Bone-Specific Alkaline Phosphatase and Exercise

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Abstract

It is a matter of discussion how physical exercise affects bone remodeling process and markers such as bone-specific alkaline phosphatase (BAP) which is the only marker that is not influenced by diurnal variation of bone remodeling. Dietary calcium intake and parathormone levels are strongly associated with the

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remodeling status during or after the physical training, and increase of BAP levels may not be always the indicator of bone formation process. Moreover, behavior of BAP may be different in physically active or sedentary people at different ages and sexes. Because skeletal muscle has the ability to adapt to a variety of changes in physical status, physical exercise has the ability to change turnover status in favor of formation by increasing BAP/pyridinoline ratio.

Keywords

Biomarker • Bone formation • Bone-specific alkaline phosphatase • Bone remodeling • Bone turnover • Exercise

List of Abbreviations

BAP	Bone-specific alkaline phosphatase
BMD	Bone mineral density
BMU	Basic multicellular unit
CTX	C-terminal telopeptide
DEXA	Dual-energy X-ray absorptiometry
D-PYR	Free deoxypyridinoline
HYP	Hydroxyproline
LRP5	Low-density lipoprotein receptor-related protein 5
NTX	N-terminal telopeptide
OC	Osteocalcin
PICP	C-terminal propeptide of type 1 collagen
PINP	N-terminal propeptide of type 1 procollagen
PYD	Free pyridinoline
RANKL	Receptor activator of nuclear factor kappa-B ligand
TRAP	Tartrate-resistant acid phosphatase

Key Facts of Exercise

- If a strain is detected as greater than the optimum strain, then bone formation will occur.
- Optimal physical exercise is an osteogenic stimulator, and long-term loading of the bone by means of exercise makes an anabolic effect on the bone mass and strength.
- Personal metabolic needs are the determinants of the bone turnover status in the presence of an unsteady physical loading.
- Biomarkers identified as the reflectors of bone metabolic activity enable to estimate the rate and direction of the bone turnover status.

Definition of Words and Terms

Bone remodeling (bone turnover)	Bone turnover refers to the total volume of the bone that is both resorbed and formed over a period of time which can be estimated by

	measuring bone biomarkers. Bone remodeling, on the other hand, is defined as an active process throughout the skeleton, essential for calcium homeostasis and preserving the integrity of the skeleton, through the coupled activity of osteoclasts and osteoblasts. Bone turnover occurs mainly throughout bone remodeling.
Bone-specific alkaline phosphatase	Bone alkaline phosphatase (BAP) is the bone-specific isoform of alkaline phosphatase, a bone formation marker that is found on the surface of osteoblasts.
DEXA: Dual-energy X-ray absorptiometry	It is the most widely used and most thoroughly studied bone density measurement technique to diagnose and follow osteoporosis.
Osteoblast	Osteoblasts are specialized, differentiated mesenchymal stem cells which produce a calcium- and phosphate-based mineral, deposited regularly into the organic matrix forming a very strong and dense mineralized tissue called the mineralized matrix.
Skeletal bone	Skeletal bones are made of a mix of hard stuff that gives them strength and tons of living cells which help them grow and repair themselves, and they do various jobs, such as storing body minerals like calcium.

Introduction

The skeletal bone is constantly remodeled in order to repair microfractures caused by excessive stress and biomechanical forces. The process called "remodeling" or "turnover" consists of consecutive resorption followed by formation in order not to change the bone mass. The "rate of remodeling" is an important determinant of bone physiology; therefore, measurements that correlate with this process provide useful information about bone diseases, monitoring treatment and exercise-induced changes. Yearly quantification of bone mass is done by dual-energy X-ray absorptiometry (DEXA) measurements. However, acute-subacute changes in bone mass for shorter durations (months) are inadequate to detect by means of densitometry measurements. Metabolic markers of bone turnover reflect a systemic response and are easy to detect by serum and urine samples whenever needed.

Bone formation process results in the release of collagen by-products, proteins, or bone-specific isoform of total alkaline phosphatase measured in the serum. There are also assays to measure bone resorption products released from osteoclasts reflecting

Table 1 Bone turnover markers

Formation markers	Circadian rhythm	Assay
OC	+	Serum
BAP	–	Serum
PINP/PICP	+	Serum
Resorption markers		
NTX	+	Serum, Urine
CTX	+	Serum, Urine
D-PYR	+	Urine
PYR	+	Urine
HYP	+	Urine
TRAP	+	Serum

