

Bone Metabolism During Exercise and Recovery: The Influence of Plasma Volume and Physical Fitness

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Abstract. Understanding the reaction of bone to physical exercise is important for the development of strategies to increase and maintain bone mass. In this study the aim was to investigate the relationship among exercise intensity, physical capacity, and the biochemical responses, estimated by measuring biochemical markers of bone metabolism in serum. As a complement to the circulating concentrations we also accounted for the plasma volume shifts during and after exercise. The study included 10 men and 10 women, mean age 29 years, with a wide range of physical capacity, who performed a standardized running exercise test on a motor-driven treadmill with loads corresponding to 47 and 76% of VO_2 max (maximal oxygen uptake) followed by a maximal effort until exhaustion. Total work time was about 35 minutes. Venous blood samples were drawn at rest, after each load, and after 30 minutes and 24 hours of recovery. The reductions in plasma volume during exercise were 4.3% ($P < 0.05$) and 15.1% ($P < 0.001$) whereas after 24 hours in recovery there was an expansion of 7.5% ($P < 0.001$). There were marked, intensity-related, increases of PICP and tALP concentrations ($P < 0.001$) during exercise. Since these were of the order of plasma volume reduction they did not correspond to a change in the calculated circulating amount (content). However, as the concentrations returned to basal during recovery, the total circulating amounts were increased at this point ($P < 0.05$). Osteocalcin was also increased during recovery ($P < 0.01$), although concentrations were unchanged during the entire study. The amount ($P < 0.001$) and concentration ($P < 0.05$) of ICTP were also increased during follow-up. Serum PTH concentrations rose ($P < 0.05$) in proportion to the intensity of exercise and remained elevated during recovery. The subjects' VO_2 max demonstrated positive relationships to the biochemical responses to exercise in bone and BMD of the legs, and a negative relationship to basal PTH levels. Bone turnover and PTH secretion was stimulated by exercise, and low basal levels of PTH and high BMD were induced by a high level of physical fitness. These observations correlate well with the favorable effects of exercise and training on bone mass.

Key words: Parathyroid hormone — Collagen markers — Osteocalcin — Exercise.

Weight-bearing exercise affects bone metabolism, and bio-

chemical markers have been used to evaluate the mechanisms involved [1–7]. Formation markers such as osteocalcin and the carboxy-terminal propeptide of type I procollagen (PICP) and resorption markers such as the carboxy-terminal cross-linked telopeptide of type I collagen (ICTP) [8] reflect the different stages of bone remodeling and provide useful instruments for studies of the remodeling process, at least in metabolic bone disease [9, 10]. Further information is provided by analysis of serum parathyroid hormone (PTH), which has both anabolic and catabolic effects on bone and is known to increase during different kinds of exercise [11–13].

The interpretation of the changes of concentrations during and after exercise poses a particular problem since there are concomitant changes in plasma volume. Exercise is accompanied by hemoconcentration and plasma volume expansion occurs during the recovery period [14]. These shifts are mainly due to redistribution of blood flow and capillary exchange dynamics [14]. Conclusions based on changes of concentrations alone could therefore be misleading, since these deviations might only reflect plasma volume shifts and not, as might be inferred, a true metabolic response.

Against this background we studied the relationship between exercise and bone metabolism, with special regard to the intensity of exercise, level of physical fitness, and plasma volume changes.

Materials and Methods

Subjects

A total of 20 healthy individuals (10 women and 10 men) were selected to represent a range in age and physical fitness. The mean age was 28 years (range 22–39 years) in women and 30 years (range 21–46 years) in men. Mean height for women was 171 cm (range 155–180 cm) and 183 cm for men (range 175–195 cm), mean weights were 64 kg (range 51–77 kg) and 79 kg (range 66–95 kg), respectively. Maximal oxygen uptake (VO_2 max) was on average $46.8 \text{ ml} \times \text{kg}^{-1} \times \text{min}^{-1}$ (range 37.8–58.8) in women and $56.2 \text{ ml} \times \text{kg}^{-1} \times \text{min}^{-1}$ (range 48.2–67.1) in men.

