

REVIEW ARTICLE

Parathyroid hormone pulsatility: physiological and clinical aspects

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Parathyroid hormone (PTH) secretion is characterized by an ultradian rhythm with tonic and pulsatile components. In healthy subjects, the majority of PTH is secreted in tonic fashion, whereas approximately 30% is secreted in low-amplitude and high-frequency bursts occurring every 10–20 min, superimposed on tonic secretion. Changes in the ultradian PTH secretion were shown to occur in patients with primary and secondary osteoporosis, with skeletal effects depending on the reciprocal modifications of pulsatile and tonic components. Indeed, pathophysiology of spontaneous PTH secretion remains an area potentially suitable to be explored, particularly in those conditions such as secondary forms of osteoporosis, in which conventional biochemical and densitometric parameters may not always give reliable diagnostic and therapeutic indications. This review will highlight the literature data supporting the hypothesis that changes of ultradian PTH secretion may be correlated with skeletal fragility in primary and secondary osteoporosis.

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INTRODUCTION

Pulsatility is a fundamental property of the majority of hormone secretion¹ and denotes the recurrence of individual punctuated events (busts, peaks or pulses) interrupting a more or less constant baseline process.¹ Many hormones have a pulsatile component to their secretory profile and pulsatility is believed to modulate target organ responsiveness.^{2–3} Interestingly, there is intra-individual variability in number and/or amplitude and/or frequency of hormone pulses with potential modifications in the target tissue responsiveness.¹ In fact, growth hormone (GH) pulse size and frequency may be influenced by several hormones such as cortisol and testosterone, physiological such as fasting and aging, and pathological conditions such as obesity and diabetes.^{3–9} Luteinizing hormone pulsatility is the prototype of dual amplitude and frequency regulation, whereas thyrotropin and adrenocorticotropin secretory patterns are examples of triple control of pulsatility with size, frequency and number bursts being influenced to several signals.¹ Although pituitary gland is the paradigm of pulsatile hormone secretion under control of several hypothalamic neuroendocrine signals, also the peripheral glands can secrete hormones in a pulsatile manner.

In this paper, we focus on parathyroid hormone (PTH) secretion, dealing with physiological, pathophysiological and clinical aspects related to the pulsatile secretion of the hormone.

PHYSIOLOGY OF PTH SECRETION

Circadian and seasonal secretion

Parathyroid glands secretory activity shows seasonal and circadian fluctuations, which are associated with changes in serum calcium, phosphate and bone turnover.¹⁰ In fact, PTH levels usually decline about 20% below the annual mean during the summer, reflecting circannual rhythms of vitamin D and bone turnover.¹¹ Moreover, it has been described a circadian rhythm for PTH with a more pronounced peak in the early morning, a nadir in the late morning and a second, lower peak in the afternoon, likely related to calcium, phosphate and calcitriol changes which can be modified by nutritional intake of these components.¹²

Pulsatile ultradian secretion

Spontaneous PTH secretion is also characterized by an ultradian rhythm with tonic and pulsatile components. In healthy young subjects, the majority of PTH (about 70%)

is secreted in tonic fashion, whereas approximately 30% is secreted in low-amplitude and high-frequency bursts occurring every 10–20 min, superimposed on tonic secretion.^{13–17} PTH pulsatile secretion is highly sensitive to changes in ionized calcium and calcitriol serum levels.¹⁰ Calcium exerts its effects on the parathyroid gland through binding to a cell surface receptor, the calcium-sensing receptor.¹⁸ Acute hypocalcemia induces a selective, several-fold increase in bursts frequency and amplitude, whereas hypercalcemia suppresses the PTH pulsatile secretion component, as does prolonged calcitriol therapy. Indeed, calcitriol in synergism with ionized calcium is the major physiological inhibitor of PTH secretion.¹⁹ Conversely, vitamin D deficiency or resistance might contribute, indirectly (throughout the reduction in calcium absorption) and even directly to PTH hypersecretion.²⁰