OC osteocalcin, *BAP* bone-specific alkaline phosphatase, *PINP* N-terminal propeptide of type 1 procollagen, *PICP* C-terminal propeptide of type 1 collagen, *D-PYR* free deoxypyridinoline, *PYD* free pyridinoline, *HYP* hydroxyproline, *TRAP* tartrate-resistant acid phosphatase. Collection of serum should be performed in the morning after an overnight fast. Collection of urine should be performed in the morning. OC lacks standardization, rapidly degrades in serum, and requires collection on ice. BAP may have cross-reactivity with liver isoform (15–20%) (Seibel 2005).

the bone turnover rate (Table 1). Resorption markers fall in 2–12 weeks, while formation markers act a little bit slower. With the exception of bone-specific alkaline phosphatase, diurnal variation and complexity of these markers however complicate their availability in clinical practice (Banfi et al. 2010).

Total serum alkaline phosphatase consists of several enzymatic isoforms originating from the liver, intestine, spleen, kidney, placenta, and bone. In adults with normal liver function, about 50% of the total alkaline phosphatase activity in serum is derived half and half from the liver and the bone. The serum concentrations of bone-specific alkaline phosphatase (BAP) reflect the activity of osteoblastic cellular membrane to form new collagen and bone mineralization process. It is functionally similar to hepatic and placental forms, with some antigenic discrepancy. It is the only marker that is not influenced by diurnal variation of bone remodeling because of its unique molecular texture. Because BAP is cleared by the liver, liver diseases may raise the levels, or liver alkaline phosphatase antibodies may cause cross-reactions with BAP to reduce the levels. There are several assays developed for BAP such as electrophoresis, isoelectric focusing, lectin precipitation, and immunoassay. Immunoassay is the method of choice because of its high specificity and precision (Watts 1999).

During linear growth in the adolescent status, bone-specific isoenzyme (BAP) raises up to 90% (Banfi et al. 2010). Though serum total alkaline phosphatase is the mostly used marker of bone metabolism, BAP is preferred rather frequently in clinical practice and considered as a useful predictor of bone osteoblastic activity in all phases of bone mineralization. It is not influenced by the diurnal variation, and treatment changes become stable at 3–6 months. Nevertheless, unstable changes may occur daily. Immediate changes may be due to changes in plasma volume and renal activity which must be separated from long-term changes afterward (Banfi et al. 2010;

Table 2 Bone-specific alkaline phosphatase levels

Males	Females
<2 years: 25–221 mcg/L 2–9 years: 27–148 mcg/L 10–13 years: 35–169 mcg/L 14–17 years: 13–111 mcg/L Adults: < or =20 mcg/L	<2 years: 28–187 mcg/L 2–9 years: 31–152 mcg/L 10–13 years: 29–177 mcg/L 14–17 years: 7–41 mcg/L Adults: Premenopausal: < or =14 mcg/L Postmenopausal: < or =22 mcg/L

When used as a marker for monitoring treatment or exercise-induced changes, it is important to determine the critical difference (or least significant change). The critical difference is defined as the difference between two determinations that may be considered to have clinical significance. The critical difference for this method was calculated to be 25% with a 95% confidence level (BC 1998)

Langberg et al. 2000). Pathologic fluctuations may be the consequences of acromegaly, osteogenic sarcoma, bone metastases, leukemia, and Paget disease of the bone, which must be interpreted carefully in the first visit. Antiresorptive therapies lower BAP from baseline measurements in Paget disease, osteomalacia, and osteoporosis. Studies have shown that antiresorptive therapies for management of osteoporosis patients should result in at least a 25% decrease in BAP within 3–6 months of initiating therapy. Metabolic causes of high BAP include bone growth and fracture healing in which age (Table 2), sex, nutrition, and calcium supplementation are the other relevant factors (Kular et al. 2012; Marsell and Einhorn 2011). The essence of the skeletal response is serum calcium concentration modified by parathormone. Intense and exhausting physical stress has the ability to fluctuate parathormone with consecutive increase in serum calcium in order to be used by the muscles.

Remodeling and Mechanical Loading at Cellular Level

Bone remodeling occurs through the bone's basic multicellular unit (BMU). The BMU consists of the osteoclasts resorbing the bone, the osteoblasts replacing the bone, the osteocytes within the bone matrix, the bone lining cells covering the bone surface, and the capillary blood supply. The remodeling cycle begins with an initiation phase for the recruitment of mature osteoclasts and activation and maintenance of bone resorption. A reversal period then follows where osteoclasts undergo apoptosis and osteoblasts are recruited to differentiate and induce formation. The final stage is bone formation by osteoblasts and is termed the termination phase. This stage is the longest, as bone formation is slower than bone resorption, and involves new bone formation and mineralisation. The length of the bone remodeling process is shorter in the cortical bone than in the cancellous bone, and the average length of the remodeling phase in the cancellous bone is approximately 150 days mostly devoted to bone formation. The signaling and interaction between the cells control this coupling process and coordinate the function of the cells.

