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Active acromegaly enhances spontaneous parathyroid hormone pulsatility

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Abstract

In healthy subjects, parathyroid hormone (PTH) is secreted in a dual fashion, with low-amplitude and high-frequency pulses superimposed on tonic secretion. These 2 components of PTH secretion seem to have different effects on target organs. The aim of our study was to evaluate whether growth hormone excess in acromegaly may modify the spontaneous pulsatility of PTH. Five male patients with newly diagnosed active acromegaly and 8 healthy subjects were evaluated by 3-minute blood sampling for 6 hours. Plasma PTH concentrations were evaluated by multiparameter deconvolution analysis. Plasma PTH release profiles were also subjected to an approximate entropy (ApEn) estimate, which provides an ensemble measure of the serial regularity or orderliness of the release process. In acromegalic patients, baseline serum PTH values were not significantly different from those measured in the healthy subjects, as well as tonic PTH secretion rate, number of bursts, fractional pulsatile PTH secretion, and ApEn ratio. Conversely, PTH pulse half-duration was significantly longer in acromegalic patients vs healthy subjects (11.8 ± 0.95 vs 6.9 ± 1.6 minutes; $P = .05$), whereas PTH pulse mass showed a tendency ($P = .06$) to be significantly greater in acromegalic patients. These preliminary data suggest that growth hormone excess may affect PTH secretory dynamics in patients with acromegaly. Potentially negative bone effects of the modifications of PTH secretory pattern in acromegaly should be investigated.

1. Introduction

Many hormones are secreted in a pulsatile fashion which has physiological significance in reflecting episodic stimulatory input to the secretory gland and in modulating target organ responsiveness [1-3]. In healthy subjects, parathyroid hormone (PTH) is secreted by low-amplitude and high-frequency pulses superimposed on tonic secretion [4-8]. No significant differences in these secretory dynamics have been observed between healthy men and women [4]. There is convincing evidence that the pulsatile component of PTH secretion may be important for the regulation of postreceptor actions of the hormone on the bone. Animal experiments have demonstrated that an intermittent administration of PTH increases bone mass and structure, whereas a continuous administration by infusion at the same mean rate leads to bone loss [9,10]. On the other hand, intermittent administration of recombinant PTH induces dramatic anabolic effects on bone in patients with severe osteoporosis [11,12]. Indeed, PTH pulsatility has been so far analyzed in patients with postmenopausal osteoporosis [13] and in chronic glucocorticoid treatment [8].

Traditionally, acromegaly is considered a cause of secondary osteoporosis [14-16]. In fact, several studies have suggested a growth hormone (GH)–mediated increase of bone turnover in acromegaly based on the evaluation of biochemical markers, calcium kinetics, and bone histomorphometry [17-20]. However, the data on PTH behavior in acromegaly are not consistent, suggesting that these values may be normal or slightly increased at the diagnosis of disease [21-24] and they may also change during the medical treatment with somatostatin analogs [23]. However,

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Table 1
Anthropometric (age and body mass index [BMI]) and baseline biochemical (serum 25-hydroxyvitamin D, BSAP, GH, and IGF-1 values) features of acromegalic patients

Patient no.	Age (y)	BMI (kg/m^2)	Serum vitamin D (ng/mL)	Serum BSAP (UI/L)	Serum GH (ng/mL)	Serum IGF-1 (ng/mL)
1	35	29	27.0	57.0	25	564
2	42	32	40.1	51.0	17	482
3	40	34	8.4	65.0	18	459
4	55	33	16.0	74.0	29	1058
5	52	30	22.0	36.0	31	522
Mean ± SEM	44.8 ± 3.8	31.6 ± 0.9	22.7 ± 5.3	56.4 ± 6.4	24 ± 2.8	617 ± 111.7
Reference range			15-70	10-50	<1.0	100-350

these data were obtained with a "crude" measure of PTH secretion, whereas data on PTH pulsatility in acromegaly have not been so far reported.

In this study, we aimed at evaluating whether the GH excess in untreated acromegaly may modify the spontaneous pulsatile PTH secretion. This issue was addressed in a small group of acromegalic male patients who were selected for being with active disease, with normal gonadal function, and without osteoporosis, to exclude possible effects of different factors other than GH hypersecretion on PTH pulsatility.

2. Materials and methods

Five male patients (mean age, 39 years; range, 35-55 years) with newly diagnosed active acromegaly and 8 healthy subjects, with comparable age (mean age, 42 years; range, 36-58 years), were studied after they had given written informed consent. Acromegaly had been previously diagnosed by failure of suppression of serum GH concentrations below 1 ng/mL after a 75-g oral glucose load together with fasting plasma insulin-like growth-factor 1 (IGF-1) concentrations above the normal ranges for age [25]. The inclusion criteria were (1) normal gonadal, thyroid, and adrenal functions; (2) normal bone mineral density (T score > -1.0), as assessed by dual x-ray absorptiometry measurement at the lumbar spine. T score was calculated by normative data from a normal young male population.

