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Original Article

The Effect of Aerobic Training on Parathyroid Hormone and Alkaline Phosphatase as Bone Markers in Men with Mild to Moderate Asthma

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Abstract

Background and Aim: Inhalation of corticosteroids in patients with asthma is associated with an increased risk of osteoporosis. This study aimed to assess the effect of aerobic training on alkaline phosphatase (ALP), parathyroid hormone (PTH) as bone biomarkers in men with mild to moderate asthma.

Methods: Twenty four sedentary middle-aged men with asthma aged 40±5 years were randomly assigned to two groups as exercise (aerobic training, n=12) and control (no training, n =12). Aerobic training was performed 3 days a week for 12 weeks in the form of running on a flat surface at 60-75% of HRmax. Fasting blood samples were taken before and after the training program for measuring serum ALP and PTH.

Results: There were no statistically significant differences between groups with regard to anthropometrical and bone markers at baseline ($p>0.05$). Aerobic training resulted in significant increase in ALP ($p = 0.023$) and PTH ($p = 0.016$) in exercise individuals. All variables remained unchanged in the control group ($p>0.05$).

Conclusion: With an emphasis on the increase in ALP and PTH, it is concluded that relatively long-term aerobic exercise is associated with improved bone formation markers in patients with asthma treated with inhaled corticosteroids.

Keywords: Aerobic training; Osteoporosis; Asthma; Bone markers.

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Introduction

Asthma is an airway disease of allergic origin that appears physiologically with narrowing of the airways and presents clinically with sudden attacks of shortness of breath, cough, and wheezing(1). This type of disease is also defined as chronic inflammation of the airways and there is evidence that systemic inflammation is involved in their pathogenesis (2). Respiratory function impairment is strongly associated with cardiovascular risk factors, atherosclerosis, vascular stiffness, cardiovascular disease, and mortality. However, the pathophysiological mechanisms responsible for this association are still unknown (3). Studies have shown that 30 to 50% of lung patients have osteoporosis of the vertebrae and femur (4, 5). These studies have supported asthma as a precursor to osteoporosis. One of the most important risk factors for osteoporosis in patients with asthma is the age of patients and the number of corticosteroids used (6). There is evidence that the use of oral or inhaled corticosteroids by patients with asthma is associated with impaired levels of markers of bone formation or destruction, mainly leading to bone destruction. High doses of inhaled corticosteroids, in addition to increasing bone resorption, inhibit bone formation by inhibiting and reducing osteoblast cell proliferation (7, 8).

It has been reported that the use or inhalation of corticosteroids is responsible for approximately 55% of changes in density, strength, and osteoporosis in patients with asthma (9, 10). Markers of bone resorption and formation such as

C-terminal type 1 collagen telopeptide (CTX), osteocalcin, serum alkaline phosphatase (ALP), parathyroid hormone (PTH) as well as plasma levels of some other biochemical parameters such as cortisol and regulating cell activity, encephalin, calcium, bone formation, and reabsorption as well as predicting the occurrence of bone metabolic diseases or osteoporosis (11-13). Among these, PTH and ALP have been introduced as the two main determinants of the bone formation process. PTH is one of the major hormones regulating calcium metabolism in both anabolic and catabolic functions of bone (14).

ALP also represents osteoblast cell activity and bone formation (15). In bone, osteoblasts are a large source of ALP, and the amount in the cell indicates the ability of osteoblasts to build bone (16, 17). Decreased ALP levels are associated with bone destruction or reduced bone formation. Considering the effects of inhaled corticosteroids on markers of bone formation and destruction in patients with asthma, the replacement of other stimulants to reduce the severity of the disease seems to prevent the spread of osteoporosis and other irreversible complications. Meanwhile, based on the available evidence on other chronic diseases that are often associated with metabolic disorders, exercise training as a non-pharmacological treatment are likely to have beneficial effects. Although studies in this field are limited to patients with asthma, some studies in the last decade have supported the beneficial effects of various exercise methods on bone degradation or reabsorption indices in healthy or sick populations, although there are conflicting findings.