Over the past few years, much has been learned about how mechanical loading affects bone structure. The latest studies suggest that bone cells detect mechanical loads through focal integrin linkages. Loading stimulates new bone formation, due to increased signaling through the Wnt/low-density lipoprotein receptor-related protein 5 (LRP5) pathway. Conversely, physical inactivity both suppresses periosteal bone formation and increases receptor activator of nuclear factor kappa-B ligand (RANKL) signaling and bone resorption by apoptosis of osteoblasts and osteocytes, which results in rapid bone loss. However, it is unclear how mechanical signals are perceived by cells to bring about activation of diverse signaling pathways. It is likely that mechanical forces activate many receptors simultaneously to form physical link between extracellular matrix and intracellular organelles. Increasing the rate or loading frequency improves bone tissue mechanosensitivity where osteocytes serve as mechanosensors. Because bone cells quickly become insensitive to applied loads and require time to recover their mechanosensitivity, osteogenesis after mechanical loading can be improved substantially by inserting resting time between loading sessions. Bone loss following physical inactivity is greatest in weight-bearing bones, particularly the distal bones in the legs and almost not existent in bones that do not bear weight (Turner 2007).

Exercise

Aerobic exercise including brisk walking, jogging, swimming, tennis, dancing, cycling, and treadmills involves the use of large muscle groups and must be sustained for at least 20 min/session and three times a week. Muscle-strengthening exercises include weight training, weight-bearing calisthenics, or resistance training. Development of muscle strength and endurance is progressive and requires gradual increases in strengthening activities over time. It should be done a minimum of two nonconsecutive days of the week and should target eight to ten major muscle groups (abdomen, bilateral arms, legs, shoulders, and hips). Recommendations for this purpose are 10–15 repetitions of each exercise at a moderate to high level of intensity and gradually increased resistance over time.

The way in which exercise is thought to act on the skeleton is through gravitational forces or muscle pull producing strains within the skeleton which are perceived by bone cells as osteogenic and anabolic response of the skeletal bone is substantially localized to areas of strain. The skeletal muscle has the ability to adapt to a variety of changes in physical status. The type of training, endurance or resistance, affects the type of muscular adaptations. Endurance training leads to mitochondrial biogenesis, fast to slow fiber transformation, enhanced capillary circulation, and metabolic changes. Resistance training typically increases the size of muscle fibers and cross-sectional area of ligaments and tendons which leads to the ability to exert more force. In general, women and men of all ages show gain in strength although the degree of adaptation to training varies from one individual to another.

Moreover, muscle activity induces some metabolic changes which put forth the organ system-specific roles of different energy sources. A number of biochemical processes in muscle fibers are responsible for maintaining a constant supply of ATP. The main energy-producing pathways that are utilized to prevent significant decreases in ATP concentration during dynamic exercise are the phosphocreatine shuttle, oxidative phosphorylation (aerobic), and anaerobic glycolysis. The most efficient skeletal muscle ATP source is the oxidative phosphorylation of intracellular glycogen and free fatty acids (FFA) in the muscle mitochondria with a net gain of 36 ATP molecules (2 from Krebs cycle, 34 from electron transport chain). Anaerobic glycolysis is a rapid source of two molecules of ATP in which pyruvate derived from glycolysis is converted to lactate without oxygen. High-intensity strengthening exercises involve the use of anaerobic glycolysis at the first 2–5 min before activating oxidative phosphorylation (Spurway 1992).

Exercise-Induced BAP Fluctuations

In a Japanese population-based osteoporosis (JPOS) cohort study (Tamaki et al. 2013), elevated levels of resorption and formation markers were found to be associated with greater bone loss determined by BMD measurement in sedentary premenopausal women than those with lower levels, after adjustment for the effects of age, body mass index, diet, regular exercise, and smoking. Therefore, increase of BAP levels may not be always the indicator of the bone formation process.

Behavior of BAP may be different in physically active people. Male runners and gymnasts unsurprisingly have a higher BMD than male cyclists or swimmers, but markers of bone turnover do not always confirm this result (Taaffe et al. 1997). The different physical performance or different training baseline levels, sex discrepancies, and type/intensity/duration of exercise are the major contributing factors related with the changes in bone turnover status.