Experimental Protocol

The experimental design is presented in Figure 1. The experiment was carried out in the morning on a motor-driven treadmill and started with a 10-minute warm-up period at a work load corresponding to 30% of VO_2 max. This was immediately followed by work periods at successively increased inclination and speed, 10 minutes each at submaximal loads corresponding to 47 and 76% of VO_2 max. A final maximal effort until exhaustion, lasting for 4–5 minutes, gave a total work time of about 35 minutes. Venous blood samples were drawn at rest, immediately after each submaximal

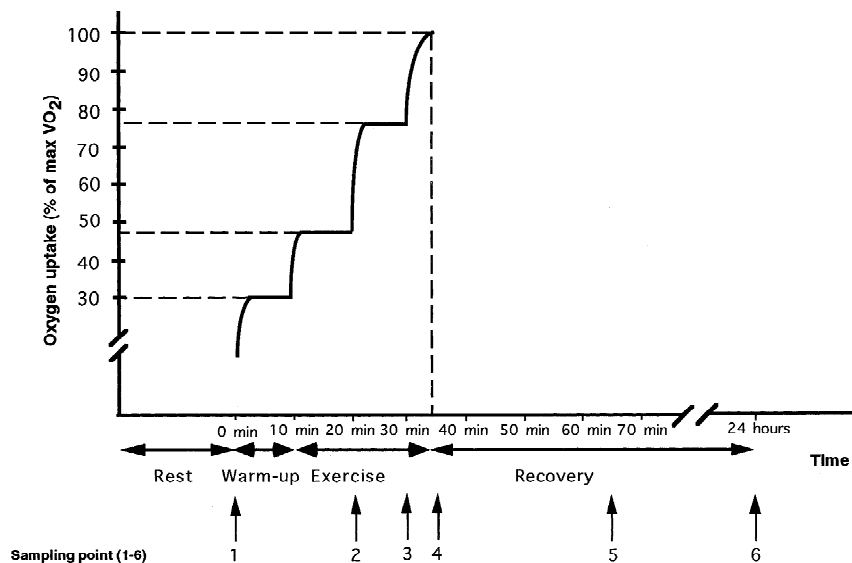


Fig. 1. Experimental design of the standardized exercise test performed on a motor-driven treadmill. Arrows indicate venous blood sampling.

load, after the maximal exercise, as well as after 30 minutes and 24 hours during the recovery period.

Methods

Blood samples at rest and after 24 hours of recovery were collected in the morning after a breakfast with a low calcium content (i.e., dairy products were excluded). Serum was obtained through centrifugation at +4°C and then stored at 70°C until analyzed for biochemical markers of bone metabolism (osteocalcin, PICP, and ICTP), total serum calcium, intact serum PTH, total alkaline phosphatase (tALP), and albumin concentrations. Samples from the same individual were always analyzed in the same assay and only two assays were needed to analyze all 120 serum samples. Interassay variation should thus be of minor importance.

Total serum calcium concentrations (intra- and interassay variation 1.29 and 1.96%, respectively) and tALP activity (intra- and interassay variation 2.11 and 1.94%, respectively) were determined spectrophotometrically as part of the clinical routine at the Department of Clinical Chemistry, Central Hospital, Falun. The calcium values were adjusted for the concomitant serum albumin values. Serum osteocalcin (intra- and interassay variation 2.7 and 5.5%, respectively) was measured by radioimmunoassay (CIS Bio International, Gif-Sur-Yvette Cedex, France) and intact PTH (intra- and interassay variation 2.9 and 3.5%, respectively) by a sandwich radioimmunoassay method (Nichols Institute, San Juan Capistrano, CA, USA) at the Department of Clinical Chemistry, University Hospital, Uppsala. Serum concentrations of PICP (intra- and interassay variation 1.8 and 6.7%, respectively) and ICTP (intra- and interassay variation 4.8 and 5.4%, respectively) were measured by radioimmunoassay using commercially available kits (Orion Diagnostika, Espoo, Finland). Lactate concentrations were immediately analyzed with a 2300 GL electrode/enzymatic-based method from Yellow Springs International, Ohio, USA on hemolyzed blood. Hematocrit was used to account for the changes in plasma volume and was analyzed by microcentrifugation at the Department of Clinical Chemistry, Central Hospital, Falun. To estimate the changes in plasma volume and to correct concentrations of substances for these changes we used the formula of van Beaumont et al. [15] which is valid for exercise lasting less than 2 hours since red blood cell volume is then constant [14]. The formula is based on the hematocrit values before (Hct_1) and after (Hct_2) exercise as well as the initial concentration (C_1) to calculate the change in plasma volume (ΔPV) and the expected concentration (C_E) if the change in plasma volume involves a shift of water alone:

$$\Delta PV(\%) = \frac{100}{100 - Hct_1} \times \frac{100(Hct_1 - Hct_2)}{Hct_2}$$

$$C_E = \frac{Hct_2(100 - Hct_1)}{Hct_1(100 - Hct_2)} \times C_1$$

The relative change in plasma content (ΔCo), i.e., total amount of the substance was calculated from the relation between the measured (C_M) and the expected concentration:

$$\Delta Co(\%) = \frac{C_M - C_E}{C_E} \times 100$$

Bone mineral density (BMD, g/cm^2) was measured with a Lunar DPX-L apparatus [16]. The precision error in our laboratory, expressed as the coefficient of variation, was tested three times a week on phantoms provided by the manufacturers and was below 1% over a period of 1 year.

Oxygen uptake was determined with an on-line registration (Medical Graphics, Spiropharma AS, Klampenborg, Denmark). Maximal oxygen uptake was defined as the level at which an increase in workload did not result in an increase in oxygen uptake.

Statistical Methods

The StatView SE+Graphics software package (Abacus Concepts, Berkeley, CA, USA) was used for all statistical analyses including calculation of mean values and the standard deviation (SD) as well as analysis of variance (ANOVA) for the description of the percentage change of substances at different times during exercise. Linear regression models were used to take age and sex into consideration in correlations between substances measured in blood. Age, sex, height, and weight were used to adjust relations between BMD or VO_2 max and other variables. A P value less than 0.05 was considered significant.

Results

The hematocrit increased from $43.0 \pm 2.8\%$ at rest to $47.3 \pm 4.9\%$ ($P < 0.001$) immediately after the maximal exercise, and decreased to below resting values ($41.3 \pm 3.3\%$; $P < 0.01$) 24 hours after exercise (Fig. 2). The calculated plasma volume thus decreased by $4.3 \pm 6.8\%$ ($P < 0.05$) after the last submaximal load and by $15.1 \pm 11.6\%$ ($P < 0.001$) at

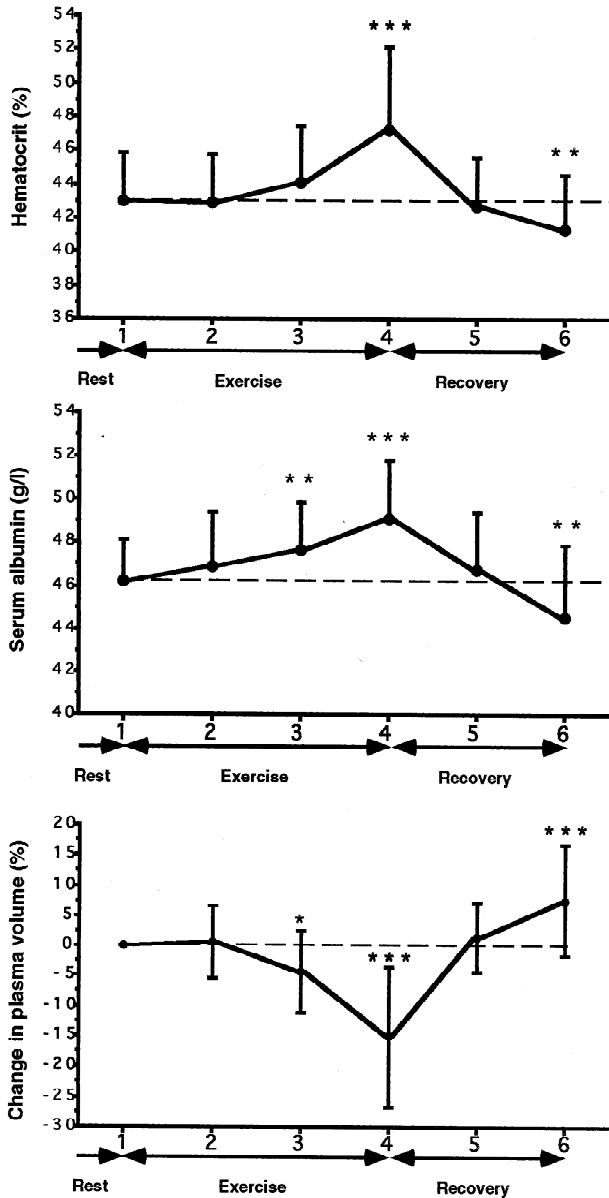


Fig. 2. Changes in hematocrit (%), serum albumin (g/liter) and plasma volume (%) during and after exercise.