For example, in the study of Khajehlandi et al., the effect of a selected aerobic training on calcium, PTH, and some other markers of bone formation or destruction in inactive women students was measured. The results showed that the levels of PTH, osteocalcin, and ALP increased significantly in the exercise group, but these variables did not change significantly in the control group (18). In the study of Tartibian et al., 9 weeks of intense aerobic exercise by young women led to a significant increase in ALP and PTH compared to the control group (19). However, in Aliye et al.'s study, an aerobic exercise session in the form of brisk walking on a treadmill resulted in a significant decrease in ALP and a significant increase in PTH in men, while the combination of submaximal exercise with weight-bearing increased ALP was delayed for 24 hours after exercise but PTH levels did not change significantly (20). PTH regulation is also affected by bone mineral density, age, sex, and other hormones and metabolic factors such as catecholamines, lactic acid, and calcium concentrations (14). Based on the evidence, despite the potential importance of exercise in maintaining bone structure in healthy or diseased populations, there are still precise mechanisms for linking bone metabolism to exercise and the precise response of hormones and markers affected by exercise to bone formation. Therefore, due to the increasing prevalence of osteoporosis in patients with asthma, in the present study, the effect of a course of aerobic exercise on serum levels of PTH and ALP in patients with asthma will be measured and compared with the control group

Methods

Patients

The population of the present quasi-experimental study consists of men with mild to moderate asthma without calcium or vitamin D supplementation of Saveh aged 35 to 45 years old. The statistical sample consisted of 24 non-athlete and non-smoking adult men with asthma treated with inhaled corticosteroids randomly divided into experimental (12 week's aerobic training, 3 times/weekly) or control (no training). The criteria for diagnosing asthma were measuring respiratory volumes (FEV1 / FVC ratio) by spirometry test and examining clinical manifestations by an asthma and allergist. The patients had mild to moderate asthma (mild persistent asthma), with asthma symptoms usually not occurring more than once a day, and inhaled steroids once or twice daily. Having at least 3 years of use of inhaled corticosteroids is one of the main criteria for inclusion in the study. Also, not participating in diet and regular exercise in the last 6 months was another inclusion criterion. The presence of other chronic diseases such as diabetes

or cardiovascular disease and other metabolic diseases affecting metabolism and homeostasis of energy and bone was also excluded from the study. Observation of orthopedic abnormalities that limits the performance of exercise is also one of the exclusion criteria. Prior to the study, all patients were informed of the objectives of the study by the administrators and completed the consent form.

Anthropometric indices

The anthropometrical markers were measured for all participants. Weight and height were measured in the morning, in fasting condition, standing, wearing light clothing, and no shoes. Body mass index (BMI) was calculated by dividing body mass (kg) by height in meters squared (m^2). Abdominal circumference and hip circumference were measured in the most condensed part using a non-elastic cloth meter. Visceral fat and body fat (%) were determined using a body composition monitor (OMRON, Finland). Each of these measurements was conducted three times and the average was reported.

Laboratory analysis and aerobic protocol

Individuals were asked to attend a hematology laboratory after 10 to 12 hours of the overnight fast. All individuals were barred from any strenuous physical activity for 2 days before blood sampling. Blood samples were taken from the brachial vein between 7 and 8 am to measure ALP and PTH (pre-test). Serums were immediately separated and stored at -80° until the assays were performed. The exercise program was performed for 12 weeks in 3 sessions of 40 to 60 minutes per week in the range of intensity of 60 to 75% of the maximum heart rate (21). Each workout session began with 10 to 15 minutes of warm-up and stretching, and ended with 5 minutes of cooling. During the training period, the volume of each session performed in the form of running on a flat surface without slope increased by 5 minutes every three weeks. Also, the intensity of training in the initial sessions in the lowest range and gradually increasing the intensity of training by 5% every three weeks. The intensity of exercise was 60% in the first three weeks, 65% in the fourth to sixth weeks, 70% in the seventh to ninth weeks, and 75% of the maximum heart rate in the last three weeks. The heart rate was monitored by a Polar Electro FS2C CE0537 (made in China). Controls did not participate in the exercise program in this period and were instructed to maintain their habitual activities. Finally, all measurements consist of fasting blood sampling and anthropometric measurements repeated 48 h after a lasting exercise session (post-test). PTH by the immunoradiometric method and immunotoxic kit made in the USA and ALP by photometric method (Pars Azmoon-Tehran, Iran) by Autoanalyser (RA-100, Canada) were measured.

Statistical analysis

All statistical analyses were performed through the use of a statistical software package (SPSS, Version 16.0, SPSS Inc., IL, USA). Normality of distribution was assessed by Kolmogorov-Smirnov. An independent sample T-test was used to compare all variables between two groups at baseline (pre-test). To determine the effect of aerobic training on various parameters (PTH, ALP), the delta values between pre and post-training of each variable were compared by an independent T-test between 2 groups. A paired t test was used to determine the mean differences between pre and post-intervention values on all variables. P-value of less than 0.05 was regarded as indicative of a significant difference. All values are reported as mean and standard deviation.