Physiologic Increase in BAP

Bone formation stimulation after aerobic training is reflected by elevations in BAP levels in male athletes, while no changes were observed in controls (Eliakim et al. 1997). Aerobic training causes a net increase in bone formation because of the suppression of the bone resorption while anaerobic training induces (Woitge et al. 1998). One-year BMD changes and bone turnover markers after regular running activity of premenopausal subjects and sedentary, low/moderate-intensity trained women were searched. Improvement in the bone mass and acceleration in bone turnover status showed that BAP, osteocalcin, and N-terminal telopeptide (NTX) had increased in 1-year time (Sumida et al. 2014; Shibata et al. 2003). Eliakim et al. (1997) showed an increase in bone formation markers after a 5-week

aerobic training program. On the other hand, study population consisted of adolescent males with a totally different osteogenic response than in adults. In the study of Lester et al. (2009), 8 weeks physical training consisting of aerobic and strengthening components was compared with strengthening exercise by means of osteogenic response. Bone densitometric measurements showed slight elevations in the areas of interest. But formation markers, BAP and osteocalcin, showed marked elevations regardless of the type or volume of exercise, while no concomitant alterations were observed in resorption or turnover markers. This systemic response also showed that biomarkers of bone formation such as BAP are more sensitive indicator of bone osteogenic response than resorption markers in a short-term physical training. These results are consistent with other studies about exercise and bone turnover markers that turnover status may be changed in favor of bone formation by aerobic and resistance training (Lester et al. 2009; Maïmoun et al. 2004; Lohman et al. 1995).

Physiologic Decrease in BAP

The behavior of BAP is sometimes different in discrete conditions depending on physical endurance and factors about the exercise. Marathon runners and high-impact trained male athletes are reported to have decreased BAP levels immediately after the activity, while short-distance runners' BAP levels remain unchanged (Banfi et al. 2010; Maïmoun et al. 2004; Jürimäe et al. 2006; Brahm et al. 1996). Suppression of the BAP is being associated with the increases in cortisol and parathormone due to the intensity and duration of the activity reflecting the changes in calcium homeostasis. Dietary calcium intake and PTH levels are strongly associated with the remodeling status during or after the physical training.

Short-Term Effects of Exercise

The acute exercise effects on bone markers in adults are unclear, and there isn't much data for growing children. The behavior of BAP after a single bout of exercise is controversial. Even one session of jumping exercises (144 jumps) was found to stimulate bone formation immediately after exercise in men and 10-year-old boys, reflected by the increase in BAP and osteoprotegerin. The boys' response by formation markers was greater than the men's, suggesting that growing immature skeletal bone is more sensitive to mechanical stimuli (Kish et al. 2015; Maïmoun et al. 2006). Though it is demonstrated that regular physical exercise increases bone mass by means of prolonged mechanical loading, change in bone markers may not be measurable immediately after exercise in active subjects (Maïmoun et al. 2009), untrained (Welsh et al. 1997; Whipple et al. 2004) or active/sedentary elderly subjects (Maimoun et al. 2011; Maïmoun et al. 2005) (Table 3).

Table 3 Short-term effects of physical activity on bone turnover

(a) In nontrained subjects

Study	Population	Exercise	Evaluation time	Change in bone markers
(Whipple et al. 2004)	M (n = 9; 21.9 ± 1.2 year)	45 min of resistance exercises at 75% of the 10-RM	Just before, just after, and 1, 8, 24, and 48 h of recovery	B-ALP, PICP and sNTX (=)
(Welsh et al. 1997)	M (n = 10; 25.7 years)	30 min of walking at 60% of HRmax	Before the test, just after, and after 0.5, 1, 8, 24, and 32 h of recovery	B-ALP (=) and OC (=) Pyr (+25.1%), D-Pyr (+28.9%) ↑ on day 2 of recovery
(Brahm, Piehl-Aulin, et al. 1997)	M (n = 6), W (n = 6); age, 23–36 years	30-min incremental one-leg knee extension exercise	Before the test and after 5 and 60 min of recovery	PICP and B-ALP ↑ just after exercise and (=) at 60 min of recovery