All study subjects (acromegalics and controls) were evaluated for the PTH secretory dynamics as previously described [8]. Two milliliters of blood were withdrawn every 3 minutes for 6 hours, from 9:00 AM to 3:00 PM. The patients and the control subjects were fasting for the whole period of the biochemical evaluation. The plasma PTH concentration profile of each subject was evaluated by multiparameter deconvolution analysis, accounting for subject-specific plasma PTH disappearance half-life which was assumed to be 2 to 5 minutes. The dose-dependent intra-assay variance associated with sample means (assay duplicates) was used in an inverse weighting function when calculating the best-fit secretory values. The plasma PTH release profiles were also subjected to an approximate entropy (ApEn) estimate, which provides an ensemble measure of the serial regularity or orderliness of the release process [7].

The acromegalic patients were also evaluated for serum 25-hydroxyvitamin D, bone-specific alkaline phosphatase (BSAP), and calcium in serum and in 24-hour urine (Tables 1 and 2).

2.1. Biochemical assays

Blood samples were collected after an overnight fast. Serum was promptly separated and stored at −20°C until assay. Growth hormone and IGF-1 were measured by Immulite 2000 (DPC, Los Angeles, Calif). The interassay coefficient of variations of GH and IGF-1 assays ranged from 5.5% to 6.2% and from 6.4% to 11.5%, respectively. All blood samples for PTH were analyzed in duplicate using an immunoradiometric assay (Nichols Allegro, San Juan Capistrano, Calif) (normal range, 7-53 pg/mL). Assay sensitivity was 1 pg/mL; intra- and interassay coefficient of variation were 4% and 6%, respectively. All samples

Table 2
Baseline serum and 24-hour urinary calcium and circulating PTH in patients with acromegaly and control subjects

Subject	Serum calcium (mg/dL)	24-h urinary calcium (mg/24 h)	Serum PTH (pg/mL)
Patients			
1	8.9	84.0	57.0
2	9.5	82.0	31.6
3	9.1	51.0	35.4
4	9.0	65.0	50.2
5	8.9	82.0	21.8
Mean ± SEM	9.1 ± 0.1	72.8 ± 6.4*	39.2 ± 6.4
Controls			
1	9.0	150.0	62.0
2	9.0	200.0	33.0
3	8.5	201.0	34.0
4	9.6	220.0	48.0
5	9.2	200.0	27.0
6	9.1	145.0	28.0
7	9.4	160.0	22.0
8	8.3	201.0	49.0
Mean ± SEM	9.0 ± 0.1	184.6 ± 10.0	37.9 ± 4.9

* $P < .05$ patients vs controls.

Table 3
Measures of spontaneous PTH secretory pattern estimated by deconvolution analysis in 5 acromegalic patients with active disease and 8 male control subjects

Patient no.	Tonic secretion rate (pg/mL per minute)	Half-duration (min)	Bursts (total number)	Fractional pulsatile PTH secretion (%)	Pulse mass (pg per pulse)	ApEn ratio
1	10.20	12.10	6.00	24.48	49.60	0.97
2	7.20	11.50	5.00	15.29	23.40	0.77
3	7.70	12.80	5.20	18.12	29.50	0.80
4	9.50	14.30	6.00	42.66	106.00	0.71
5	4.80	8.50	5.80	16.58	14.80	0.97
Controls	8.8 ± 1.4	6.9 ± 1.6	6.1 ± 0.4	18.3 ± 3.9	26.5 ± 4.3	0.85 ± 0.04

from an individual subject were run in the same assay. Serum 25-hydroxyvitamin D was measured by radioimmunoassay (DiaSorin, Saluggia, Italy). The sensitivity of the test was 1.5 ng/mL, and the intra-assay coefficient of variation ranged from 8.6% to 12.5%. In our laboratory, the reference range was between 15 and 70 ng/mL. Bone-specific alkaline phosphatase activity was measured by Alkaphase-B (Metra Biosystem, Mountain View, CA) (normal range, 10-50 IU/L). Serum and 24-hour urinary calcium concentrations were measured by standard procedures. In our laboratory, the reference ranges were 8.9 to 10.5 mg/dL and 100 to 300 mg/24 hours, respectively.

2.2. Statistical analysis

Data were presented as mean ± SEM. The comparisons between the acromegalic patients and the control subjects were performed by *t* test for unpaired data. Statistical significance was assumed when *P* values were equal to or less than .05.