PTH effects on target tissues

The pulsatile secretion of PTH may have a role in physiological regulation of bone metabolism and structure. Although there are no animal models investigating specifically the skeletal effects of pulsatile PTH secretion, there is experimental evidence that intermittent administration of pharmacological doses of PTH has a bone anabolic effect, while continuous PTH administration is detrimental for the skeleton due to stimulation of bone resorption.²¹ Consistently with these experimental findings, daily injections of PTH produce significant increase in bone mass and decrease in fracture risk in patients affected by osteoporosis.^{22–23} The initial effect of PTH intermittent administration is the stimulation of bone modeling, which prompts to an increase in bone formation markers, whereas the subsequent stimulation of bone remodeling is characterized clinically also by an increase in bone resorption markers: this sequence gives rise to the so called 'anabolic window' during which the osteoanabolic actions of PTH take place.²⁴ Comparable anabolic effects may be produced by treatment with short-acting antagonists of calcium sensing receptor, the so-called calcilytics, which induce an acute stimulation of PTH secretion by the parathyroid gland mimicking a pulsatile secretory pattern which may lead to improvement of bone mineral density (BMD) and decrease in fracture risk.^{25–26} Over the recent years, there has been convincing evidence that PTH exerts extra-skeletal effects, mainly on cardiovascular system and glucose metabolism.^{27–29} However, it is still unknown whether and how the pulsatile PTH secretion may influence these extra-skeletal targets.

ASSESSMENT OF PTH PULSATILITY

Accurate characterization of hormonal pulses requires specific and sensitive assays, intensive schedule of blood

sampling, and validated and objective methods of pulse analysis.^{13,17,30–31} Due to the intrinsic characteristics of PTH physiological secretion with very frequent and small pulses, PTH pulsatility studies are complex to perform and this explains in part the lack of published data on this topic. PTH is measured with immunoradiometric assays (sensitivity about 1 pg·mL⁻¹; intra- and inter-assay coefficients of variation between 4% and 6%). PTH half-life is approximately 2–5 min and PTH pulses are estimated to occur with a frequency of 10–20 min. Therefore, in all the experimental studies on PTH pulsatility so far carried out, two milliliters of blood are withdrawn (samples are analyzed in duplicate) every 2–3 minutes for 6 h, usually from 9:00 a.m. to 3:00 p.m., in fasting subjects. Plasma PTH levels need to be analyzed by a deconvolution analysis in order to obtain an accurate estimate of secretion and clearance. The most representative parameters of this analysis are: basal PTH secretion rate (pg·mL⁻¹·min⁻¹), secretory bursts half-duration (minutes), maximal amplitude of secretory bursts (pg·mL⁻¹·min⁻¹) and the total number of secretory bursts. Plasma PTH levels can also be subjected to an approximate entropy analysis, which provides a measure of the orderliness of the release process.

PTH PULSATILITY IN SKELETAL DISEASES

Primary hyperparathyroidism

Primary hyperparathyroidism (PHPT) is a common endocrine disorder characterized primarily by hypercalcemia and elevated levels of PTH. The common clinical presentation of PHPT has changed over the last two–three decades from an overt disease characterized by hypercalcemic symptoms and kidney stones to a mild or even asymptomatic disease.³² Although PHPT occurs at all ages, the majority of patients are postmenopausal women, in whom a variable degree of bone loss is commonly found, with a greater involvement of cortical sites. Increased fracture risk has been reported at both vertebral and non-vertebral sites in PHPT.³³

PHPT is accompanied by qualitative and quantitative abnormalities of PTH secretion (Table 1). Harms *et al.*³⁴ measured PTH in nine female patients with PHPT, compared with 10 postmenopausal control women. The analysis of pulsatile secretory pattern revealed significant increase in total PTH secretion per hour, basal PTH secretion per hour and average PTH secretion per pulse in PHPT patients as compared to the control subjects, without significant differences in the number of bursts between the two groups in which the pulsatile secretion accounted for about 50% of the total secretion.³⁴ The cross-correlation of PTH and calcium indicated an impaired feedback regulation in PHPT. This study did not give insights on the possible clinical impact of PTH pulsatility on skeletal and extra-skeletal targets in PHPT patients.