Results

The baseline (pre-training) of anthropometrical and clinical indexes of the two groups are shown in Table 1. Data by independent t-test showed no significant differences between groups with regard to mentioned variables (p-value > 0.05). Based on what was mentioned, to determine the level of change of each anthropometric index, first, the delta of each variable (pre-test and post-test difference) in each group was determined, then the delta of each variable in the two groups was compared by independent t-test. Statistical findings showed a significant difference between the delta of each of the variables between the two groups (p-value <0.05) which indicates a significant decrease in anthropometric indices (weight, abdominal circumference, body mass index, body fat

percentage) after exercise training in the experimental group. On the other hand, based on intra-group changes by paired t-test, all anthropometric indices in response to aerobic exercise in the experimental group decreased significantly compared to baseline levels (p-value <0.05). But no significant difference was observed in any of these variables between the two conditions in the control group (p-value >0.05) (Table 2).

Table 1. Baseline level of anthropometrical and clinical indexes of 2 groups (Mean ± SD)

Variables	Exercise group	Control group	Sig
Weight (kg)	94.7 ± 11.7	94.9 ± 8.93	0.456
AC (cm)	106 ± 11.27	106 ± 10.96	0.982
BMI (kg/m2)	31.5 ± 3.49	31.7 ± 2.80	0.436
Body fat (%)	28.6 ± 5.55	31.4 ± 2.85	0.280
PTH (pg/mL)	25.3 ± 7.97	27.7 ± 7.67	0.455
ALP (U/L)	248 ± 64	242 ± 57	0.834
Calcium (mg/dL)	9.74 ± 0.46	9.59 ± 0.16	0.463
Phosphorus (mg/dL)	3.42 ± 0.37	3.61 ± 0.46	0.517

AC, abdominal circumference; **BMI:** body mass index; **PTH**, parathyroid hormone; **ALP**, alkaline phosphatase

Table 2. Pre and post-training of anthropometrical indexes of 2 groups (Mean ± SD)

Variables	Exercise group			Control group		
	Pre-training	Post-training	Sig	Pre-training	Post-training	Sig
Weight (kg)	94.7 ± 11.7	90.9 ± 13.3	< 0.0001	94.9 ± 8.93	93.8 ± 8.44	0.242
AC (cm)	106 ± 11.27	103 – 11.6	< 0.0001	106 ± 10.96	105.8 ± 10.8	0.166
BMI (kg/m2)	31.5 ± 3.49	30.4 ± 3.97	< 0.0001	31.7 ± 2.80	31.3 ± 2.60	0.223
Body fat (%)	28.6 ± 5.55	26.7 ± 5.82	< 0.0001	31.4 ± 2.85	31.3 0± 2.60	0.740

AC, abdominal circumference; **BMI:** body mass index

Findings from the independent t-test showed a significant difference in PTH delta (p-value = 0.021) and ALP delta (p-value =0.019) between the two groups. On the other hand, findings from intra-group changes by paired t-test indicate that the aerobic training leads to a significant increase in PTH (p-value= 0.016) and ALP (p-value =0.023) in the experimental group, but no change was found in these variables in control individuals (p-value> 0.05). Table 3 shows the significant levels of intra-group changes in serum PTH and ALP of the 2 groups.

Table 3. Pre and post-training of clinical markers of 2 groups (Mean ± SD)

Variables	Experimental group			Control group		
	Pre-training	Post-training	Sig	Pre-training	Post-training	Sig
PTH (pg/mL)	25.3 ± 7.97	33.68 ± 11.4	0.016	27.7 ± 7.67	27.40 ± 5.09	0.853
ALP (U/L)	248 ± 64	272 ± 72	0.023	242 ± 57	238 ± 55	0.550

