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Response of Parathyroid Hormone to Exercise and Bone Mineral Density in Adolescent Female Athletes

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Abstract

Background: This study investigates 1) the effects of amount of exercise on levels of serum parathyroid hormone (PTH) and calcium, and 2) the relationship between PTH response and bone mineral density in adolescent female athletes.

Subjects: Twenty-one female athletes on a top-ranked high school basketball team in Japan participated in a one-month intensive basketball program. Subjects were divided into moderate-exercise and strenuous-exercise groups.

Methods: The amount of exercise was quantified using estimated metabolic equivalent (METs) and exercise hours. Levels of serum intact-PTH and calcium were examined five times: twice before training to establish a baseline (T_{-1} and T_0), once 3rd week of the training period (T_1), once immediately at the end of the program (T_2), and again one week later (T_3). Bone mineral density of forearm (distal-BMD) was measured one week after the end of the program. PTH levels at T_1, T_2 and T_3 were regressed on PTH at baseline (T_0) for both groups and examined for statistical significance. Multiple regression analyses of the changes of PTH and distal-BMD were conducted.

Results: 1) Strenuous-exercise subjects showed both increased and decreased PTH levels, while moderate-exercise subjects showed a uniform decrease in PTH throughout the exercise period. 2) Increased PTH was an independent negative predictor of distal-BMD, while high lean body mass, increased serum Ca, and exercise volume were positive predictors.

Conclusion: The amount of exercise affects PTH response: moderate exercise suppresses PTH secretion, while strenuous exercise is apt to induce continuous secretion, which has a negative effect on BMD.

Key words: Exercise, Bone mineral density, Calcium, Female, Parathyroid hormone

Introduction

Most of the studies on young females have indicated that exercise increases bone mineral density (BMD) [1-4]. In contrast, some studies have shown no significant change in BMD [5,6]. The varying results in these studies suggest that the effects of exercise on BMD may be influenced by quality or quantity of exercise.

Calcium-regulating hormone plays an important role in bone metabolism [7]. The examination of calcium-regulating hormone levels during physical exercise will contribute to the evaluation of the effect of physical exercise on bone metabolism. It is known that parathyroid hormone (PTH) stimulates both bone resorption and bone formation [8], and serum calcium level and the autonomic nervous system regulate the synthesis and secretion of PTH [9]. Parathyroid hormone, mostly intact-parathyroid hormone (intact PTH) is secreted episodically from the parathyroid gland, and has several spikes a day [10]. The biological half-time of intact PTH (1-84 PTH) is 4 to 6 minutes. In addition, PTH (1-34 fragment) has biological activity, whereas midportion PTH (M-PTH) and carboxyl terminal PTH (C-PTH) are devoid of biological activity [11]. The measurement of serum intact PTH is the most valid indicator of secretory function [12]. Yamamoto et al. have suggested that through the anabolic effects of PTH on bone a balance of bone resorption and formation could be maintained with exercise [13]. Initial bone resorption followed by bone formation may be triggered by exercise in response to catecholamine-induced stimulus [14-16]. In this study, all blood samples were taken at 7 a.m. prior to physical training in order to avoid any variation due to time of day and to minimize the influence of the sympathetic nervous system.

The purpose of this study is to evaluate: (A) the effects of physical exercise on levels of serum intact-PTH and serum calcium and (B) their influence on bone mineral density in adolescent female basketball players during a one-month training program.

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Subjects

Twenty-three female athletes (age16 to 17) on a top-ranked high school basketball team in Japan, consented to participate in this study. Among them, one with amenorreheia and one who had growth hormone disorder were excluded from this study. Consequently, 21 subjects were included in the final analyses. Eleven of them were participating in the All-Japan High-School Basketball Championship Tournament during the study and the other 10 were non-participants. All 21 subjects had one month of intensive training. They were requested not to have exercise for 10 days proceeding one month of the training to elude the influence of their usual exercise which had continued until then. The training for participants was more intensive than for the non-participants. Having finished the training including the tournament, they spent a non-exercise period of one week. During the study, they were all served the same meals.