Table 1. Clinical studies investigating the changes of PTH pulsatility in human diseases

| Ref no. | Patients (n) | Sex (M/F) | Disease | PTH pulsatility | | | | |
|---------|--------------|-----------|---------|-----------------|-----------------|------------------|---------------|------|
| | | | | Basal secretion | Bursts duration | Bursts amplitude | Bursts number | ApEN |
| 34 | 9 | 0/9 | PHPT | ↑ | ↔ | ↑ | ↔ | ↔ |
| 30 | 25 | 0/25 | PMO | ↔ | ↔ | ↔ | ↔ | ↔ |
| 37 | 6 | 0/6 | PMO | ↓ | ↔ | ↓ | ↔ | ↔ |
| 17 | 6 | 6/0 | GIO | ↓ | ↑ | ↑ | ↔ | ↔ |
| 31 | 5 | 5/0 | ACRO | ↔ | ↑ | ↑ | ↔ | ↔ |

Abbreviations: ACRO, acromegaly; ApEN, approximate entropy; F, females; GIO, glucocorticoid-induced osteoporosis; M, males; n, number; PHPT, primary hyperparathyroidism; PMO, post-menopausal osteoporosis.

↑, increased; ↓, decreased; ↔, unchanged.

Post-menopausal osteoporosis

Osteoporosis is a chronic, progressive bone disease in which bone resorption exceeds bone formation, leading to a reduction in BMD, disruption of bone microarchitecture and increase in fracture risk.³⁵ The incidence of osteoporosis increases with age and it occurs most frequently in postmenopausal women due to the cessation in ovarian activity with consequent increase in bone resorption.³⁶ Very few cross-sectional studies have investigated spontaneous PTH secretion in patients with post-menopausal osteoporosis, reporting discordant results^{30,37} (Table 1). Harms *et al.*³⁷ observed a decrease in basal secretion and pulse amplitude of PTH during estrogen replacement therapy in early post-menopausal women, whereas Samuels *et al.*³⁰ did not find relevant differences in structure and modality of PTH secretion in postmenopausal women versus young adults. Indeed, in all of these studies the number of subjects was too low to draw meaningful conclusions. In fact, it has to be taken into account the possible variability induced by several factors, such as nutritional and vitamin D status, daily calcium intake, duration and age of menopause.

Glucocorticoid-induced osteoporosis (GIO)

GIO is the most common cause of secondary osteoporosis.³⁸ Fractures are often asymptomatic and occur in about 30%–50% of patients receiving chronic glucocorticoid therapy.³⁹ Vertebral fractures occur early after exposure to glucocorticoids, and they tend to occur at higher BMD levels than in women with postmenopausal osteoporosis.⁴⁰ Glucocorticoids impair the replication, differentiation and function of osteoblasts and induce the apoptosis of mature osteoblasts and osteocytes.³⁸ These effects lead to a suppression of bone formation. Glucocorticoids also increase bone resorption by increasing osteoclastogenesis.³⁸ In addition to the direct effects of glucocorticoids on bone cells, other skeletal effects are mediated by neuroendocrine changes, such as functional GH deficiency, hypogonadism and possible qualitative abnormalities of PTH secretion.⁴⁰ Most explanatory diagrams of GIO include a secondary, compensatory, rise in PTH which is believed to be due to the effects of glucocorticoids in limiting calcium absorption in the gastrointestinal tract (by decreasing the expression of