Discussion

A significant increase in PTH and ALP is the main findings of the present study. In other words, 12 weeks of aerobic training in the range of 60 to 75% of maximum heart rate leads to a significant increase in PTH and ALP in adult men with asthma with a history of at least one year of inhaled corticosteroids. In this regard, although studies on the response or adaptation of components affecting

bone metabolism in patients with asthma are less common, some studies on other healthy or diseased populations are available, which are often reported to be inconsistent. For example, in a study by Zargar et al. (2016), 12 weeks of aerobic exercise resulted in a significant increase in PTH and ALP in obese adult men, although calcium levels were reported unchanged (22). On the other hand, in the study of Baghery et al. (2012), both 8-week resistance and aerobic training led to a significant increase in PTH and ALP compared to the control group in postmenopausal women (23). However, Bijeh et al. (2011) based on their findings have pointed out that 6 months of aerobic exercise does not lead to significant changes in PTH, calcium, and ALP in middle-aged women (24). In the study of Lester et al. (2009), 8 weeks of aerobic and resistance training were not associated with changes in PTH (25). In Eizadi et al.'s (2018) study, 3 months of aerobic exercise did not lead to a significant change in CTX levels as another component of the hormone affecting bone metabolism in male smokers (21).

A review of the evidence points to a kind of discrepancy in the response or adaptation of hormonal or metabolic components affecting bone metabolism to exercise in different populations. On the other hand, the findings in this field are very limited in patients with asthma and so far few studies have been reported to determine the response of bone metabolism reagents, especially PTH and ALP, to exercise in patients. However, in the study of Ghasemalipour et al. (2017), 3 months of aerobic exercise led to a significant increase in osteocalcin as another indicator of bone formation in men with asthma (26). In another study by these researchers, 3-month aerobic exercise was associated with a significant reduction in CTX as a marker of bone destruction in patients with asthma (27).

Lack of adequate studies on the response of hormonal or metabolic indicators indicating bone metabolism in patients with asthma is observed while the prevalence of osteoporosis in these patients is increasing sharply and most studies are sedentary and use some stimulants of airway dilation. Inhaled corticosteroids have been reported to cause osteoporosis in these patients (7, 8). Based on the evidence from clinical studies, glucocorticoids affect the connective tissue fibers of the bone far more than the cortex, which is probably due to their greater activity in these areas. Glucocorticosteroids reduce proliferation and differentiation in bone formation cells or osteoblasts and lead to increased cell death in osteoblasts. They inhibit type 1 collagen synthesis and beta integrin 1 while increasing type 3 collagen synthesis also weakens the ability of osteoblasts to form bone. However, the precursors of osteoclasts and bone-derived macrophages and monocytes can lead to the formation of adult osteoclasts by glucocorticosteroids (28). Glucocorticoids also affect some cytokines and prostaglandin growth factors, which are topical regulators of bone metabolism. Insulin-like growth factor (IGF-I, II), HGF-binding proteins, hepatocyte growth factor (PGE) and prostaglandin E2 are among the consequences of glucocorticosteroids (28). In a retrospective study by Wang et al. (2000) in the United Kingdom on whether inhaled corticosteroids affect bone density independently of physical activity and systemic corticosteroids (29), 196 people used high doses of corticosteroids. Most of these people have previously used systemic corticosteroids. At the end of the study, an inverse relationship was observed between the doses of inhaled corticosteroids and bone density in the lumbar vertebrae, large bulges and femoral neck. Also, increasing the dose by 2 times as much as inhaled corticosteroids led to a significant reduction in bone density in the lumbar vertebrae. Similar changes were also observed at other scanned sites (29).

Despite insufficient studies, the findings of the present study indicate an increase in ALP in response to 12 weeks of aerobic exercise in men with asthma. ALP is a bone-derived isoenzyme that represents osteoblast cell activity and bone formation (30). Therefore, apart from other metabolic processes, its increase is a kind of indicator of increasing bone formation. The increase in levels is a reflection of the increased activity of osteoblasts. As the increase in serum levels is directly related to the bone formation

process. Researchers believe that physical activity and exercise increase the anabolic effect of ALP on bones (31). In this regard, Erickson et al. (2010) reported a significant increase in ALP after 8 weeks of jumping or plyometric exercises (32). However, Bembenx et al. (2007) reported no change after a period of low-intensity resistance training (33).

Increased PTH is another finding of the present study. The role of PTH in renal calcium reabsorption has been repeatedly reported. Higher levels of total calcium and ionized calcium have been reported in people with physical activity than inactive people (34).