(b) In trained (active) subjects

Study	Population	Exercise	Evaluation time	Change in bone markers
(Maïmoun et al. 2009)	M and W (n = 18; 71.7 years) active M and W (n = 18; 71.9 years) less active M and W (n = 9; 25.8 years) active	Maximal exercise test (VO2max)	Just before and just after exercise	OC, B-ALP, CTX (=)
(Maïmoun et al. 2005)	M (n = 11) and W active (n = 10; 73.8 years)	Maximal exercise test (VO2max)	Just before and just after exercise	B-ALP, OC, CTX (=)
(Malm et al. 1993)	M (n = 8; 29.9 years) runners W (n = 15; 40.3 years) runners	Marathon running	Day 10, just after marathon,and 1, 3, and 5 days later	OC↓ in M and W after marathon and after 1, 3, and 5 days (only in W) B-ALP ↓ in W after marathon and until 5 days Hydroxyproline (=)
(Maïmoun et al. 2006)	M cyclists (n = 7; 24.4 years)	2 × 50 min at −15% of VT and +15% of VT	Just before, after 30 and 50 min of exercise, and after 15 min of recovery	B-ALP ↑ at 30–50 min, (=) after 15 min recovery, CTX ↑at 30–50 min, (=) after 15-min recovery

(*continued*)

Table 3 (continued)

(b) In trained (active) subjects				
Study	Population	Exercise	Evaluation time	Change in bone markers
(Wallace et al. 2000)	M athletes (n = 8, 28.3 ± 2.8 years) M athletes (n = 8, 25.5 ± 1.5) with placebo	30-min incremental cycle exercise	–60 min, −30 min, and just before exercise and at 15-min intervals during 2 h after the start of the exercise	OC (=) B-ALP (+7.4%) and PICP (+9.2%) at the end of the exercise and remain elevated thereafter (+7%)
(Guillemant et al. 2004)	M trained (n = 7; 30.7 years)	60 min at 80% VO2max on cycle ergometer	–60 min, −30 min, and just before the test 30 and 60 min during the test 30, 60, 90, and 120 min of recovery	Ca supplementation: CTX (=); B-ALP (=) No Ca supplementation: CTX ↑ until 120 min of recovery; B-ALP(=)

M men, *W* women, *HRmax* indicates maximal heart rate, *VT* ventilatory threshold, *GH* growth hormone treatment, VO2maxth, theoretical VO2max, Nontrained = <60 min/week exercise

In Active Individuals

Professional athletes, who have a higher bone turnover than sedentary individuals have shown that short exercise (20–30 min) is insufficient for modifying serum concentrations of bone metabolism markers. Marker variations are more evident after several hours or days after exercise, especially bone formation markers are more sensitive than bone resorption markers. The bone formation markers, BAP and osteocalcin (OC), change approximately after 1 month and 2 months of an exercise program, respectively. In addition, BAP is found to be sensitive to aerobic exercise, and OC is found to be sensitive to anaerobic exercise (Banfi et al. 2010).

Though it is not confirmed in 30 min (Wallace et al. 2000) and 50 min of cycling (Maïmoun et al. 2006), an activity of long duration (>60 min) and high intensity such as in marathon runners, a decline in BAP and osteocalcin may be observed without any change in resorption markers just after the exercise and recovery (Malm et al. 1993). The bone cell metabolic activity in response to cycling for 30–50 min was similarly investigated (Maimoun et al. 2011). BAP and osteocalcin levels were shown to be elevated transiently in both groups with a marked elevation in 50 min high- intensity training group which suggested the existence of a bone formation-stimulation threshold. All markers returned to initial values during the recovery. In a similar protocol, no variation was observed in BAP and CTX after 60 min of cycling and 30 min of recovery in calcium supplementation group (Guillemant et al. 2004). However the increased CTX in the group without supplementation highlights the importance of metabolic balance. BAP is reported to remain unchanged immediately after the exercise and recovery period by high-intensity exercise with cycle

ergometer (Whipple et al. 2004; Guillemant et al. 2004). Marathon runners with high-intensity and long-duration (>2 hours) physical activity may cause an immediate or longer-lasting decrease in BAP without any modification in resorption markers (Malm et al. 1993). There are several hypotheses to explain this negative metabolic modulation as a stress response such as overproduction of glucocorticoids, high lactic acid, and parathormone concentrations after the marathon. It is also shown that calcium intake can reverse this effect in favor of formation after an exhaustive exercise (Banfi et al. 2010;Guillemant et al. 2004).

In Sedentary Individuals

No immediate change in bone markers was observed in any of the studies on strength training except one, in which BAP increased and osteocalcin decreased at 60 min of recovery after 30 min of leg extension exercises (Brahm et al. 1997b).

In sedentary subjects, most of the studies report no immediate variations in BAP levels after 30-min endurance training (Welsh et al. 1997). In contravention of this conclusion, an anabolic effect was also reported associated with an increase in BAP and decrease in resorption markers with 30-min exercise of 60% of peak VO2 max. In postmenopausal women, jogging is capable of raising BAP at the end of the exercise with normalization after 20 min. However the same exercise was not sufficient to change BAP in healthy young females, highlighting the bone cell function variability at different ages. Exercise that exceeds 20–30 min seems to induce a change in bone turnover markers (Maimoun et al. 2011). It takes 60 min–24 hours of recovery for the stabilization process as observed in most of the studies. In bone formation marker, BAP appears to be a very attractive tool for investigating the immediate response of osteoblasts to exercise, particularly in choosing the type and intensity of the exercise to improve bone health.

