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**Review article**

# PARATHYROID HORMONE AND PHYSICAL EXERCISE: A BRIEF REVIEW

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**ABSTRACT**
Parathyroid hormone (PTH) is the major hormone regulating calcium metabolism and is involved in both catabolic and anabolic actions on bone. Intermittent PTH exposure can stimulate bone formation and bone mass when PTH has been injected. In contrast, continuous infusion of PTH stimulates bone resorption. PTH concentration may be affected by physical exercise and our review was designed to investigate this relationship. The variation in PTH concentration appears to be influenced by both exercise duration and intensity. There probably exists a stimulation threshold of exercise to alter PTH. PTH regulation is also influenced by the initial bone mineral content, age, gender, training state, and other hormonal and metabolic factors (catecholamines, lactic acid and calcium concentrations).

**KEY WORDS:** Parathyroid hormone, physical exercise, calcium, catabolic/anabolic effects.

## INTRODUCTION

Physical exercise has frequently been shown to induce bone mass gain, especially in load-bearing bone sites (Maïmoun et al., 2003). Exercise may thus be an important factor in preventing osteoporosis (Dalsky, 1987), by either increasing the peak bone mass during childhood growth (Bradney et al., 1998) or decreasing the rate of bone loss in the elderly (Lane et al., 1990).

Anabolic effects of exercise training are not limited to individuals participating in competitive sports who focus particularly on improvements of muscle strength and endurance. For example, physical inactivity (Layne and Nelson, 1999), prolonged immobilization (Uebelhart et al., 1995) or lack of gravitational mechanical loading (e.g. space flight) (Cavanagh et al., 2005) lead to destructive bone loss, while bone formation dramatically increases when immobilized subjects resume exercise (Marcus, 1996). This has led to the popular conclusion that physical activity enhances bone formation and, consequently, bone mineral density (BMD) (Eliakim and Beyth, 2003; Vainionpaa et al., 2006). BMD is also influenced by heredity (Pocock et al., 1987) and environment (Ziegler et al., 1995). Mechanical load represent one of the major environmental factors to influence BMD and bone metabolism (Frost, 1988).

Moreover, the potential contribution of physical activity to increase bone mass is particularly important in children and adolescents

since BMD reaches about 90% of its peak by the end of the second decade (Glastre et al., 1990) and because about one quarter of adult bone is accumulated during the two years that surround the peak bone velocity (Baily, 1997). This supports the idea that patterns of physical activity during childhood and adolescence can act to prevent bone disorders (like osteoporosis) later in life.

Osteoporosis and low bone mass are one of the major public health problems affecting elderly subjects (Kelley et al., 2000). Several pharmacological treatments have been used in preventing or attenuating osteoporosis, notably alendronate sodium, risedronate sodium, zoledronic acid, and selective estrogen receptor modulators, such as raloxifene (Cavanagh et al., 2005). There has also been interest in anabolic agents such as parathyroid hormone (PTH), vitamin D and calcium (Cavanagh et al., 2005) recently. Exercise has been recommended as a nonpharmacological approach for maximizing bone mineral density during the younger years (Snow-Harter and Marcus, 1991).

Measurement of bone biochemical markers can also provide a practical way for early detection of the exercise response on bone cells. Serum bone alkaline phosphatase (B-ALP) and serum osteocalcin were used to reflect newly synthesized bone (Price et al., 1980; Garnero and Delmas, 1993). Maimoun et al., (2006) reported a significant rise (10 and 12%) in both biochemical markers to 50-min cycling tests performed at 15% above the ventilatory threshold. This observation likely indicates an immediate anabolic effect of exercise on bone tissue.

Parathyroid hormone (PTH) which is the major regulator of bone metabolism functions to maintain the calcium-ion concentration of the extracellular fluids within physiological limits (Arnaud et al., 1967). PTH is also a primary determinant of intracellular calcium homeostasis (Rasmussen, 1968). The principal target organs for PTH are the kidney (increasing proximal tubular resorption of calcium, phosphate excretion and 1,25 dihydroxyvitamin D formation) and the skeleton. An indirect effect, increasing intestinal calcium absorption, is mediated by the increase in 1,25 dihydroxyvitamin D formation in the kidney (Poole and Reeve, 2005).