the termination of the maximal exercise. There was a $7.5 \pm 9.2\%$ volume expansion ($P < 0.001$) after 24 hours of recovery (Fig. 2). Blood lactate concentrations increased from 2.1 ± 0.8 mmol/liter after warm-up, to 2.2 ± 1.1 mmol/liter and 4.0 ± 2.3 mmol/liter on the submaximal loads, and to a maximal value of 10.6 ± 2.7 mmol/liter.

The changes of serum concentrations of the biomarkers, together with adjustments for the shifts in plasma volume, are given in Figure 3. No changes in the serum osteocalcin concentrations were evident during the entire study period despite the changes in plasma volume. A $13.6 \pm 15.4\%$ decrease ($P < 0.001$) in the circulating amount (content) of osteocalcin immediately after the maximal exercise as well as a $8.3 \pm 15.5\%$ increase ($P < 0.01$) after 24 hours of recovery was thus calculated. In contrast, there was a marked increase ($P < 0.001$) in the serum PICP concentration in proportion to the increasing intensity of exercise (7.4

$\pm 7.4\%$ and $15.5 \pm 11.0\%$), closely following the changes of plasma volume, and the total circulating amount of PICP was consequently unchanged during exercise. The concentrations returned to basal levels soon during recovery when, as the volume expanded, the amount increased ($6.6 \pm 17.0\%$; $P < 0.05$). The serum concentrations of tALP increased during exercise ($3.6 \pm 5.0\%$; $P < 0.01$ and $9.0 \pm 6.2\%$; $P < 0.001$, respectively) and an increased circulating amount was demonstrated during recovery ($5.2 \pm 11.3\%$; $P < 0.05$), a pattern similar to that of PICP. The ICTP concentrations demonstrated an inconsistent pattern during exercise but were increased at the end of exercise ($11.0 \pm 15.5\%$; $P < 0.001$). The content of ICTP remained unchanged during exercise, but after 24 hours of recovery both concentrations ($5.7 \pm 11.1\%$; $P < 0.05$) and total amount ($13.6 \pm 15.2\%$; $P < 0.001$) were increased.

There was an increase of serum PTH concentrations immediately after exercise ($20.8 \pm 46.4\%$; $P < 0.05$), and during the recovery period both concentrations (maximal increase $36.8 \pm 47.0\%$; $P < 0.001$) and total amount (maximal increase $39.0 \pm 48.5\%$; $P < 0.001$) were increased (Fig. 4). Total serum calcium concentrations, adjusted for concomitant albumin levels, were slightly increased after termination of exercise ($3.0 \pm 3.1\%$; $P < 0.001$) (Fig. 4). Absolute values for concentrations of PTH, calcium, and biomarkers are presented in Table 1.

The individual level of physical fitness (VO_2 max in $ml \times kg^{-1} \times min^{-1}$) was inversely related to the basal concentration of PTH ($\beta = -0.73$, $P = 0.02$; Fig. 5) and remained significant after adjustment for age and sex ($\beta = -0.9$, $P = 0.04$). Though VO_2 max displayed no relationship to basal levels of bone biomarkers, positive relations were found between VO_2 max and the changes in osteocalcin (Fig. 5) which remained after adjustment for age and sex. Maximal lactate concentrations were not related to either basal levels or changes in biomarkers, PTH, or total serum calcium during or after exercise.

VO_2 max was also positively related to BMD of the legs ($\beta = 0.01$, $P = 0.008$), also after adjustment for age, sex, height, and weight ($\beta = 0.009$, $P = 0.03$) (Fig. 6), and BMD at different sites was inversely related to the basal concentrations of osteocalcin, tALP, ICTP, and total serum calcium, but not to PICP or PTH (Table 2).

Discussion

Understanding the reaction of bone to physical exercise is important for the development of strategies to achieve high peak bone mass and prevent bone loss. In this study the aim was to investigate the relationship among exercise intensity, physical fitness, and the biochemical responses of bone biomarkers. Furthermore, calculations were made of the shifts in plasma volume in order to correct for spurious changes caused by volume shifts alone.