Procedures

Physical exercise assessment

We operationally defined exercise-volume as the product of estimated metabolic equivalent (METs) and hours of exercise. One MET is defined as the oxygen consumption while at rest. It is reported that the exercise intensity while playing basketball games ranges from 7 to 12 METs with a mean of 8.3 METs [17]. We assumed that there was no significant difference in exercise volume for players in different positions because in recent years all players have played both offense and defense. Consequently, exercise volume for each game was calculated by multiplying 8.3 METs by the number of hours of participation. It is also reported that the exercise intensity is from 3 to 9 METs during normal basketball practices (normal*1 and pre-game*2) with a mean of 6 METs and 3 to 8 METs during conditioning exercises*3 with a mean of 5.5 METs [17]. Exercise volume for each practice and training session was calculated by multiplying the number of hours by 6 METs and 5.5 METs respectively. For each subject, regardless of body weight, total MET-hours for each day (daily exercise-volume) was calculated as above, and was summed up for all 31 days of the program (total exercise-volume).

Anthropometry

Body height (BH), body weight (BW), and body fat percentage (% Fat) were measured prior to training in order to control for the effects of body composition on BMD [18-23]. % Fat was estimated using tetrapolar bioelectrical impedance analysis. The subjects stood barefooted on the scale of a tetrapolar impedance analyzer (TBF-202, Tanita, Co. Tokyo; Constant current: 50kHz, 0.8 mA). Current-injector electrodes were placed just below the balls of the feet, and detector electrodes were placed just below the heels. Then bioelectrical impedance was measured. It is reported that the correlation between % Fat as measured by TBF-202 and hydrodensitometry methods is as $r=0.841$ ($p<0.001$) for women, and coefficients of variation for estimated % Fat is CV%=0.38% [24]. Formula 1 was used to calculate the estimated body density (Db) from BH, BW and bioimpedance (Z) [24]. % Fat, fat mass (FM) and lean body mass (LBM) were derived from Db using Formulas 2-4 shown below [25].

$$Db = 1.0907 - 0.112 \times BW(kg)/[BH(cm)]^2 \times Z(ohms) + 0.000134 \times Z(ohms) \cdots (1)$$

$$\%Fat = (4.570/Db - 4.142) \times 100 \cdots (2)$$

$$FM = BW \times \%Fat/100 \cdots (3)$$

$$LBM = BW - FM \cdots (4)$$

The impedance analyzer (TBF-202) includes scales for measuring BW and BH, which were also automatically measured at the same time.

Bone mineral density of the distal end of the radius and ulna (distal-BMD) of the right forearm was measured one week after the end of the training program, using the Dual-energy X-ray Absorptiometry (DXA) method with DTX-200 (Toyo Medic, Co.). The distal end was operationally defined as being 24mm towards the elbow from the point at which the radius and ulna are separated by 8mm. Dual energy X-ray absorptiometry has been shown to be both valid and reliable [26, 27]. CV% for distal-BMD is below 1%. The correlation between distal-BMD as measured by DTX-200 and Lumbar 2-4 BMD as measured by QDR-2000, HOLOGIC is $r=0.697$ ($p<0.01$), and for Lumbar 2-4 BMD as measured by XR-26, NORLAMD is $r=0.668$ ($p<0.01$) [27].

Blood sampling

Five venous blood samples were taken for each subject. The first sample (T_{-1}) was drawn one week before training; together with the second sample (T_0) which was drawn on the day just before training started, and the two samples provide a set of baseline values. The third sample (T_1) was drawn 3rd week of the training period; the fourth (T_2) on the morning after the final game (the 31st day of the training program); and the fifth (T_3) one week later. All blood samples were collected at 7:00 a.m., which was prior to breakfast and before undergoing any physical exercise. They were immediately carried to FALCO Biosystems Laboratory Co., which is certified by Japan Data Control Institute for analysis.

Blood analyses

Biochemical analyses were carried out for Hematocrit (Ht)– as a parameter for hemoconcentration, serum albumin (Alb), serum total calcium (Ca) and serum intact-PTH. Alb was measured by bromocresol binding technique, serum total Ca by o-cresolphtalein complexion method, and intact-PTH by a two-site immunnoradiometric assay method (Allegro intact PTH Immunoassay system, Nichols Institute Diagnostics) [11]. The serum total Ca value was corrected to control for variation in albumin levels using the Payne's formula (Formula 5) commonly used in the clinical field.

$$\text{corrected serum total Ca} = [\text{serum total Ca}] + 4\text{mg/dl} - [\text{Alb}] \cdots (5)$$

*1 Normal Practices consisted of free warming up and running, 120 sit ups, 30 push ups, 60 back extensions, 100 squats, 10 jumping jacks, a 20-minute post-man-defense exercise, 20 minutes of three-on-three, 20 minutes of two-on-two, and 20 minutes of one-on-one practice, 30-60 minutes of half-court five-on-five, a 20-minute full-court practice game, and 30-90 minutes of shooting practice or 300 practice shots.