Long-Term Effects of Exercise

Study populations have demonstrated distinctly different behaviors about remodeling and BAP. High-intensity resistance training seems to have a bigger impact on BAP/pyridinoline ratio in favor of bone formation confirmed also by bone mineral density measurements (Vincent and Braith 2002) (Table 4).

In Active Individuals

Studies that focused on both bone formation and resorption markers indicated that physically active people (athletes, swimmers, judoists) present accelerated bone turnover (Creighton et al. 2001; Hetland et al. 1993; Lima et al. 2001; Maïmoun et al. 2004, 2008; Karlsson et al. 2003) which the bone metabolic balance is mostly in favor of formation. In contrast and as an exception, endurance athletes may have

Table 4 Long-term effects of physical activity on bone turnover

(a) In nontrained subjects

Study	Population	Exercise	Evaluation time	Change in bone markers
(In children) (Eliakim et al. 1997)	M training group (n = 20; 16 year)	2 h/day, 5×/week: aerobic training (90%) and resistance training (10%) during 5 weeks	Before and after 5 weeks	In trained subjects: OC (+15%), B-ALP (+21%), PICP (+30%) UrNTx (−21%) DPD (=), urCTx (=) In control group: no variation
In adults (Woitge et al. 1998)	M aerobic training (n = 10; 25.3 ± 2.6 years) M anaerobic training (n = 10; 23.5 ± 2.9 years) M control (n = 12; 25.3 ± 2.7)	Aerobic or anaerobic training program 60 min/day; 3×/week during 8 weeks	Before and after 4 and 8 weeks	Aerobic group: B-ALP and OC 1 at week 4 and (=) at week 8. PYD and DPD 1 at week 4 and week 8 Anaerobic group : B-ALP, OC, and PYD↑ At week 8
(Fujimura et al. 1997)	M training group (n = 8; 26.4 ± 1.2 years) M control (n = 7; 24.6 ± 1.0 year)	Weight training program 45 min/day; 3×/week during 4 months	Before and after 1, 2, 3, and 4 months of training	OC (+26.3%) and B-ALP (+30%), in trained PICP (−18%) 1, in controls DPD (=)
(Menkes et al. 1993)	M training (n = 11; 59 ± 2 year) M control(n = 7;55 ± 1 year)	16 weeks strength training; 3×/ week	Before and after 12–16 weeks of training	Variation in trained subjects: OC (+19%) At 12–16 weeks, B-ALP(+26%) at 16 weeks and TRAP (=)
(Yamazaki et al. 2004)	W training (n = 27; 64.2 ± 2.9 years) W control (n = 15;65.7 ± 2.7 years)	1 year of walking; 1 h/session; 4×/week at 50% of VO2max	Just before and after 1, 3, 6, 9, and 12 months in the trained and every 6 months in the control group	In trained group: B-ALP (−20%), uNTX (−25%) OC (=) after 3–12 months In control group uNTX (=)

(Vincent and Braith 2002)	M and W HRG (n = 22; 66.6 ± 7 years) M and W LRG (n = 22;67.6 ± 6 year) M and W control (n = 16;71 ± 5 year)	6 months, 30 min/day; 3×/week. Training at 80% of their 1-RM training or at 50% of their 1-RM	Before and after 6 months	OC LRG (+25.1%) and HRG (+39%) B-ALP (+8%) and PYD (=)in HRG Ratio OC/PYD HRG > LRG > control Ratio B-ALP/PYD HRG > LRG and control
(Ryan et al. 1994) (Alp 2013)	M training (n = 21; 61 ± 1 y) Premenopausal W training (n = 50;47 ± 7 years), W control (n = 50; 49 ± 5)	16 weeks of strength training, 3×/week 8 weeks of submaximal aerobic exercise 5×40 min/week	Before training and after 16 weeks of training Just before and after 8 weeks	TRAP↑ in trained. OC, B-ALP (=) CTX ↓, BAP(+26%) in trained