Several previous investigations have described changes in the serum concentrations of bone biomarkers during exercise [1–7], and generally inferred that those reflected bone metabolism. Only by calculating the total circulating amount (content) is it possible to evaluate the net results, i.e., whether there is an influx to or efflux from the vascular pool. These movements depend on several factors, e.g., production/secretion, metabolism, clearance, degradation, distribution, diffusion, and excretion. Estimation of the relative contribution of these different components was not the subject of the present study. In general, it has been suggested

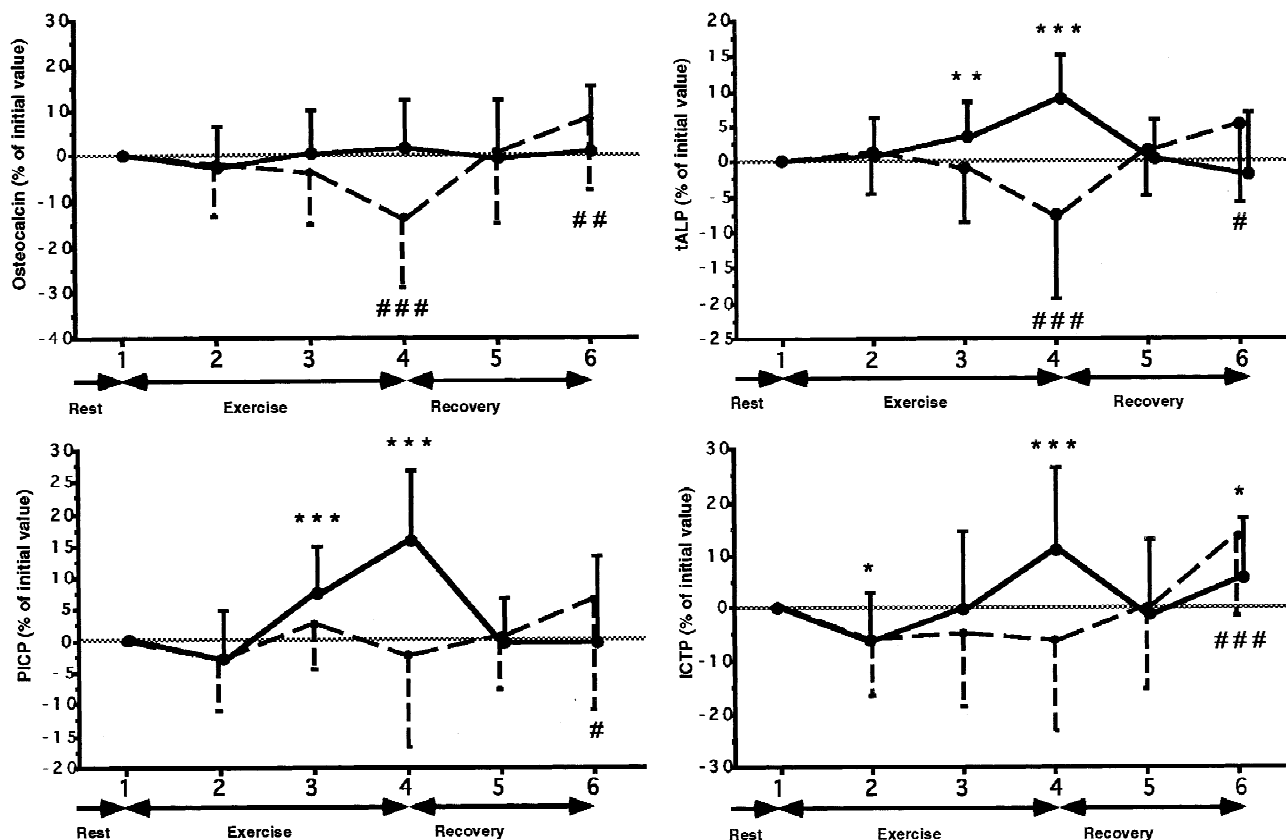


Fig. 3. Percentage changes in concentrations (plain line) and total amount (dashed line) of biochemical markers of bone metabolism. *[#]*P* < 0.05, **^{##}*P* < 0.01, ***^{###}*P* < 0.001. Vertical bars denote SD.

