COMMENTARIES

Are Osteoclasts Necessary for PTH Anabolism? A Reappraisal from Osteoprotegerin Studies

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Commentary on:


Antiresorptive drugs such as the bisphosphonates protect against fractures by decreasing bone turnover; intermittent parathyroid hormone (iPTH), on the other hand, prevents fractures by stimulating bone remodeling. If increased bone resorption is the cost of the anabolic effect of iPTH, couldn’t we achieve the best of both worlds by combination therapy with iPTH and an antiresorptive? Clinical studies say no; in humans there is an actual inhibition of the effect of PTH by concomitant treatment with alendronate. On the other hand, a prior study in ovariectomized (OVX) rats, using iPTH in combination with the potent osteoclast inhibitor osteoprotegerin (OPG), suggested that treatment with iPTH plus OPG was superior to treatment with PTH alone. Two new rodent studies (1;2) in which coadministration of PTH with alendronate and OPG are compared now further highlight the role of osteoclasts in PTH anabolism.

Potent antiresorptive drugs currently available for osteoporosis treatment, such as bisphophonates, decrease bone turnover, preventing osteoclasts from further degrading cancellous bone structure (i.e., they prevent the thinning and perforation of trabeculae), but initially allow osteoblasts to refill the remodeling space; they later increase the degree of mineralization, and perhaps diminish cortical porosity (3). Due to the high affinity of antiresorptives for the bone matrix, the effect of these agents may last for months to years after treatment withdrawal. However, bisphosphonates do not reconstruct bone microstructure. In contrast, administration of iPTH stimulates bone remodeling, which directly increases trabecular thickness and bridging, and may prompt some de novo bone modeling and subsequent thickening of the cortex (4). However, as a result of increased bone turnover, PTH causes cortical porosity and decreases the degree of mineralization, which may account for the apparent decline of BMD at the hip in patients previously treated with alendronate and switched to iPTH (5). Moreover, the effects of PTH on BMD and cancellous bone structure are short-lived once the treatment is stopped (6;7). Is it possible then to get the best of both worlds by combining antiresorptive agents with PTH? In postmenopausal women receiving estrogen or alendronate, the addition of PTH further improved BMD (8;9), but others have shown that combination therapy with alendronate is no better, actually, it is less effective, on spine BMD and cancellous bone volume, than PTH alone (10). The reason for this lack of additivity remains unclear but it has been hypothesized that osteoclasts may function as a primer for the anabolic effects of PTH.
on the skeleton (11). Alternatively, bisphosphonates could directly alter the osteoblastic response to PTH.

Osteoprotegerin (OPG) is produced mainly by osteoblasts and B lymphocytes and acts as a potent natural antagonist of RANK ligand (RANKL), itself an indispensable factor for the development and activation of osteoclasts (12). Recombinant OPG has subsequently been shown to be a potent inhibitor of osteoclastogenesis and to improve BMD, microstructure and strength in a number of animal models. Interestingly, PTH regulates the expression of OPG and RANKL, in that brief exposure to PTH during intermittent administration increases OPG, whereas prolonged exposure to the hormone has opposite effects (13). These observations raised the intriguing hypothesis that OPG production and/or administration could potentiate the positive bone mineral balance induced by iPTH. In pioneering work by Kostenuik et al. (14), 5.5 months of treatment with iPTH plus OPG was superior to PTH alone for improvement of BMD, trabecular bone volume relative to tissue volume (BV/TV), and biomechanical properties/resistance to fracture at the spine and femur/tibia in very old, estrogen-deficient rats. Most interestingly, effects of combination therapy on the spine were observed even though histomorphometry showed a virtually complete absence of osteoclasts on trabecular bone surfaces at this site. These results cast doubt on the necessity for osteoclasts to be present and/or active in order to allow for PTH anabolism. Furthermore, PTH induced a marked increase in osteoblasts on tibial bone surfaces that was not impaired in the presence of OPG. The latter observation was consistent with the fact that high concentrations of OPG prevent apoptosis of osteoblast-like cells in vitro by acting as an antagonist on TRAIL death receptors (15). Hence, this study suggested that OPG could behave as an uncoupling factor between osteoclasts and osteoblasts, and raised new prospects for combination therapy.