(b) In trained (active) subjects

Study	Population	Exercise	Evaluation time	Change in bone markers
(Etherington et al. 1999)	M military recruits (n = 40;18.5 ± 1.6 years) 10 weeks of military training	Habitual training	Before and after 10 weeks	OC↑, B-ALP ↑ (−13.6%) TRAP (=)
(L. Maïmoun et al. 2004)	M military recruits (n = 7; 19.2 years) 15 h/week	Habitual training	Before and after 32 weeks	B-ALP (−22%), CTX (=)
(Sartorio et al. 2001)	M trained (n = 16; 72.9 ± 0.95) M control (n = 14; 73.3 ± 1.04), 45–60 min/day moderate physical activity	16 weeks high-intensity strength training, 3×/week	Before and after 16 weeks	B-ALP (+31.7%) in trained OC and PINP (=) in trained and controls

GY indicates gymnasts, *T* an increase compared with pretraining values, = no change compared with pretraining values, *j* a decrease compared with pretraining values, *HRG* high-resistance intensity group, *LRG* low-resistance intensity group

lower bone formation and resorption marker levels in comparison with less active controls (Brahm et al. 1997a). Female athletes may have normal BAP and lower resorption markers (Ryan and Elahi 1998), or amenorrheic marathon runners may have lower bone turnover with lower BAP levels and established osteopenia which is due to estrogen deficiency (Zanker and Swaine 1998; Crespo et al. 1999). In young athletes the relative stability of bone mass (decrease in BAP and no change in osteocalcin) during sport season requires new more sensitive ways of detecting minor variations in bone turnover. Anaerobic or strengthening exercises induce bone turnover or accelerate BAP with suppression or no variation of resorption (Etherington et al. 1999; Maimoun et al. 2004). The exercise intensity seems to play an important role in the bone's cellular response. A positive effect on the bone is the maintenance or gain of bone mineral density as well as decrease (Yamazaki et al. 2004) or increase (Sartorio et al. 2001) in BAP.

In Sedentary Individuals

Five to eight weeks aerobic training improves bone remodeling in favor of formation because it reduces resorption transiently (Woitge et al. 1998) or in the longer term (Eliakim et al. 1997; Woitge et al. 1998; Eliakim et al. 1996). Anaerobic and resistance training may induce bone turnover or exactly the opposite with a decrease in resorption markers and a relative increase in BAP (Woitge et al. 1998). Training intensity and its components (strength and endurance) are the contributing factors on bone remodeling. Aerobic endurance training seems to improve bone turnover in favor of formation; however, anaerobic exercise induces an overall acceleration in bone turnover.

Ten weeks of military training was reported to have a decrease in BAP (Etherington et al. 1999), while 15 weeks of training in a similar study population induced an increase in formation markers (Casez et al. 1995). Exercise intensity and duration are the key factors for this anabolic effect in young subjects. It needs a few months of training at least to stabilize the turnover for a net gain in bone mass. Eight-week training of aerobic and anaerobic exercises in young adults was investigated by Woitge et al. (1998), and it was concluded that both demonstrated different metabolic effects. While aerobic exercise led to reduction in bone formation (BAP) and resorption (pyridinoline) markers, anaerobic activity induced an accelerated bone turnover. Prolonged oxygen deficiency was charged to imbalance in bone remodeling "uncoupling." Markers of bone formation returned to baseline after the eight-week training. The influence of exercise on bone mineral density is evaluated in adolescents (Eliakim et al. 1997) and sedentary elderly subjects (Menkes et al. 1993) in which BAP is found to be elevated after an aerobic training by 21% and 19%, respectively. BAP/pyridinoline ratio was shown to be a more reliable indicator for bone formation, and it was higher in resistance training group when compared with the group of low-intensity training (Vincent and Braith 2002). Anaerobic or strengthening exercises accelerate BAP with no variation of resorption

(Fujimura et al. 1997). BAP increase accompanied by gain in bone mass may be interpreted as the positive effects of exercise (Ryan et al. 1994).

Bone turnover effects of moderate-intensity aerobic exercise in premenopausal women were investigated by Alp (2013) in comparison with a control group. Though the rise of BAP from baseline was not statistically significant at the end of the second month, marked decrease was observed in CTX levels. It seemed that submaximal aerobic exercise may be effective in preserving bone mass for this type of population, but is not enough to enhance the bone mass. In another randomized controlled study, the effects of low-intensity yoga-based exercise program twice a week were evaluated in hemodialysis patients (Yurtkuran et al. 2007). After 3 months of intervention, significant decrease in BAP (by 15%) was observed in the yoga group as the reflection of attenuated bone remodeling status when compared with the controls. These changes were determined to be related to general effects of regular exercise rather than specific effects of yoga which was accompanied by clinical improvement in pain, sleep disturbances, fatigue, and grip strength. In conclusion, if a strain is detected as greater than the standard strain for an optimum time, then bone turnover lessens and bone formation can dominate (Lanyon 1984). Studies investigating the long-term (4 months–4 years) exercise have shown a reduction (Yamazaki et al. 2004), an increase (Sartorio et al. 2001; Menkes et al. 1993; Vincent and Braith 2002), or no change (Ryan et al. 1994) in BAP in postmenopausal subjects and old men.