Table 1. Concentrations of parathyroid hormone (PTH), total serum calcium, and biochemical markers of bone metabolism before, during, and after exercise

	Rest	10 minutes at 47% of VO ₂ max	10 minutes at 76% of VO ₂ max	5 minutes at VO ₂ max	30 minutes of recovery	24 hours of recovery
PTH (ng/liter)	31.9 ± 10.9	30.0 ± 12.7	35.9 ± 13.3	37.0 ± 14.2	42.1 ± 14.6	38.1 ± 18.2
Serum calcium (mmol/liter)	2.38 ± 0.05	2.40 ± 0.05	2.41 ± 0.08	2.45 ± 0.06	2.39 ± 0.06	2.36 ± 0.06
Osteocalcin (μg/liter)	12.5 ± 3.4	12.1 ± 3.1	12.5 ± 3.1	12.6 ± 3.2	12.3 ± 3.3	12.5 ± 3.4
PICP (μg/liter)	162 ± 55	154 ± 41	172 ± 54	184 ± 51	159 ± 48	158 ± 46
tALP (μkat/liter)	2.8 ± 0.7	2.8 ± 0.7	2.9 ± 0.7	3.0 ± 0.7	2.8 ± 0.7	2.7 ± 0.7
ICTP (μ/liter)	4.4 ± 1.5	4.1 ± 1.3	4.3 ± 1.4	4.8 ± 1.4	4.3 ± 1.4	4.6 ± 1.5

Mean values are given with their standard deviation (SD)

that the concentration rather than the content of hormones is most important since target tissues are exposed to higher biological concentrations [17]. Also, decreased amounts of freely diffusible substances in plasma may yield higher concentrations at the target tissue level.

The changes in the marker of type I collagen synthesis, PICP, are instructive for this discussion. The concentrations were increased during exercise but since these changes closely followed the reduction in plasma volume they are likely to mainly reflect retention of the molecules (with a size of about 100 kDa) in the circulation during exercise, when plasma water moves into the extravascular space [18]. The increased content of PICP after 24 hours of follow-up (unaltered concentration in an increased circulating volume), on the other hand, is not likely to be caused by a

passive influx but rather an increased synthesis of type I collagen, presumably stimulated by exercise. Osteocalcin is a highly specific marker of osteoblastic activity [19]. The unchanged concentrations of this small molecule (about 5.8 kDa) during exercise suggest free movements across the vascular bed. The decreased plasma content during exercise could thus result from diffusion to the extravascular space. The increased amount during recovery indicates either a stimulation of the osteoblasts or a "rediffusion" of osteocalcin during plasma volume expansion. The increased amount of total ALP after 24 hours of recovery could also indicate enhanced bone turnover since the bone-specific ALP is the major contributor to the total circulating enzymatic activity [19], at least during resting conditions. The concentrations of ICTP, a 10 kDa marker of type I collagen

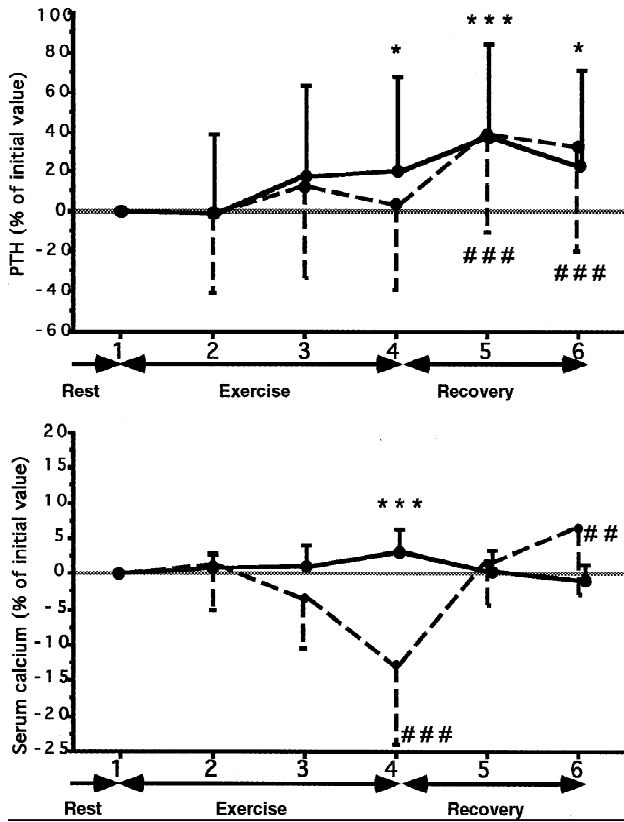


Fig. 4. Percentage changes in concentrations (plain line) and total amount (dashed line) of PTH and total serum calcium. $^*/\#$ Statistical significance for change in concentration and total amount, respectively. $^*/\#P < 0.05$, $^{**}/\#\#P < 0.05$, $^{***}/\#\#\#P < 0.01$, $^{****}/\#\#\#\#P < 0.001$. Vertical bars denote SD.

degradation, increased at the end of exercise, probably as a result of volume contraction. The finding that both the concentration and total amount increased after 24 hours of recovery again favors increased bone turnover as the most probable explanation.