specific calcium channels in the duodenum) and in facilitating renal calcium excretion.⁴⁰ Some studies have not found an association between GIO and increased PTH levels; conversely, other studies have shown that patients with GIO did exhibit frankly elevated PTH serum levels.⁴¹ These data can be reconciled thinking to the relatively low clinical relevance of baseline PTH levels, since the hormone is secreted in a pulsatile fashion. However, very few data are so far available on the effect of chronic glucocorticoid excess on spontaneous fluctuations of PTH in humans. Bonadonna *et al.*¹⁷ evaluated spontaneous PTH pulsatile secretion in patients chronically treated with pharmacological amounts of glucocorticoids (Table 1). They enrolled six adult male patients (aged 31–64 years) receiving chronic (>6 months) therapy with glucocorticoids (daily dosage >7.5 mg of prednisone or dose equivalent of other corticosteroid) and compared their spontaneous PTH secretion with that of a control group of 10 age- and sex-matched normal subjects. In the glucocorticoid-treated group, the PTH tonic secretory rate was reduced; however, there was an increase in the fractional pulsatile PTH secretion in glucocorticoid-treated vs normal subjects. Mean overall PTH concentration, as well as mean integrated area, was similar among normal and glucocorticoid-treated subjects. Therefore, it can be concluded that chronic glucocorticoid treatment induces a redistribution of spontaneous PTH secretory dynamics by reducing the amount released in tonic fashion and increasing the amount released as pulses. The clinical importance of this finding is unclear: a compensatory mechanism cannot be excluded although unable to restore the physiological bone metabolism (the alteration of which could only be overcome by much larger PTH peaks such as those obtained by exogenous administration). Other possible explanations include direct effect of glucocorticoids on parathyroid glands or subtle changes in ionized calcium levels. The decrease of circulating osteocalcin induced by glucocorticoids could also be hypothesized to feedback at the parathyroid gland level.

Acromegaly

GH and IGF-1 are anabolic hormones for bone with important regulating effects of bone homeostasis

throughout life.⁴² Both GH deficiency and acromegaly are traditionally considered as causes of skeletal fragility. Patients with GH deficiency have low bone turnover osteoporosis,^{42–43} whereas patients with acromegaly have increased bone turnover, as determined by changes in biochemical markers, calcium kinetics, and bone histomorphometry.⁴⁴ Chronic GH/IGF-I excess in acromegaly is associated with high bone turnover, which in turn can cause bone loss and skeletal fractures, despite modestly decreased or normal BMD, as measured by DXA.⁴⁵ Several cross-sectional and prospective studies demonstrated that acromegaly is associated with an increased prevalence and incidence of radiological and morphometric vertebral fractures.^{45–48} Biochemical activity of acromegaly is significantly correlated with the risk of vertebral fractures, but incident fractures are shown to occur also in patients with controlled disease, in relationship with the coexistence of untreated hypogonadism and prevalent vertebral fractures at baseline.⁴⁸ Also in acromegaly, as expected based on previous considerations, data on PTH are not consistent, since they have been shown to be normal or slightly increased at the diagnosis of disease and they may also be influenced by medical treatment with somatostatin analogs.^{49–50} Mazziotti *et al.*³¹ evaluated whether GH excess in acromegaly could modify spontaneous pulsatile PTH secretion (Table 1). Five male patients with newly diagnosed active acromegaly and eight healthy subjects were evaluated by 3-min blood sampling for 6 h. Plasma PTH concentrations were evaluated by multiparameter deconvolution analysis and plasma PTH release profiles were also subjected to an approximate entropy estimate. PTH pulse half-duration was significantly longer and PTH pulse mass tended to be greater in acromegaly patients versus healthy subjects. So it can be hypothesized that GH excess may affect PTH secretory dynamics in patients with acromegaly, but potentially negative bone effects of the modifications of PTH secretory pattern in acromegaly still remain to be investigated.

CONCLUSIONS

Assessment of spontaneous PTH secretion is made complex by its physiological pattern which requires very frequent and prolonged sampling with consequently elevated number of PTH samples to assay. Therefore, studies in this area are experimental and difficult to undertake and may cause discomfort to patients. Due to these limitations and despite the currently very limited amount of relevant informations which can be given by baseline PTH values, this approach has found no or very limited space in the assessment of patients with bone metabolic diseases. This procedure has been so far confined to small research studies that can only be defined proof of concept studies often

unfortunately giving conflicting results. Nevertheless, pathophysiology of spontaneous PTH secretion remains an interesting area to be explored, particularly in those conditions such as secondary forms of osteoporosis, in which conventional biochemical and densitometric parameters may not always give reliable diagnostic and therapeutic indications.

Competing interests

The authors declare no conflict of interest.

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