PTH has biphasic effects on bone: continuous treatment is catabolic (Qin et al., 2004; Thomas et al., 2006) whereas intermittent treatment is anabolic (Locklin et al., 2003; Qin et al., 2004). Several investigations showed that graded exercise until exhaustion (Brahm et al. 1997a) and continuous (2 exercises of 21 minutes each at respectively 70 and 85% of $VO_2$max) or intermittent (2 exercises of 21 minutes each at respectively 70 and 85% of $VO_2$max separated by 40 minutes recovery) sub-maximal exercise (Bouassida et al., 2003) enhances PTH concentrations. On the other hand, Kristoffersson et al. (1995) and Brahm et al., (1997 b) have failed to demonstrate significant changes in PTH concentration after a short-term maximal work (modified Wingate test at 7.5% of body weight) (Kristoffersson et al., 1995) and a short lasting dynamic exercise (15 minutes at 61% of peak one leg oxygen uptake) (Brahm et al., 1997 b).

Although the effects of PTH on bone metabolism have been intensively studied, there is a paucity of literature relating the effect of physical exercise on PTH concentrations. In this review, we discuss the biological effects of PTH on bone and we outlined the present knowledge about its concentrations in response to physical exercise.

## BIOLOGICAL EFFECTS OF THE PARATHYROID HORMONE ON BONE

A key factor in the control of bone remodeling is parathyroid hormone, the principal regulator of calcium homeostasis. Calcitonin (Rong et al., 1999), pH (Chambers et al., 1983) and catecholamines (Joborn et al., 1990) can also modify PTH secretion. Elevated levels of PTH increase bone turnover, leading to either anabolic or catabolic effects on the skeleton depending upon the pattern and duration of elevation (Poole and Reeve, 2005). The normal reference range of PTH concentrations is 0.5-5.0 $pmol^{-1}$ in young adults (Hodsman et al., 1993) and is 0.40-1.08 IU in males below the age of 50 (Ljunghall et al., 1988).

### *Anabolic effects of PTH on bone*

Daily recombinant human PTH [PTH (1-34)] injections (30 $mg \cdot kg^{-1}$ during 35 days) in male rats with femoral fractures enhanced fracture-healing by increasing bone mineral content and density and strength, and it produced a sustained anabolic effect throughout the remodeling phase of fracture-healing (Alkhiary et al. 2005).

Two groups of rabbits underwent right tibia lengthening by callus distraction, and it was found that intermittent PTH (1-34) treatment (5 or 25 $mg \cdot kg^{-1}$ during 20 days) improved mineralization, and structural indices of regenerated distracted rabbits' tibia. Treatment at a dose of 25 $mg \cdot kg^{-1}$ of PTH (1-34) was significantly more effective than 5 $mg \cdot kg^{-1}$ of PTH (1-34) dose treatment when compared to the control group (Aleksyniene et al., 2006).

In humans, Miki et al. (2004) showed that intermittent subcutaneous administration of 1-34 N-terminal peptide of human parathyroid hormone

(hPTH 1-34) (100 units/week during 1 year) in patients with primary osteoporosis increased the mean lumbar bone mineral density by 1.8%, 3.4%, and 4.6% after 12, 24, and 48 weeks of hPTH administration. These authors concluded that intermittent weekly subcutaneous injections of hPTH (1-34) for 48 weeks increased trabecular bone volume and improved microstructure, without causing the appearance of abnormal bone elements in primary osteoporosis (Miki et al., 2004).

The mechanisms responsible and implied in these two mechanisms are not yet entirely elucidated. It has been proposed that intermittent PTH injection exerts its anabolic effects at three steps of bone formation: (1) stimulating the proliferation of preosteoblasts; (2) promoting the differentiation of preosteoblasts and osteoblasts; and (3) inhibiting osteoblast apoptosis (Qin et al., 2004).

***Catabolic effects of PTH on bone***

The catabolic effects of PTH result from pathological conditions in which one or more parathyroid glands secrete too much hormone continuously at a sustained level. Such continuous secretion of PTH (as occurs in chronic renal disease and primary hyperparathyroidism) can lead to bone destruction (Poole and Reeve, 2005).

Iida-Klein et al. (2005) suggested that short-term infusion of PTH (1-34) (40 $ug \cdot kg^{-1} \cdot day^{-1}$for10 weeks) in old female mice was catabolic with decreased trabecular connectivity density. Continuous infusion of PTH in female patients with osteoporosis (dose of 800 IU for 28 days) may inhibit bone formation by decreasing significantly the biochemical markers of bone formation (serum alkaline phosphatase, osteocalcin and the carboxy-terminal extension peptide of pro-collagen 1) (Hodsman et al., 1993).