Potential Applications to Prognosis, Other Diseases, or Conditions

Osteoporosis is a metabolic bone disease characterized by low bone mass and abnormal bone microarchitecture with increased risk of fracture. It can result from a number of clinical conditions with high bone turnover identified by high BAP levels. These conditions may be endocrine disorders (primary and secondary hyperparathyroidism and thyrotoxicosis), osteomalacia, renal failure, gastrointestinal diseases, long-term corticosteroid therapy, multiple myeloma, and malignancy with metastasis to the bones. Paget disease is another common metabolic bone disease caused by high rates of bone remodeling resulting in local punched lesions. It is usually not recognized until the subsequent bone formation response resulting in enlarged and deformed bones. This excessive resorption and formation bring out an abnormal mosaic pattern of the lamellar bone associated with increased vascularity and fibrous tissue deposition in adjacent marrow spaces. These lesions can result in fractures or neurological involvement as the consequence of mechanic pressure. Antiresorptive therapies are used to restore the normal bone structure.

Utility of BAP as a Prognostic Factor

BAP, as a bone formation marker, is determined to be an indicator of the bone turnover status, and therefore, physical training consequences can be established and measured

by its serum levels. BAP can be used for demonstrating the existence of metabolic bone diseases or assessing the severity of Paget disease, osteomalacia, and other states of high bone turnover. Monitoring efficacy of systemic antiresorptive therapies including postmenopausal osteoporosis treatment may be another means of use.

Cautions

When used as a marker for monitoring purposes, it is important to determine the critical difference or least significant change. The critical difference is defined as the difference between two determinations that may be considered to have clinical significance. The critical difference for this method was calculated to be 25% with a 95% confidence level (Table 2).

Liver-derived alkaline phosphatase has some cross-reactivity in this assay: 100 U/L of liver ALP activity gives a result of 2.5 mcg/L to 5.8 mcg/L. Accordingly, serum specimens with significant elevations of liver ALP activity may yield elevated results.

Conclusions

The interpretation of accelerated or ameliorated bone remodeling must be done cautiously according to study populations mentioned above; thus, crucial data is still lacking on how physical exercise effects bone remodeling process and BAP. Despite the wide discrepancies among studies, some conclusions can be drawn.

The overview of the regulation in remodeling establishes that bone mass can be enhanced by both strenuous aerobic exercise and strength training (Creighton et al. 2001). Protection against osteoporosis by physical training is a will, but it somehow may not happen because of a variety of personal factors. Therefore, the need arises for a homogenous group and a crucial study design for bone metabolism investigations with serial laboratory measurements if possible. A common profile and homogenous behavior of bone turnover markers, especially BAP, must be defined entirely for sedentary subjects and professional athletes of both sexes. In conclusion, present data lacking evidence for a general use of bone formation/turnover markers to detect metabolic changes enables to recommend a certain exercise prescription for a standardized group at the moment.

Summary

- Bone mass is the net product of counteracting metabolic processes: bone formation and resorption. BAP is generally used in the prediction of high bone turnover.
- Experimental studies have revealed that long-term (6–12 months) training with high strain rates and excessive forces are more effective in the anabolic adaptation process than low-strain physical exercise of the same duration.

- Acceleration of bone remodeling may be the consequence of various metabolic conditions extremely different in athletes and sedentary healthy subjects.
- Individuals or adolescents with high-intensity training have more stable bone turnover status during and after physical activity, compared to untrained sedentary subjects. Untrained sedentary subjects may have an accelerated or suppressed bone turnover reaction to physical training, depending on personal metabolic needs as the acute or delayed effect in the recovery period.
- Female high-intensity trainers may have suppressed BAP levels immediately or at the recovery period contrary with men trainers highlighting the sex discrepancy or estrogen deficiency. It must be retained that unbearable or unusual concentrated mechanical stress especially in amenorrheic runners may be associated with a metabolic uncompensated remodeling process in favor of resorption which may lead to microdamage and stress fractures of the involved bones.
- It seems that mild general exercise such as walking is effective in preventing postmenopausal bone loss but not enhancing bone mass in younger age. Bone turnover markers associated with fracture risk reduction need to be determined in the management of osteoporosis.

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