*2 Pre-Game Practices consisted of free warming up and running; triangle passing; lay up shooting; screen play; four-on-four practice; pass, run and jump shooting; and 30 minutes of shooting practice.

*3 Conditioning Exercises consisted of 300 repetitions each of a tube expansion exercise, a tube pulling exercise, and a tube opening exercise; ball gripping; 1,000 sit ups and 1,000 push ups; and ventipress, aero-bike, and squatting.

Statistical analyses

Initially, in order to compare tournament participants and non-participants, two sample t-tests were computed for BH, BW, FM, LBM, distal-BMD and physical exercise volume. Participants' and non-participants' levels of PTH were compared at baseline using t-tests, separately at time points T_0 and T_{-1}.

To obtain separate time profiles of mean levels of Ht, PTH and Ca at T_{-1}, T_0, T_1, T_2 and T_3 for the participant and non-participant groups, repeated measures ANOVAs were employed. In addition, PTH levels at times T_1, T_2 and T_3 were regressed on PTH at baseline (T_0) for both the non-participant and participant groups and examined for statistical significance. The slopes of significant regressions were compared to examine if relationships remained the same at different time points, using a student's t-test. Then, the PTH responses of participants were compared to those of the non-participant group by examining the scatterplot of individual participants.

To identify factors related to changes in PTH (d-PTH1:T_0 to T_1; d-PTH2:T_0 to T_2; d-PTH3:T_0 to T_3) due to exercise, three multiple linear regression analyses with stepwise procedure (Fin=2, Fout=2) were conducted. All three analyses (d-PTH1, d-PTH2, and d-PTH3) used FM, LBM, distal-BMD, total exercise-volume, baseline Ca (Ca at T_0), baseline PTH (PTH at T_0), and the corresponding d-Ca variable (d-Ca1:T_0 to T_1; d-Ca2:T_0 to T_2 ; or d-Ca3:T_0 to T_3) as hypothesized independent variables. In addition, d-PTH1 was used in the analysis of d-PTH2 and then both d-PTH1 and d-PTH2 were used in the analysis of d-PTH3.

To identify factors related to distal-BMD, a multiple linear regression analysis with stepwise procedure (Fin=2, Fout=2) was conducted. FM, LBM, total exercise-volume, baseline Ca, d-Ca1, d-Ca2, baseline PTH, d-PTH1 and d-PTH2 were considered as hypothesized independent variables.

Results

1) Descriptive data on subjects in both groups are shown in Table 1. There were no significant differences in the mean values of BH, BW, FM, LBM, distal-BMD between the non-participant and the participant groups, while total exercise-volume was higher in the participant than in the non-participant group ($p < 0.01$).

2) As shown in Table 2, no significant differences in the PTH levels between the participant and the non-participant groups, either at T_0 or T_{-1}, were observed.

3) As shown in Table 2, it was also confirmed that there was no significant differences between the two baseline values at T_{-1} and T_0 for any variable in either the participant or non-participant groups. Neither was there any significant difference, over time, in Ht (a parameter of hemoconcentration). This held true for both participant and non-participant groups.

Table 1 Descriptive data.

	Non-participants n=10	Participants n=11	All n=21
	mean (SD)	mean (SD)	mean (SD)
Body height (cm)	168.0 (7.7)	171.4 (6.7)	169.8 (7.6)
Body weight (kg)	60.0 (6.4)	61.4 (5.9)	60.7 (6.4)
Fat mass (kg)	14.8 (2.7)	14.9 (2.9)	14.8 (2.9)
Lean body mass (kg)	45.2 (4.3)	46.5 (3.8)	45.9 (4.2)
Distal-BMD (g/cm^2)	0.48 (0.06)	0.49 (0.04)	0.49 (0.05)
Total exercise-volume (METs ×hours)	531 (96)	790** (25)	667 (147)

**p<0.01 compared with non-participants.
Distal-BMD: Bone mineral density of distal end of radius and ulna.

Table 2 Results of blood analyses as time in participant and non-participant groups.

