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Commentary

Bone metabolism is controlled by endocrine, paracrine, and inflammatory signals that continuously operate in health and disease. While these signals are critical for skeletal adaptation during development, longitudinal growth, and repair, disturbances such as sex hormone deficiency or chronic inflammation have unambiguously been linked to bone loss and skeletal fragility across species. In the current issue of the *JCI*, Khosla et al. evaluated the role of sympathetic outflow and present evidence to support the idea that the sympathetic nervous system regulates bone metabolism in humans, primarily via the β_1 -adrenergic receptor.

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Bone metabolism is controlled by endocrine, paracrine, and inflammatory signals that continuously operate in health and disease. While these signals are critical for skeletal adaptation during development, longitudinal growth, and repair, disturbances such as sex hormone deficiency or chronic inflammation have unambiguously been linked to bone loss and skeletal fragility across species. In the current issue of the *JCI*, Khosla et al. evaluated the role of sympathetic outflow and present evidence to support the idea that the sympathetic nervous system regulates bone metabolism in humans, primarily via the β_1 -adrenergic receptor.

β_1 -Adrenergic receptor-mediated effect of the sympathetic nervous system on bone metabolism

Ample evidence suggests that besides endocrine, paracrine, and inflammatory signals, the sympathetic nervous system (SNS) also controls bone metabolism. In seminal studies conducted in mice, activation of the SNS through the hypothalamic signaling of leptin ultimately led to the activation of β -adrenergic receptors (β -ARs) on bone-forming osteoblasts, resulting in bone loss (1, 2). On the basis of tissue-specific deletion studies in mice, this effect appeared to be mediated predominantly through the β_2 -AR subtype (3). However, subsequent murine studies have also implicated β_1 - and β_3 -AR subtypes in the modulation of SNS effects on bone. Interventional studies, which used the nonselective β -blocker propranolol in normotensive (4) and hypertensive rats (5), reported bone-preserving effects only with low doses (0.1 and 1 mg/kg/day), but not higher doses. In line with these results, a prospective clinical study in humans using a high dose of propranolol (160 mg/day), as used in patients with arterial hypertension, failed to show an effect on serum markers of bone turnover (6). Thus, the β -AR specificity and dose range of β -block-

ers and their implications in human skeletal health remained elusive.

In this issue of the *JCI*, Khosla and colleagues (7) provide compelling evidence that in humans, the β_1 -AR is critical in mediating SNS effects on bone cells and that β_1 -selective blockers may confer a small but consistently positive effect on bone microarchitecture and turnover. Notably, in this work, all studies were exclusively conducted in humans or on human tissue. First, RNA transcripts for the β_1 -AR and the β_2 -AR were detected in bone biopsies and in a human immortalized osteoblastic cell line, with the β_2 -AR being the predominant subtype. Second, despite higher expression of the β_2 -AR in human bone, a population-based study indicated that β_1 -selective blockers improve trabecular microarchitecture parameters at the tibia and radius. Third, in order to corroborate these findings, the authors conducted a randomized, controlled study, in which 155 postmenopausal and normotensive women received either placebo or one of three different β -blockers for a total duration of 20 weeks. The β -blockers included the nonselective propranolol at different doses (40 or 80 mg/day), the predominantly β_1 -AR-selective atenolol (50 mg/day), and the exclusively β_1 -AR-selective nebivolol (5 mg/day). In support of the observational

data, both β_1 -AR-selective drugs decreased bone resorption markers and increased bone mineral density (BMD) at the ultradistal radius, whereas propranolol had no such effect. This exploratory short-term, proof-of-concept study, however, was not designed to assess beneficial effects on lumbar spine or hip BMD. It would be of interest in future studies to determine whether the beneficial effects of β_1 -AR-selective blockade also extend to these sites. Taken together, this elegant piece of translational research indicates a critical role of β_1 -AR and its pharmacological inhibition on human bone health (Figure 1).

A recent meta-analysis (8) reported a 15% lower fracture risk in patients receiving β -blockers when compared with controls. Of note, the reduction in fracture risk was attributable to the β_1 -AR selectivity of the pharmacological agent used, thus confirming the hypothesis raised by Khosla et al. (7). However, questions remain regarding the mechanism(s) underpinning this effect. Presumably, the local effect of a β -blocker-driven skeletal intervention would depend on the distribution of sympathetic nerve endings within the skeleton and its compartments, i.e., cortical versus trabecular, as well as the expression of β -ARs on bone cells. While Khosla et al. show that human osteoblasts express both the β_1 -AR and the β_2 -AR, it is unclear whether the activation of the SNS relays its deleterious skeletal effects through a direct interaction with its receptors on osteoblasts or via alternative target structures, such as the cardiovascular system. Increased sympathetic signaling may also affect other bone cells such as osteocytes or osteoclasts, or interfere with the action of other systemic modifiers of bone biology such as parathyroid hormone, thyroid hormone, glucocorticoid signaling, or physical activity.

