Review Article

Catabolic and anabolic actions of parathyroid hormone on the skeleton

B.C. Silva, A.G. Costa, N.E. Cusano, S. Kousteni, and J.P. Bilezikian
Metabolic Bone Diseases Unit, Division of Endocrinology, Department of Medicine, College of Physicians and Surgeons, Columbia University, USA

ABSTRACT. PTH, an 84-amino acid peptide hormone synthesized by the parathyroid glands, is essential for the maintenance of calcium homeostasis. While in its traditional metabolic role, PTH helps to maintain the serum calcium concentration within narrow, normal limits and participates as a determinant of bone remodeling, more specific actions, described as catabolic and anabolic are also well known. Clinically, the catabolic effect of PTH is best represented by primary hyperparathyroidism (PHPT), while the osteoanabolic effect of PTH is best seen when PTH or its biological amino-terminal fragment [PTH(1-34)] is used as a therapy for osteoporosis. These dual functions of PTH are unmasked under very specific pathological (PHPT) or therapeutic conditions. At the cellular level, PTH favors bone resorption, mostly by affecting the receptor activator of nuclear factor κB (RANK) ligand (RANKL)-osteoprogererin-RANK system, leading to an increase in osteoclast formation and activity. Increased bone formation due to PTH therapy is explained best by its ability to enhance osteoblastogenesis and/or osteoblast survival. The PTH-induced bone formation is mediated, in part, by a decrease in SOST/sclerostin expression in osteocytes. This review focuses on the dual anabolic and catabolic actions of PTH on bone, situations where one is enhanced over the other, and the cellular and molecular mechanisms by which these actions are mediated.

©2011, Editrice Kurtis

INTRODUCTION

Parathyroid hormone (PTH), an 84-amino acid peptide hormone, is synthesized in the cells of the parathyroid glands. Release of PTH occurs both with circadian dynamics and in pulsatile fashion stochastically. Through its direct actions on bone and kidney, the principle target organs, and indirectly on the gastrointestinal tract (by facilitating the activation of vitamin D), PTH helps to maintain the serum calcium within normal limits. At the level of bone, it promotes calcium release; at the level of the kidney, it promotes tubular calcium reabsorption. The indirect effect on the gastrointestinal tract promotes calcium absorption (1). A hypocalcemic signal will lead to greater PTH release (and synthesis), thus leading to these organ-specific events and restoring the serum calcium to normal.

The direct actions of PTH are initiated by an interaction with its receptor (PTH1R), a G-protein-coupled receptor expressed in target cells, such as osteoblasts in bone and tubular cells in the kidney (2). Events following the binding of PTH to the PTH1R include stimulation of Gaα-mediat ed activation of adenyl cyclase, which in turn promotes cAMP production and subsequent activation of protein kinase A (PKA). The PTH1R is also linked to Goα-mediated activation of phospholipase and protein kinase C (PKC) (3, 4). Regulation of these activation events occurs, in part, at the level of the PTH1R when it is internalized (5). Recently, PTH has been shown to downregulate sclerostin, an important regulator of bone formation. This effect is also mediated by cAMP signaling in osteocytes (6).

The catabolic effect of PTH is best represented by the classic disorder of PTH excess, primary hyperparathyroidism (PHPT). In this setting, in which patients are exposed to continuously high amounts of circulating PTH, bone loss is common. When PHPT was invariably a symptomatic disease, bone loss was often accompanied by fractures. With the more modern clinical profile of PHPT emerging at around the time that dual energy X-ray absorptiometry (DXA) became available in the 1980's, discovery of PHPT was likely to be in asymptomatic individuals whose bone loss could be gleaned only by DXA. Insights into this phenotype revealed clues to the anabolic proclivity of this hormone (7), namely that cancellous bone microstructure is preserved in comparison to postmenopausal women without PHPT (8-10).

Further insight that exploited the idea that PTH could be primarily anabolic under certain circumstances came in the 1990's when studies by Dobnig et al. (11) showed that the way in which PTH is administered dictates whether it will serve primarily an anabolic or catabolic role. In rats treated once daily (i.e., intermittently) with low doses of PTH, marked anabolic effects on the skeleton were observed while continuous, 24-h exposure was associated with the catabolic effects. This key observation was developed further as the foreshortened amino-terminal fragment of PTH, teriparatide [PTH(1-34)] and, later, the full-length hormone [PTH(1-84)] were shown to be anabolic when administered once daily in low doses (12, 13).

At the cellular level, gene expression profiling of inter-
mittent vs continuous PTH administration in vivo and in vitro suggests that the two modes of administration of PTH can regulate different set of genes, one favoring bone formation and the other favoring bone resorption (14, 15).