	T_{-1}	T_0	T_1	T_2	T_3
Non-participants (n=10)	mean (SD)	mean (SD)	mean (SD)	mean (SD)	mean (SD)
Ht (%)	38.4 (2.2)	39.0 (1.7)	39.3 (1.2)	40.2 (2.5)	38.1 (3.1)
PTH (pg/dl)	38.3 (9.4)	39.8 (8.3)	26.4** (5.9)	29.6** (7.7)	29.8* (7.5)
Ca (mg/dl)	8.8 (0.1)	8.9 (0.1)	9.3** (0.2)	9.2** (0.2)	9.0* (0.2)
Participants (n=11)	mean (SD)	mean (SD)	mean (SD)	mean (SD)	mean (SD)
Ht (%)	40.4 (1.1)	41.0 (1.6)	40.5 (1.8)	40.6 (1.4)	40.4 (1.1)
PTH (pg/dl)	39.2 (7.6)	37.1 (8.6) n.s.	33.6 (8.1)	33.2 (9.9)	32.5* (8.3)
Ca (mg/dl)	8.9 (0.2)	8.8 (0.2) n.s.	8.9 (0.2)	9.1** (0.2)	8.8 (0.1)

**p<0.01; * p<0.05 compared with T_0 by repeated measures ANOVA.
n.s.: not significant compared with T_{-1} by repeated measures ANOVA.
T_{-1} : One week before training.
T_0 : The day just before training.
T_1 : Third week of the training period.
T_2 : The day after the final game.
T_3 : One week after the final game.
PTH: Serum intact-PTH.
Ca: Corrected serum total calcium.

Comparing mean values, using repeated measures ANOVAs, in the non-participant group, the mean PTH values during, immediately after, and one week after training were lower (26.4±5.9, $p<0.01$; 29.6±7.7, $p<0.01$; 29.8±7.5pg/dl, $p<0.05$, respectively) than the baseline value (at T_0) (39.8±8.3pg/dl), while conversely the mean Ca values were higher (9.3±0.2, $p<0.01$; 9.2±0.2, $p<0.01$; 9.0±0.2mg/dl, $p<0.05$, respectively) than their baseline value (8.9±0.1mg/dl). In the participant group, the mean PTH value did not change significantly during or immediately after training (33.6 ±8.1; 33.2±9.9pg/dl, respectively), but showed a slight decrease (32.5±8.3pg/dl $p<0.05$) from the baseline value (37.1±8.6pg/dl) one week after the program was over. Although the mean Ca value did not change significantly (8.9±0.2mg/dl) during training, it was significantly higher (9.1±0.2mg/dl, $p<0.01$) than the baseline value (8.8±0.2mg/dl) immediately after training, and then returned to the baseline value (8.8±0.1mg/dl) after one week (Table 2).

4) In the scatterplots in Figure 1, we notice that all non-participants' values at T_1, T_2 were below the diagonal line of slope=1, so that values of PTH were reduced from baseline. However, for participants, at two time points after baseline, PTH levels were distributed roughly equally, above and below the slope=1 line, and PTH levels at T_3 were mostly equally and below the slope=1 line. Two PTH regression lines for the participant group ($T_0 \times T_1$, $T_0 \times T_2$) and one for the non-participant group ($T_0 \times T_3$) showed no statistically significant slope, while two regression lines ($T_0 \times T_1$, $T_0 \times T_2$) for the non-participant group and one for the participant group ($T_0 \times T_3$) showed stutistical significance. However, the slope of these three regressions were not significantly different from one another.