3. Results

All acromegalic patients had high serum BSAP values and serum 25-hydroxyvitamin D values prevalently in the low-normal range (Table 1). The 24-hour urinary calcium values were lower than those found in the control subjects, without significant difference in serum calcium levels (Table 2). In acromegalic patients, baseline serum PTH values were not significantly different from those measured in the healthy subjects (39.2 ± 6.4 vs 37.9 ± 4.8 pg/mL; $P = .9$). Table 3 shows the deconvoluted parameters of spontaneous PTH secretory pattern in our acromegalic patients. As compared with the healthy subjects, the acromegalic patients showed no significant differences in tonic PTH secretion rate (7.9 ± 0.9 vs 8.8 ± 1.4 pg/mL per minute; $P = .6$), number of bursts (5.6 ± 0.2 vs 6.1 ± 0.4; $P = .4$), fractional pulsatile PTH secretion (23.4% ± 5.1% vs 18.3% ± 3.9%; $P = .4$), and ApEn ratio (0.84 ± 0.05 vs 0.85 ± 0.04; $P = .9$). By contrast, the half-duration of PTH pulse was longer in acromegalic patients vs healthy subjects (11.8 ± 0.95 vs 6.9 ± 1.6 minutes; $P = .05$) (Fig. 1A). Moreover, acromegalic patients also showed greater, with borderline statistical significance, PTH pulse mass than control subjects (44.7 ± 16.4 vs 26.5 ± 4.3 pg per pulse; $P = .06$) (Fig. 1B).

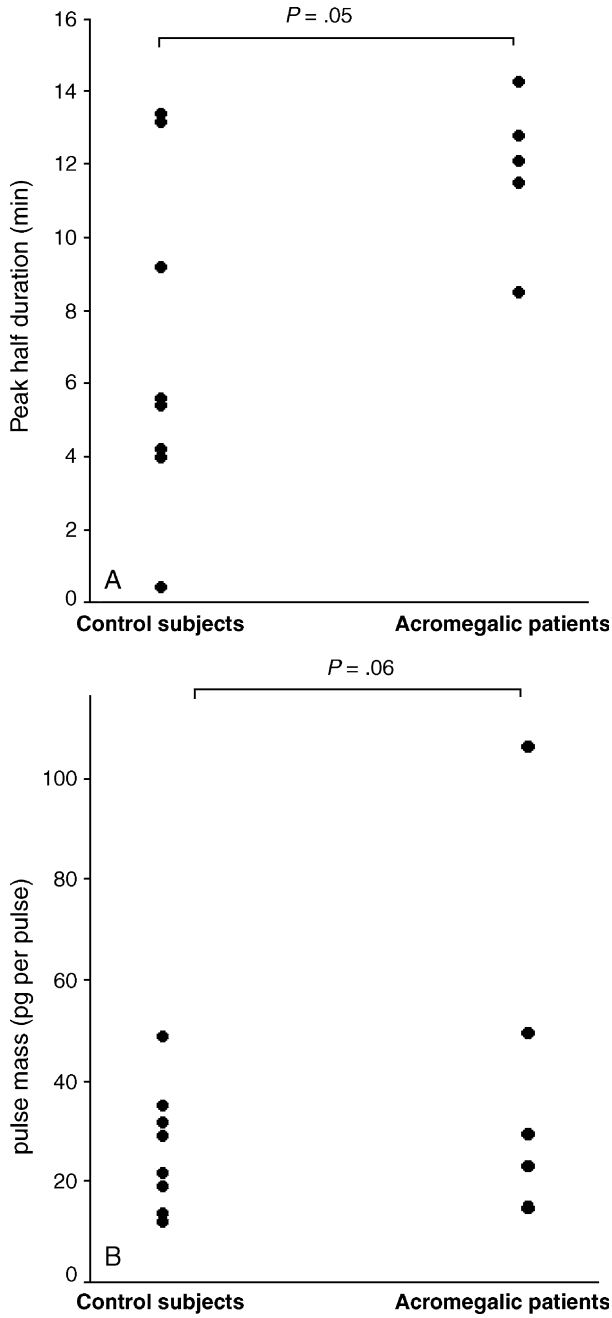

Fig. 1. (A) Half-duration (minutes) of PTH peaks and (B) mass (picograms per pulse) of PTH peaks in 5 acromegalic patients vs 8 healthy control subjects. The data comparison between the 2 groups was performed by *t* test for unpaired data.

4. Discussion

This study shows that non-osteoporotic male patients with active acromegaly have a preserved spontaneous PTH pulsatility in terms of global organization, but that the peak half-duration and amplitude may be greater than in normal subjects.