Within this fairly small group of healthy subjects there was a relationship between VO_2 max and bone mass. A similar relationship has been reported in a larger population of women over 65 years of age [20]. These findings clearly support the view that regular exercise improves skeletal health. The positive relationships between VO_2 max and the changes in bone biomarkers during and after exercise imply that a proportion of the biochemical response to exercise is dependent on the fitness level and thus, that a better effect of physical activity on bone metabolism is achieved with training. The negative relationships between both formation and degradation markers and BMD at different sites indicate that a low turnover, estimated by biochemical markers, may be favorable for the skeleton.

As found in earlier investigations [11–13] there was also an increase of serum PTH concentrations during exercise in the present study, despite a rise in total serum calcium concentrations. PTH is probably rapidly equilibrated between plasma and extravascular fluid [21], but the persistent elevations of both the concentration and total amount of serum PTH during 24 hours of follow-up are in line with an anabolic role of PTH [11] in the metabolic response to exercise. Chronic hypersecretion of PTH (hyperparathy-

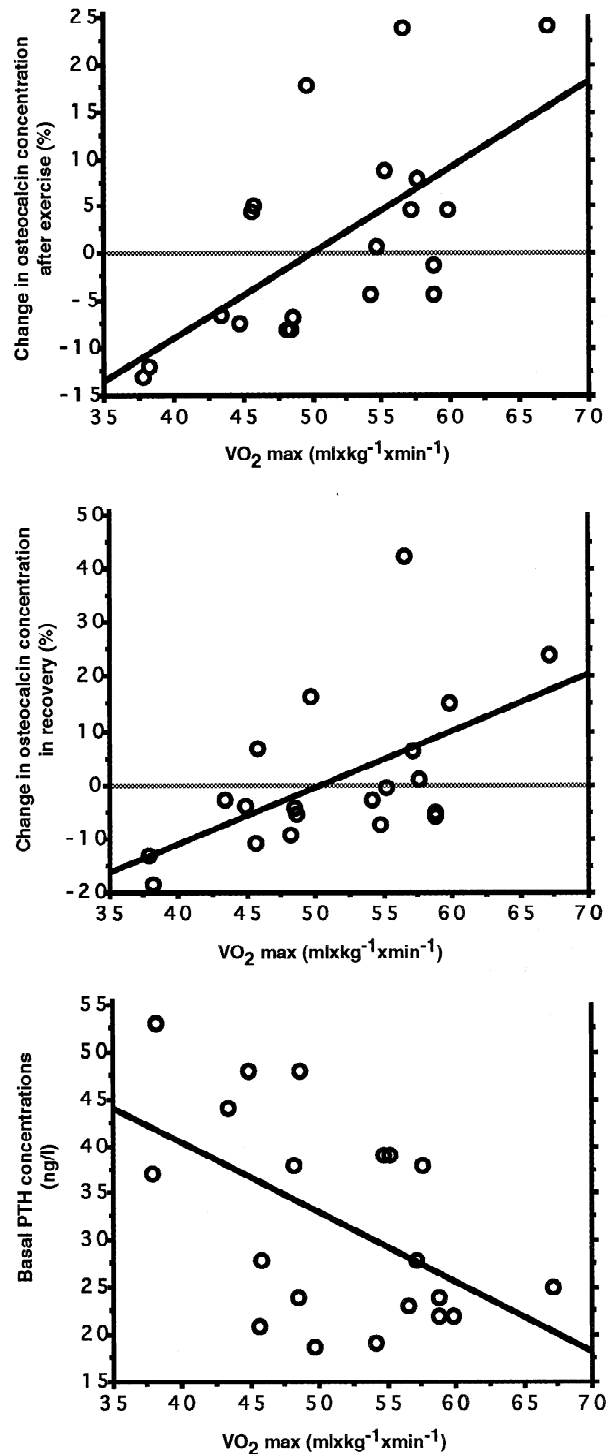


Fig. 5. Relationships between the maximal oxygen uptake (VO_2 max) and the changes of osteocalcin concentrations immediately after exercise ($\beta = 0.91$, $P = 0.003$) and after 24 hours of recovery ($\beta = 1.1$, $P = 0.009$) as well as basal PTH concentrations (ng/liter) ($\beta = -0.73$, $P = 0.02$).