5) Multiple linear regression analyses of the changes in PTH

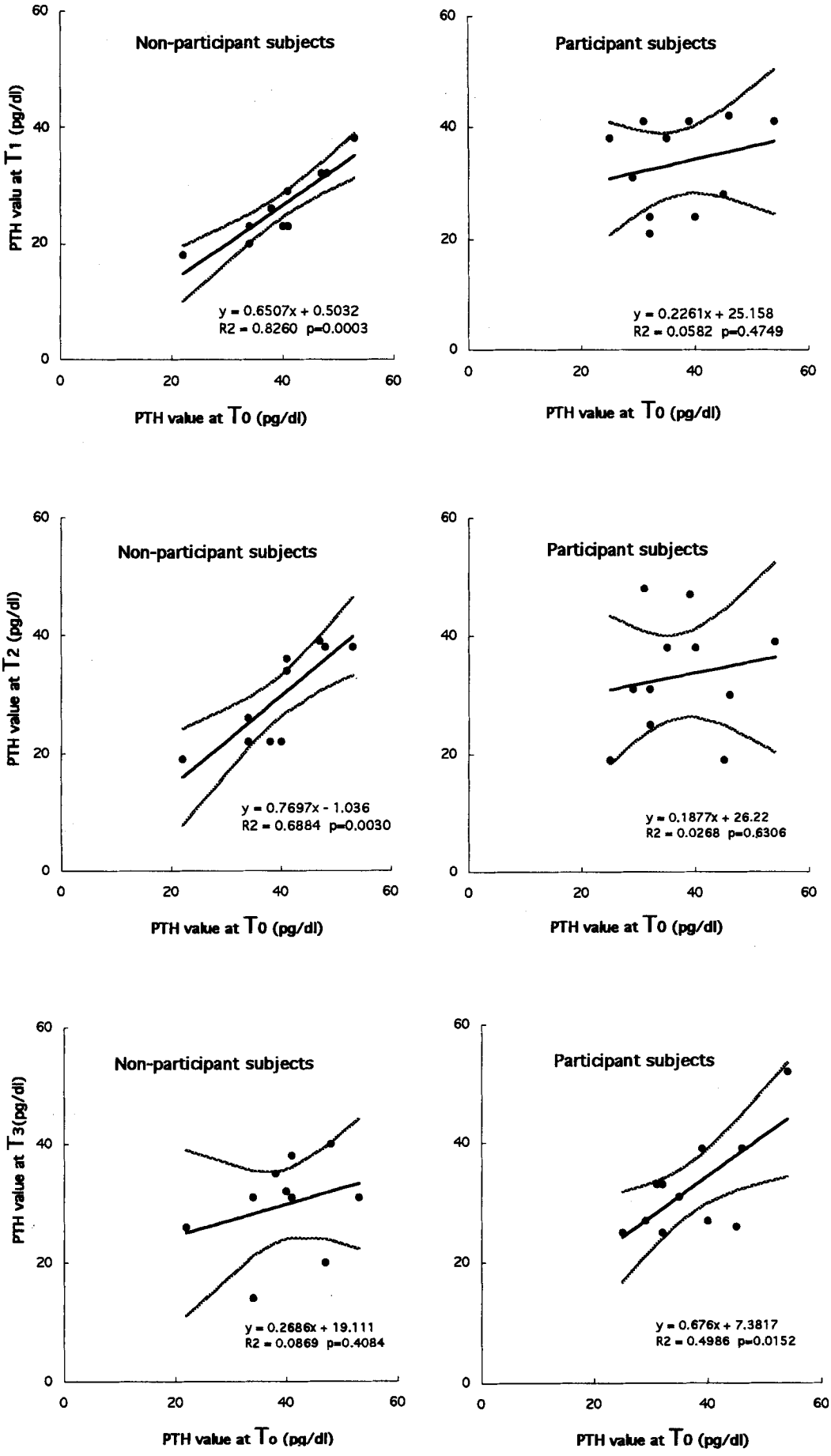

Fig. 1 PTH regression lines for the non-participant and the participant subjects.

showed the following significant associations: d-PTH1 was negatively related to baseline PTH (p=0.005) and positively related to exercise-volume (p=0.024) (Table 3). d-PTH2 was positively related to d-PTH1(p=0.0009) and negatively related to distal-BMD (p=0.0213) (Table 4). There were no factors with significant associations with d-PTH3.

6) Multiple linear regression analysis of distal-BMD showed four significant associations: distal-BMD was negatively related to d-PTH2 (p=0.0118), and positively related to LBM (p=0.0016), d-Ca1 (p=0.0074), and total exercise-volume (p=0.0298) (Table 5).

Table 3 Factors related to change in PTH (d-PTH1).

Variables		Regression coefficient	p value
PTH baseline	(pg/dl)	-0.5680	0.005
Total exercise-volume (METs ×hours)		0.0257	0.024
Constant		-3.5455	0.027

R: 0.7234, Adjusted R: 0.6858, F value: 9.8810.
p=0.0013 by multiple linear regression analysis.

d-PTH1(from T_0 to T_1): Change in serum intact-PTH from T_0 to T_1.

Table 4 Factors related to change in PTH (d-PTH2).

Variables		Regression coefficient	p value
d-PTH1 (from T_0 to T_1)	(pg/dl)	0.6315	0.0009
Lean body mass	(kg)	0.7721	0.0538
Distal-BMD	(g/cm^2)	-81.8588	0.0213
d-Ca2 (from T_0 to T_2)	(mg/dl)	15.9115	0.1250
Constant		-2.0635	0.9171

R: 0.8197, Adjusted R: 0.7680, F value: 8.1912.
p=0.0009 by multiple linear regression analysis.

d-PTH2 (from T_0 to T_2): Change in serum intact-PTH from T_0 to T_2.
d-PTH1 (from T_0 to T_1): Change in serum intact-PTH from T_0 to T_1.
Distal-BMD: Bone mineral density of distal end of radius and ulna.
d-Ca2 (from T_0 to T_2): Change in corrected serum total Ca from T_0 to T_2.