Less is known of the mechanisms whereby continuous PTH is catabolic to the bone. Several recent studies suggested that continuous (but not intermittent) PTH can result in an increase in receptor activation of nuclear factor-kB ligand (RANKL) expression and consequent osteoclastogenesis, with an associated inhibitory effect on osteoprotegerin expression in culture (Ma et al., 2001; Locklin et al., 2003).

## PARATHYROID HORMONE CONCENTRATION DURING PHYSICAL EXERCISE

The data of the literature concerning the relation between PTH and exercise have shown that physical exercise is an important modifier of PTH concentrations depending on intensity and duration of exercise.

Maïmoun et al., (2006) measured PTH concentrations in young male cyclists during and after two 50-min cycling tests performed at 15% below the ventilatory threshold (VT) (-VT) and 15% above (+VT) and reported a significant increase in PTH concentrations at the end and during the recovery only in the exercise performed at +VT. For both intensity levels of exercise, no significant variation in calcium serum levels was observed. These authors suggested the existence of a bone stimulation threshold for exercise to increase PTH serum concentration. Maïmoun et al., (2005) studied PTH responses before and following a maximal incremental exercise test in elderly men and women and noted that PTH concentrations were increased after the exercise and that this increase could have an anabolic action on bone turnover.

We recently showed an increase in PTH concentrations during and after two high intensity exercise protocols continuous or intermittent (continuous protocol: 2 periods running of 21 minutes each at 75% and 85% of $VO_{2max}$; intermittent protocol: similar running exercises with a 40 minutes recovery period between the two exercises) performed in 12 healthy male. Our results indicate that PTH concentrations increased during and at the end of the two protocols. The comparison between the two tests indicate that PTH concentration was greater at the end of continuous protocol ($p < 0.01$) and that PTH remained elevated for 24 hours only in the continuous protocol ($p < 0.05$). This increase of PTH concentrations during these tests was accompanied by a decrease of the ionized calcium concentrations ($p < 0.01$). In these conditions we demonstrated that recovery between two bouts of sub-maximal exercises may have anabolic effects on bone health, however, the small physiological changes observed prevent us from forming any firm conclusion (Bouassida et al., 2003).

Thorsen et al., (1997) observed a reduction of plasma ionized calcium at 1 and 72 hours and an increase of PTH concentrations at 24 and 72 hours after endurance exercise (45 minutes running at 45% of maximal oxygen uptake ($VO_{2max}$) among young women. Even though the significant increase of PTH concentration was not observed until 24 hours after the exercise, the results of Thorsen et al., (1997) indicated a preserved feedback between calcium and PTH. These results are well in line with a previous observation by Ljunghall et al., (1986) concerning long-term moderate endurance exercise (5 hours pedalling at 50% of $VO_{2max}$) performed by males where serum ionized calcium was found to be

slightly lowered during exercise and serum concentration of PTH elevated during the last part of the prolonged 5-hour test. In addition, Ashisawa et al. (1997) reported that strenuous exercise increased urinary calcium excretion by decreasing renal calcium re-absorption, with the development of severe metabolic acidosis. In addition, other biological factors such as catecholamines may modulate PTH secretion during exercise (Blum et al., 1978).

As found in an earlier investigation (Brahm et al., 1997 a) there was also an increase in PTH concentration after a maximal exercise (10 minutes at 30% of $VO_{2max}$ followed by work periods of 10 minutes each at increased work loads corresponding to 47% and 76% of $VO_{2max}$ and at final maximal effort until exhaustion for 4-5 minutes, with a total work time of about 35 minutes) in 10 men and 10 women. During this study, PTH concentration rose in proportion to the intensity of exercise and remained elevated during the 24 hours recovery despite an increase in total serum calcium concentration. PTH is probably rapidly equilibrated between plasma and extravascular fluid (Ljunghall et al., 1985), but the persistent elevation of the concentration of serum PTH during 24 hours recovery is in line with an anabolic role of PTH (Salvesen et al., 1994) in the metabolic response to exercise.

The PTH concentration was increased during prolonged exercise at constant intensity (50 minutes at 4.2 $m \cdot sec^{-1}$) and progressive intensity (5 steps of 8 minutes with an increase of 0.25 $m \cdot sec^{-1}$ per step) performed by long distance runners (Salvesen et al., 1994). In the test with constant velocity, the runners displayed a marked increase in PTH concentration despite a rise in serum calcium. In the test with increased load, there was no correlation between the changes in PTH and total serum calcium, however, an association between the changes in PTH and lactate was reported. Indeed, subjects with a marked increase in PTH also displayed a rise in plasma lactate (Salvesen et al., 1994).

