induces human mesenchymal stem cell differentiation. *Wound Repair Regen.* 2006;14:343–349.
 31. Wixted JJ, Fanning PJ, Gaur T, et al. Enhanced fracture repair by leukotriene antagonism is characterized by increased chondrocyte proliferation and early bone formation: a novel role of the cysteinyl LT-1 receptor. *J Cell Physiol.* 2009;221:31–39.
 32. Chiappetta N, Gruber B. The role of mast cells in osteoporosis. *Semin Arthritis Rheum.* 2006;36:32–36.
 33. Travis WD, Li CY, Bergstralh EJ, et al. Systemic mast cell disease: analysis of 58 cases and literature review. *Medicine (Baltimore).* 1988; 67:345–368.
 34. Johansson C, Roupe G, Lindstedt G, Mellstrom D. Bone density, bone markers and bone radiological features in mastocytosis. *Age Ageing.* 1996;25:1–7.
 35. Theoharides TC, Boucher W, Spear K. Serum interleukin-6 reflects disease severity and osteoporosis in mastocytosis patients. *Int Arch Allergy Immunol.* 2002;128:344–350.
 36. Kushnir-Sukhov NM, Brittain E, Reynolds JC, Akin C, Metcalfe DD. Elevated tryptase levels are associated with greater bone density in a cohort of patients with mastocytosis. *Int Arch Allergy Immunol.* 2006; 139:265–270.
 37. Barete S, Assous N, de Gennes C, et al. Systemic mastocytosis and bone involvement in a cohort of 75 patients. *Ann Rheum Dis.* 2010;69: 1838–1841.
 38. Rico H, Gomez M, Revilla M, et al. Effects of promethazine on bone mass and on bone remodeling in ovariectomized rats: a morphometric, densitometric, and histomorphometric experimental study. *Calcif Tissue Int.* 1999;65:272–275.
 39. Lesclous P, Guez D, Saffar JL. Short-term prevention of osteoclastic resorption and osteopenia in ovariectomized rats treated with the H2 receptor antagonist cimetidine. *Bone.* 2002;30:131–136.
 40. Fitzpatrick LA, Buzas E, Gagne TJ, et al. Targeted deletion of histidine decarboxylase gene in mice increases bone formation and protects against ovariectomy-induced bone loss. *Proc Natl Acad Sci U S A.* 2003;100:6027–6032.
 41. Biosse-Duplan M, Baroukh B, Dy M, de Vernejoul MC, Saffar JL. Histamine promotes osteoclastogenesis through the differential expression of histamine receptors on osteoclasts and osteoblasts. *Am J Pathol.* 2009;174:1426–1434.
 42. Ferencz V, Meszaros S, Csupor E, et al. Increased bone fracture prevalence in postmenopausal women suffering from pollen-allergy. *Osteoporos Int.* 2006;17:484–491.
 43. Kinjo M, Setoguchi S, Solomon DH. Antihistamine therapy and bone mineral density: analysis in a population-based US sample. *Am J Med.* 2008;121:1085–1091.
 44. Yang YX, Lewis JD, Epstein S, Metz DC. Long-term proton pump inhibitor therapy and risk of hip fracture. *JAMA.* 2006;296:2947–2953.
 45. Cantorna MT, Zhu Y, Froicu M, Wittke A. Vitamin D status, 1,25-dihydroxyvitamin D3, and the immune system. *Am J Clin Nutr.* 2004; 80(6 suppl):1717S–1720S.

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