Table 5 Factors related to distal-BMD.

Variables		Regression coefficient	p value
Lean body mass	(kg)	0.0081	0.0016
d-Ca1(from T_0 to T_1)	(mg/dl)	0.1050	0.0074
d-PTH2 (from T_0 to T_2)	(pg/dl)	-0.0028	0.0118
Total exercise-volume (METs ×hours)		0.0002	0.0298
Constant		-0.0037	0.7759

R: 0.7654, Adjusted R: 0.6944, F value: 5.6572.
p=0.0049 by multiple linear regression analysis.

Distal-BMD: Bone mineral density of distal end of radius and ulna.
d-Ca1(from T_0 to T_1): Change in corrected serum total Ca from T_0 to T_1.
d-PTH2 (from T_0 to T_2): Change in serum intact-PTH from T_0 to T_2.

Discussion

Studies of PTH response to exercise have produced a number of different conclusions. Ljunghall et al. reported that despite the increase in Ca levels, there was no discernible suppression of PTH concentration during a one-hour exercise period[28]. It was documented by O'Neill that corrected plasma total Ca increased after exercise on a treadmill, but intact PTH did not change[29]. Salvesen et al. reported that during 50-minute running exercise, long distance runners, but not fire-fighters, displayed a significant increase in PTH. The rise in total serum Ca, however, was similar in both groups[30]. These studies have attempted to evaluate the effects of exercise by measuring shifts in PTH levels after single, short periods of exercise. In order to evaluate the effects of exercise on bone mass, however, it is essential to investigate the long term effects of regular exercise on PTH secretion and serum Ca level for a longer period of time.

Our study has found different PTH responses for moderate and for strenuous exercise subjects. For the moderate exercise group (non-participants), PTH regressions were always reduced after exercise (at times T_1 and T_2). However, the slopes of the regressions from baseline at times T_1 and T_2 were not significantly different. This suggests that PTH uniformly decreases in response to one month of moderate exercise. For strenuous-exercise subjects (participants), PTH responses are not necessarily unidirectional. PTH levels at time T_1 and T_2 for the 11 strenuous-exercise subjects were distributed roughly with no significant regressions. Five at T_1 and four at T_2 out of 11 subjects showed the increased PTH response during training, and others at T_1 and T_2 showed the decreased or unchanged response. However, PTH levels after one week rest (at T_3) returned back to the same level at T_1 or T_2 as for moderate-exercise subjects. Thus, strenuous exercise induced mixed PTH responses. Simultaneous elevation of serum Ca level, on the other hand, had no influence on PTH response. This elevation of calcium level may have been attributed to the metabolic acidosis and influx from extracellular sources[28, 31]. From our statistical analyses, it has become clear that changes of total Ca level within normal limits do not contribute to PTH response. Rather, PTH response to exercise may largely depend on the amount of exercise.

The result of our multiple linear regression analysis of d-PTH1, which shows the positive association between change in PTH and total exercise-volume, also suggests that large amount of exercise induces the increase of PTH levels. In addition, the result of our multiple linear regression analysis of distal-BMD confirms the independent effects of the four factors: exercise-related decrease in PTH (d-PTH2), increase in LBM, exercise-related increase in serum total Ca (d-Ca1) and larger total exercise-volume. In other words, exercise-related increase in PTH is a negative factor for BMD, while we can see the positive effect of LBM on BMD as suggested in our previous study[32]. Some investigators, however, suggested that the circulating levels of PTH is affected by estrogens in females[33, 34]. Additional study on the influence of phases in the menstrual cycle on PTH response would further our understanding of its physiological effects on the determinants evaluated in the present study. Moreover, our result with respect to distal-BMD and PTH response may then partially support a previous study which shows that long distance running aggravates low spinal bone density in females[5].

Conclusions

1) The amount of exercise affects PTH response. Moderate exercise contributes to the suppression of PTH, while strenuous exercise is apt to induce a continuous secretion of PTH.

2) Exercise-related increase in PTH is an independent negative predictor for BMD.

3) Changes of serum total Ca level do not influence PTH response to exercise.

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