roidism) causes negative bone balance [22] whereas intermittent injections have anabolic properties [23]. The inverse relationship between basal serum PTH concentrations and VO_2 max indicates that, besides the induced elevations of

Table 2. β coefficients obtained in linear regression models of BMD (g/cm^2) and BMC (g) and basal levels of biochemical markers of bone metabolism (independent variable)

	Osteocalcin ($\mu\text{g}/\text{l}$) ^a		PICP ($\mu\text{g}/\text{l}$) ^a		tALP ($\mu\text{kat}/\text{l}$) ^a		ICTP ($\mu\text{g}/\text{l}$) ^a		PTH (ng/l) ^a		Total serum calcium (mmol/l) ^a	
	β	<i>P</i> value	β	<i>P</i> value	β	<i>P</i> value	β	<i>P</i> value	β	<i>P</i> value	β	<i>P</i> value
Total body BMD	-0.02	0.006	-0.0004	0.30	-0.06	0.01	-0.04	0.04	-0.001	0.72	-0.6	0.16
BMC	-63	0.0008	-1.5	0.23	-225	0.003	-107	0.07	1.6	0.80	-2329	0.06
Regional BMD												
Arms	-0.01	0.06	-0.001	0.09	-0.08	0.003	-0.04	0.06	0.001	0.49	-0.9	0.03
Legs	-0.02	0.02	-0.001	0.18	-0.07	0.04	-0.05	0.02	-0.002	0.35	-0.8	0.14
Trunk	-0.01	0.03	-0.00009	0.80	-0.04	0.08	-0.02	0.17	0.0003	0.87	-0.5	0.23
Ribs	-0.01	0.03	-0.0002	0.60	-0.04	0.02	-0.02	0.12	0.001	0.41	-0.5	0.10
Pelvis	-0.02	0.02	0.00004	0.94	-0.04	0.19	-0.03	0.17	0.00001	1.0	-0.6	0.29
Spine	-0.02	0.02	-0.0002	0.74	-0.08	0.06	-0.07	0.02	0.003	0.30	-1.1	0.11
Lumbar spine BMD (L2-L4)	-0.02	0.07	-0.001	0.44	-0.11	0.02	-0.06	0.11	0.003	0.45	-0.7	0.34
Femur BMD												
Neck	-0.03	0.007	-0.001	0.24	-0.11	0.002	-0.07	0.01	0.001	0.86	-1.3	0.02
Ward's triangle	-0.03	0.001	-0.001	0.20	-0.12	0.001	-0.07	0.009	0.001	0.75	-1.1	0.08
Trochanter	-0.03	0.008	-0.001	0.25	-0.11	0.009	-0.07	0.03	-0.001	0.67	-1.5	0.02

^a Adjusted for sex, age, height, and weight

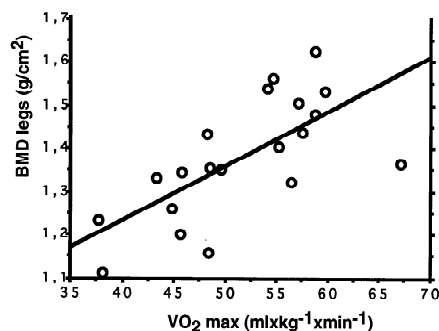


Fig. 6. Relationship between the maximal oxygen uptake (VO_2 max) and BMD of the legs ($\beta = 0.009$, $P = 0.03$).

PTH concentrations during acute exercise, physical fitness is also important for the resting level of PTH. Possibly the most favorable effects on the skeleton are achieved with low resting levels and large increases during acute exercise.

In summary, the stimulation of bone turnover and PTH secretion by exercise, as well as the low basal levels of PTH and higher BMD found in more physically fit individuals, indicate favorable effects of physical exercise and training on the skeleton in healthy subjects.

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