Two recent studies (1;2) have compared OPG and alendronate with/without daily iPTH in estrogen-deficient mice. The study design, including drug doses and duration (2 months), was consistent with previously published studies and was very similar in these two experiments, except for the fact that combination therapy was started at the time of ovariectomy in the first study (1), while in the second study, administration of iPTH was delayed until four weeks after initiation of the antiresorptive (2). In the first study, each treatment alone or in combination significantly increased BMD at the spine and femur, as well as trabecular BV/TV in the vertebrae, compared to no treatment. At the spine, iPTH plus alendronate, as well as iPTH plus OPG, both increased BMD and/or BV/TV above single drug effects. In the femur, combination therapy was somewhat better than PTH alone at increasing BMD but not mechanical strength (stiffness, for example, was similarly increased by PTH alone, PTH plus alendronate and PTH plus OPG). The latter observation suggests that combination therapy did not further improve cortical bone structure beyond the effects of PTH. As expected, osteoclastic surfaces and serum osteoclastic markers (TRAP-5b) were completely suppressed by OPG, but not by alendronate. Of note, osteoblast surfaces and osteocalcin were also significantly lower in OPG-treated animals. With the addition of PTH to OPG, numbers of both osteoclasts and osteoblasts remained markedly lower compared to PTH alone, in contrast with previous observations in old rats (above). Intriguingly, in vitro assays using bone marrow cultures indicated that OPG significantly increased osteoblast differentiation compared to alendronate, perhaps by suppressing the production of osteoclast inhibitory factors of osteoblastogenesis (although a direct effect of OPG on preventing osteoblast apoptosis is also possible, see above (15)). If this is true, then how are we to explain the decrease in osteoblast numbers observed with OPG in vivo? One hypothesis is that inhibition of bone resorption would prevent the release of osteoblastic growth factors from the bone matrix, a phenomenon that could obviously not occur in vitro. In this case, one might conclude that some osteoclastic activity might indeed be needed to allow PTH to exert its full anabolic effects in vivo. Nevertheless, the results obtained at the spine and discussed above would argue
that osteoclasts are dispensable for the anabolic effects of PTH on trabecular bone.

The second study, in which iPTH was administered alone or in combination with the antiresorptive after 4 weeks inhibition of bone resorption by OPG or alendronate, gave somewhat different results. PTH alone in naive animals, as well as in mice pre-treated with OPG, significantly increased spine BMD and distal femur trabecular BV/TV compared to no PTH, whereas PTH post alendronate was much less effective. However, when OPG or alendronate was continued during the administration of iPTH, BMD and trabecular BV/TV at the spine and/or femur ultimately was no better than PTH alone in mice that had not previously received any antiresorptive. Moreover, bone formation indices (mineral apposition rate (MAR), and bone formation rate, (BFR)) were highest in the iPTH only group, lowest in the OPG and OPG plus PTH groups, and intermediate in the alendronate plus PTH groups.

In summary, these studies in estrogen-deficient mice first confirmed that concomitant administration of OPG plus iPTH increased BMD at the spine and femur better than iPTH alone, provided that OPG was not started before iPTH. However they did not fulfill the full promise of the first experiment in ovariectomized rats (14). Indeed, they provide clear indications that potent inhibition of osteoclast development and/or activity by an antiresorptive, be it OPG or alendronate, will blunt the anabolic effects of PTH on osteoblasts and bone formation, perhaps explaining the lack of additivity on cortical bone strength in the first experiment. Alternatively, the latter observation may result from the absence of an intrinsic effect of alendronate or OPG on this compartment in rats, due to the absence of intracortical bone remodeling in this species. Also of note, combination therapy with alendronate plus PTH was in some ways superior to each treatment alone when started concomitantly, which differs from the observations previously reported in clinical trials (10). Altogether, these findings point towards the differences in bone remodeling that may exist between rodents and humans, and to the intrinsic limitations of this kind of study.

Inhibition of PTH anabolism was particularly obvious when OPG was started before and pursued during PTH treatment, as in the second experiment, in which case no additive effects were seen on either the cancellous or the cortical bone compartment. In this case, and contrary to the situation where PTH and the antiresorptive are started simultaneously, it is possible that the early anabolic effects of PTH (i.e., on the pre-existing bone remodeling space) would be cancelled (since the remodeling space has already been markedly reduced by the antiresorptive). However, whether this phenomenon can be explained by the disappearance of bone remodeling sites, of osteoclasts per se, and/or of osteoclast activity still remains unclear. Hence, to fully understand the molecular and cellular determinants of PTH anabolism, more studies are needed to identify the role of local mediators from the bone matrix and from the bone resorbing cell, as well as the role of cell-cell contact involving osteoclasts and osteoblasts.

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References


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