This review focuses on both the anabolic and catabolic skeletal effects of PTH, and discusses the cellular basis by which PTH exerts these effects.

**PHPT**

Historically, symptomatic PHPT is associated with a devastating, catabolic destruction of the skeleton with bone loss, brown tumors, bone cysts, and subperiosteal bone resorption of the phalanges (16, 17). Osteitis fibrosa cystica, the term given to this severe bone disease, is still seen in the developing world, but in most regions where biochemical screening is routine, asymptomatic PHPT predominates. Asymptomatic PHPT rarely is accompanied by these specific skeletal features (18-20). Rather, bone densitometry technology has permitted a different kind of insight into the skeleton of subjects with PHPT.

Bone density and skeletal microarchitecture

Silverberg et al. (7) evaluated the presence and extent of bone disease in patients with asymptomatic PHPT, by DXA and by histomorphometry of bone biopsies. The greatest reduction in bone mineral density (BMD) was found at the distal 1/3 radius, a site of predominantly cortical bone. The ability to perform 3-site DXA gave further information at the other 2 sites, the lumbar spine, a site primarily comprised of cancellous bone, and the hip, a site that is an even admixture of cortical and cancellous bone. BMD of the lumbar spine was within 5% of expected for non-hyperparathyroid, post-menopausal women. The hip regions showed values that were intermediate between the preferentially reduced cortical bone of the distal radius and the maintained BMD of the lumbar spine (Fig. 1).

The findings by DXA were followed up by an extensive series of histomorphometric studies by Dempster et al. (7, 9, 10, 21). Preferential involvement of cortical bone with preservation of cancellous areas was confirmed by histomorphometric analysis. The vast majority of patients with PHPT showed reductions in cortical width. In contrast, the cancellous compartment of the bone biopsy specimen showed greater than average values for trabecular bone volume. Other features of trabecular bone such as trabecular number, connectivity and separation indicated preservation of this compartment of bone in most patients with PHPT. Analysis of bone biopsy specimens by microcomputed tomography (μCT) also demonstrated in mild PHPT preserved cancellous bone architecture (Fig. 2) (8). Histomorphometric studies of bone biopsies in PHPT have confirmed that while the trabecular compartment is preserved, the cortical compartment is at risk with cortical thinning and increased cortical porosity commonly seen (9, 10, 21, 22). The 10- and 15-yr natural history studies of Silverberg et al. (18, 20) showed that lumbar spine bone density remains stable for as long as subjects were followed, while the sites with more cortical bone, namely the distal 1/3 radius and the femoral neck, began to experience substantial declines after 10 yr of observation.

The characteristic densitometric and histomorphometric pattern described above, with preferential reduction of the cortical compartment, is not always seen in PHPT. The descriptions provided are the most common ones. Obviously, these features will vary with the extent of the disease, and predisposing factors that could favor losses in other skeletal compartments and thus other patterns. For example, Silverberg et al. described a minority of patients with PHPT whose lumbar spine bone density was preferentially reduced (23). This could reflect preferential loss of cancellous bone due to the menopause per se, prior to the development of PHPT. Other studies have demonstrated more universal loss of BMD in PHPT (24-26), a finding that would not be unexpected in patients with more severe disease. Recently, Hansen et al. (24), using a newer non-invasive technology, high-resolution peripheral CT (HR-pQCT), showed decreased bone mass in the radius in both the cortical and trabecular compartments, in 27 women with mild PHPT, as compared to a normal control group. In this study, subjects with PHPT had reduced BMD at the lumbar spine by DXA. It is not surprising, therefore, that the cancellous compartment would be abnormal by HR-pQCT in this cohort. It is likely that when more typical phenotype of PHPT is examined by HR-pQCT, microstructural analysis by HR-pQCT will be consistent with preserved cancellous bone.

**Fracture risk**

Given the catabolic skeletal actions of continuously elevated PTH levels, typically at cortical sites, one would expect increased non-vertebral fracture risk in patients with PHPT. The preserved cancellous skeleton would be expected to be associated with reduced fracture risk in the spine. Some studies, though, have reported an increase in overall fracture risk (27, 28), including vertebral (17, 28, 29), forearm, rib, and pelvic fractures (28) in PHPT. Increased risk of vertebral and hip fractures has not, how-

![Fig. 1 - The densitometric signature of primary hyperparathyroidism (PHPT) in the modern era. Bone densitometry at lumbar spine, femoral neck and radius in PHPT. Bone mineral density (BMD) is presented in comparison to expected values for normal controls. [Adapted from (7)].](image)