In addition, Ljunghall et al. (1988) demonstrated a significant increase in PTH and stability in total serum calcium concentration after a prolonged physical exercise (7 days of military service: field exercise maneuvers with intense physical activity) in 17 young men. These authors noted a significant relationship between the increase of serum myoglobin and the PTH concentration after the prolonged exercise indicating that the subjects who performed the largest amount of work also experienced the greatest stimulus of PTH (Ljunghall et al., 1988),

On the other hand, PTH concentration remained unaffected in seven male cyclists after 50 min cycling at 15% below the ventilatory threshold (Maïmoun et al., 2006), after 50 minutes of running at 3.3 $m.sec^{-1}$ in 6 fire-fighters (Salvesen et al., 1994), after 30 seconds maximal exercise by 7 male athletes (modified Wingate test) (Kristoffersson et al., 1995) and after an intense exercise (isokinetic work with one leg with maximal force for 2 minutes) carried by 5 healthy subjects (Ljunghall et al., 1985).

During these studies, the concentration of ionized calcium or total calcium was increased. Several factors such us intensity, duration, recovery and type of exercises could explain the heterogeneity of results concerning PTH concentration and exercise.

During physical exercise, other physiological factors other than calcium can modify the secretion of the PTH such as catecholamines, acidosis and training. Several studies showed that the variations in the concentration of the PTH response during exercise were independent of the ionized calcium concentration (Henderson et al., 1989; Salvesen et al., 1994; Rong et al., 1997). In contrast, the adrenergic system is activated during physical exercise (Sagnol et al., 1990) and it was proven that this system played a role in the regulation of the PTH secretion (Joborn et al., 1990). More work is needed to ascertain the interaction of the adrenergic effects with the PTH changes with exercise.

Lactic acid and or pH can also influence the PTH concentration. Studies in animals (Lopez et al., 2002) and in humans (Lu et al., 1994; Movilli et al., 2001) showed that acidosis can stimulate PTH secretion. A study undertaken in the rat showed that acute acidosis causes, in the absence of hypocalcemia, an increase in the concentration of circulating PTH (Bichara et al. 1990).

Training (Zerath et al., 1997) and physical fitness (Brahm et al., 1997a) can also influence the response of the PTH to the exercise. Indeed, Zerath at al. (1997) demonstrated that six weeks of endurance training (75-80% of maximal heart rate, 1 hour/day, 4 days/week) enhanced exercise-related release of PTH in elderly men. These authors suggested that their findings might be important regarding bone status in the elderly, as exercise is proposed as a preventive measure against osteopenia. In addition, Brahm et al. (1997a) indicated an inverse relationship between basal serum PTH concentrations and $VO_{2\ max}$ in 10 men and 10 women with a wide range of physical capacity (range 48.2-67.1 $ml \cdot kg^{-1} \cdot min^{-1}$ for men and range 37.8-58.8 $ml \cdot kg^{-1} \cdot min^{-1}$ for women).

## CONCLUSION

The variations of PTH concentration during and after physical exercise were both exercise duration- and intensity-dependent, which suggests the probable existence of a PTH stimulation threshold. The marked rise in PTH concentration was noted only during high-intensity (15% above VT) and long-duration (>50 minutes) or low-intensity (50% of $VO_{2max}$) and very long-duration (5 hours) exercise suggests that a minimal intensity and duration is needed to induce a modification in PTH concentration. On the other hand, short-duration (30 sec) maximal exercise or long-duration (50 min) low-intensity (15% below VT) exercise seems to have no impact on PTH secretion. Consequently, in addition to the mechanical strains generated by physical exercise, both duration and intensity appear to be important parameters of PTH secretion process.

There are many interesting directions for future research in this area. It would be interesting to investigate whether higher intensities lead to increased and earlier responses of PTH secretion and it remains to be demonstrated to what extent the PTH threshold depends on factors such as age, gender, physical fitness, training status, hormonal and metabolic modifications (catecholamines, lactic acid and calcium concentrations).

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## KEY POINTS

- Physical exercise can improve PTH secretion.
- Parathyroid hormone has both anabolic and catabolic effects on bone: intermittent treatment of PTH is anabolic whereas continuous treatment is catabolic.

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