The good and the bad of β -blocker intervention

The study by Khosla et al. highlights the importance of the nervous system as a regulator of bone health. While endocrine

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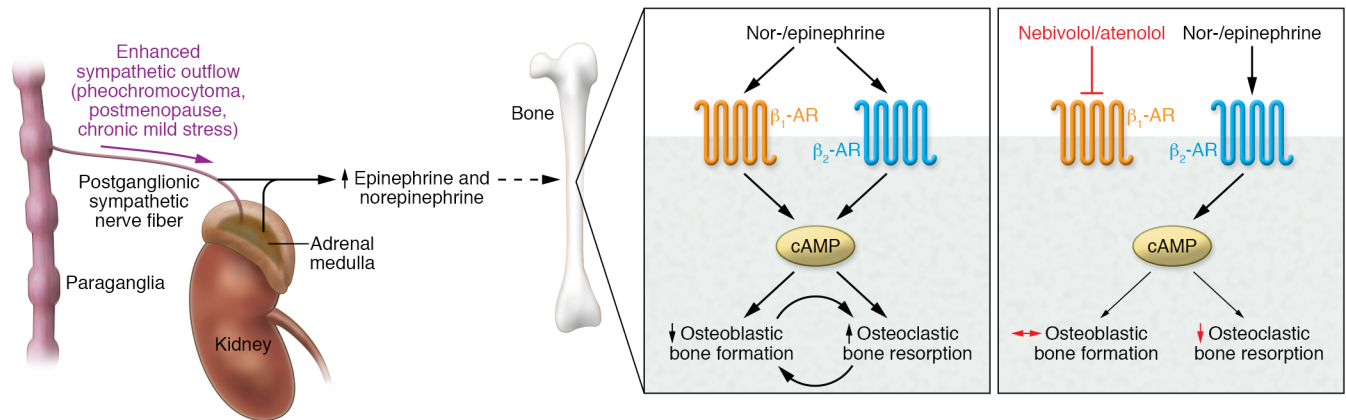


Figure 1. The major catecholamines epinephrine and norepinephrine are produced in the adrenal medulla and in postganglionic sympathetic fibers projecting from paraganglia. Activated sympathetic outflow with elevated production occurs in pheochromocytoma and more subtly in the postmenopausal phase, at an older age, or in conditions of chronic mild stress. Activation of the widely expressed β -AR transmits its signal to the second messenger cyclic adenosine monophosphate (cAMP). In bone, sympathetic activation stimulates osteoclastic bone resorption and suppresses osteoblastic bone formation, thus contributing to bone loss. With the use of the β_1 -AR-selective blockers nebivolol and atenolol, mainly bone resorption is reduced, and bone loss is prevented.

signals have been appreciated as determinants of bone quality for decades, the nervous system has only recently been brought to the attention of clinicians and scientists alike. Given the continuous activity of the SNS due to its physiological role of homeostatic maintenance combined with its established deleterious effect on the skeleton, the pharmacological disruption of sympathetic signaling becomes a viable option to improve bone health. Apart from pheochromocytomas and paragangliomas, which are rare catecholamine-producing tumors (9), a number of diseases have been linked to increased bone loss and/or enhanced fracture risk due to an enhanced sympathetic outflow. These include common conditions, such as postmenopausal osteoporosis (10), old age (11), chronic stress, as well as mood disorders such as depression (12). In elderly patients with low bone mass and a high risk for fragility fractures, some of these factors may coincide.

In their interventional trial, Khosla et al. treated normotensive patients with significant doses of β -blockers. The authors did not explicitly report cases of hypotension or bradycardia; however, a number of patients discontinued the intervention because of intolerance to the drug. Thus, this raises a practical clinical question: Do normotensive patients with a normal heart rate tolerate a β -blocker intervention? On that note, a large proportion of elderly patients are affected by coronary artery disease, arterial hypertension, heart failure, and essential tremor, all of

which benefit from the use of β -blockers. In light of the multitude of medications elderly patients are frequently exposed to, many physicians and patients are hesitant to expand the medication repertoire and initiate osteoporosis therapy. In addition, there has been a recent dramatic drop in the prescription of osteoporosis drugs despite their efficacy, safety, and overall well-documented benefit/risk ratio (13). The potential dual modality of β -blockers may encourage the use of these drugs if they confer benefits outside their cardiovascular indications. For instance, in patients who display both cardiovascular risk factors and low or intermediate risk for osteoporotic fractures, e.g., a low bone mass in the absence of clinical fractures, β -blockers may represent a reasonable treatment strategy to prevent osteoporosis. In more severe cases of osteoporosis, it will be important to assess how β_1 -AR-selective blockers interact with established antiresorptive or osteoanabolic drugs in terms of bone strength and fractures. It is now paramount to conduct large-scale randomized, controlled trials in order to provide definitive data on the skeletal benefits of β_1 -AR-selective intervention. In the absence of this evidence, clinicians are left to carefully selecting the β -blocker of choice in patients with low bone mass if another indication demands their use.

Concluding remarks

Overall, mounting clinical evidence suggests that pharmacological β_1 -AR-selective

blockade may deliver a small but significant increase in bone mass and thus aid in the prevention of fractures. Given the small effect size, β_1 -AR-selective blockers may be an insufficient treatment for osteoporosis, per se, but could potentially represent a cost-effective and safe treatment for patients with osteopenia — particularly in light of recent evidence that increased SNS signaling contributes to a spectrum of bone-loss phenotypes. With large numbers of patients already using β -blockers, the comparatively small effect size may be able to deliver significant benefits over the long term on the population level. The study by Khosla et al. is a good starting point. Careful assessment of β_1 -AR-selective blockade for age-related bone loss and other disorders will answer the question of what is best for bone health and beyond in the elderly.

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