Parathyroid hormone is one of the main modulators of bone metabolism in healthy subjects as well as in individuals with osteoporosis. It has been hypothesized that the increase in serum PTH concentrations with aging is one of the major factors responsible for the age-related increase in bone resorption [26]. Indeed, the fluctuations in PTH plasma concentrations over short time intervals have been suggested to play an essential role in maintaining the physiological balance of bone resorption and bone formation [6]. Moreover, up- and down-regulations of PTH receptor pathway type I and type II in bone cells are a prerequisite for a coordinate regulation of osteoblast function [27]. There is also evidence that chronic glucocorticoid treatment is accompanied by a subtle but critical alteration of pulsatile PTH secretion with enhanced pulsatility and a relative decrease of tonic component of the secretory dynamics [8].

Over the recent years, it has been widely emphasized that GH has anabolic effects on bone [14]. Bone metabolism and density improve during GH treatment in patients with hypopituitarism [28]. Recent studies have also proposed GH and IGF-I as therapeutic tools in osteoporosis [29,30]. However, it is still controversial whether chronic GH excess, as it occurs in acromegaly, may lead to negative or positive effects on bone. Traditionally, acromegaly is considered as one of the causes of secondary osteoporosis [15,16], but the data on bone mineral density are conflicting [24,31-33]. Indeed, the effects of GH excess on bone are likely variable in relation to the site as well as to the gonadal status of the patients, with hypogonadal patients having shown to be at higher risk for osteoporosis [32,33] and bone fractures [34].

The mechanisms by which GH excess may cause osteoporosis in acromegaly are not completely known. In particular, it is not clear whether PTH may have a role in this process. Data of the literature would suggest that GH may modulate the end-organ (ie, bone and kidney) responsiveness to the effects of circulating PTH [35]. In fact, the correction of GH deficiency in adult patients decreases serum PTH concentrations as an effect of improvement in kidney and bone responsiveness to the hormone [35]. Conversely, the few data available in the literature seem to suggest that in acromegaly serum PTH values are not influenced by GH hypersecretion [21-24]. According to this notion, our patients with active acromegaly had baseline serum PTH levels comparable to those measured in the healthy subjects. However, interestingly, we found some differences in the pulsatile secretory pattern between normal and acromegalic patients. The patients with active acromegaly showed longer duration and tendency to greater amplitude of PTH pulses than the healthy age-matched subjects. The homogeneity of the group enrolled (ie, the patients were all young, male, with normal gonadal and thyroid function and without osteoporosis) allowed us to hypothesize that the difference in PTH secretory dynamics between acromegalic and non-acromegalic individuals may have been a primary rather than a secondary effect of GH hypersecretion. In fact, there is convincing evidence of the existence of a cross-talking between PTH and GH/IGF-1 axis. Parathyroid hormone stimulates the production and release of IGF-1 by bone cells in in vitro [36] and in vivo conditions [37]. Indeed, IGF-1 seems to be required for the anabolic actions of PTH on bone formation [38]. It has been suggested also that the excess of PTH, even if mild, may impair GH secretion [39]. Finally, there is evidence that parathyroid glands may respond to circulating IGF-1 by specific receptors [40].

However, we cannot rule out in our acromegalic patients indirect effects of GH hypersecretion by subtle changes in circulating calcium levels. On the other hand, although previous PTH pulsatility studies in other human models did not support this hypothesis [15], one could argue that the increase in GH secretion may have induced a modulation of end-organ responsiveness to PTH with consequent modifications of serum calcium and phosphate concentrations which in turn may have influenced the secretion of PTH [35]. Alternatively, the low-normal serum vitamin D observed in our patients may be hypothesized to exert a significant influence on the pattern of spontaneous PTH secretion. Future studies on a larger population will help to clarify whether the changes in PTH pulsatility observed by us may potentially produce detrimental effects on bone metabolism in acromegaly. In fact, as in other endocrine systems [1-3], available evidence suggests that the amplitude of the PTH pulses, as well as the frequency modulation of PTH signals, is likely to be implicated in the mode of hormonal responses of the organism [27]. The cross-talk between 2 bone anabolic hormones such as GH and PTH may represent a sort of positive feedback with the aim of protecting/preserving bone mass. However, in pathological conditions such as acromegaly the increase in PTH pulsatility caused by GH may be detrimental, leading to bone loss and, ultimately, to an increased risk of fractures [34].

In conclusion, our preliminary data suggest that GH excess may affect the PTH secretory dynamics in patients with acromegaly. These data would encourage to further investigation in this field, with particular attention to the potentially negative bone effects of the modifications of PTH secretory pattern in acromegaly.

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