Increasing PTH through exercise has been shown to reduce urinary excretion of calcium by reducing renal reabsorption (35). Despite the evidence, there are conflicting answers about the effect of exercise on calcium levels. Some studies have reported decreased calcium levels (34, 36) and others reported no change or increase following exercise (37, 38). On the other hand, in line with the findings of the present study, an increase in PTH and ALP levels in response to aerobic training has been reported several times before. Tartibian et al. (2009) reported an increase in PTH and ALP after 9 weeks of aerobic training (19). However, Bouassida et al. (2003) also reported an increase in PTH following two types of intermittent and strenuous exercise (39). Based on this evidence, it appears that increased exercise-induced PTH helps maintain blood and bone calcium levels by reducing calcium excretion and increasing renal calcium reabsorption. However, Iwamoto et al. (2004) reported a decrease in PTH following low-intensity exercise (40).

The discrepancy in the findings regarding the response or compatibility of the indicators indicating metabolism or osteoporosis in different studies can be attributed to differences in duration, intensity, and type of exercise program or type of population studied. In two previously reported studies, Bouassida et al. (2003) attributed the increase in PTH levels following intermittent and continuous exercise to the high intensity of exercise (39), but Iwamoto et al. (2004) decreased PTH after exercise has been attributed to the low intensity of exercise (41). On the other hand, Maimon and Sultan (2009) based on their findings have pointed out that intense short-term training cannot change PTH and attributed the cause to a short training period(41). In another study, Bouassida et al. (2006) concluded that stimulation of PTH release has a threshold, and that exercise that lasts more than 50 minutes is able to increase the concentration of PTH, and if the activity is less than 50 minutes is not associated with a stimulatory effect on PTH release (42).

In addition to the evidence, the type of exercise program and the type of exercise tool also affect the release of markers of bone metabolism. In this context, it has been suggested that weight-bearing exercises are necessary to prevent osteoporosis in high-risk individuals, while aerobic exercises such as running on a treadmill alone are not sufficient to maintain bone mass (43).

In a two-year prospective study, an exercise program was designed to determine bone density in a group of women in the early postmenopausal period. 24 months of aerobic exercise was performed to maintain bone mass in the distal part of the femur and spine. Intense aerobic exercise increased growth hormone secretion and mechanical strength and stimulated bone formation (44). The researchers found that the exercises prescribed should be designed depending on the level of tolerance of each patient, especially those at risk for osteoporosis, such as those using inhaled or systemic corticosteroids (45). The effects of exercise on bone density are not lasting for long periods after cessation of activity. In a study on a group of elderly women, no significant difference in bone density was observed in 5 years after cessation of one-year exercise in the experimental group with the control group who did not participate in the exercise program (46).

On the other hand, weight-bearing exercises can increase ALP due to pressure and tension on the skeletal muscle system, but Tsang et al. (2010) have pointed out that swimming exercises with both high and low intensities cannot stimulate ALP release (47). However, the effectiveness of some exercises, such as swimming, that do not involve weight-bearing is somewhat controversial. In a recent study, a period of prolonged swimming training did not result in a change in bone density, osteocalcin,

and ALP in 10- to 22-year-old swimmers (48). But researchers note that different pressures and shocks during swimming can cause other types of pressure or resistance on the bone. In the study of Falcai et al. (2015), all three training programs in the form of swimming, jumping and vibration led to a significant increase in bone mass, bone strength, bone formation and serum levels of bone formation markers in Wistar rats (49).

In this study, although there was no significant difference in the mentioned variables between the two training programs of swimming and jumping, the rate of improvement in both training groups was much higher than in the vibration group. Based on this evidence, researchers have suggested that the exercises prescribed should be designed depending on the tolerance of each patient, especially those at risk for osteoporosis, such as those taking inhaled or systemic corticosteroids (45).

It should be noted that although ALP and PTH are markers of bone formation, however, the measurement of these components alone does not indicate the effectiveness of aerobic exercise on osteoporosis, and accurate conclusions require the measurement of other markers of bone formation or resorption such as Osteocalcin, CTX, PICP, PINP, calcium, phosphorus, etc. and Lack measurement of them is main limitation of the present study

Conclusion

Based on the available findings, long-term aerobic training leads to a significant increase in PTH and ALP as markers of bone formation in men with asthma that have a history of using inhaled corticosteroids. Increasing the levels of these variables in response to exercise in the presence of continued use of corticosteroids is one of the strengths of the present study.

Because in the present study, the use of inhaled corticosteroids continued during the training intervention. Lack of measurement of other hormonal components affecting bone metabolism is one of the limitations of the present study, which warns of the need for further studies by measuring other components.

Conflict of Interest

The authors declared that they have no conflict of interest.

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Ethics

The study protocol was approved by the Ethics Committee of Research Deputy of Saveh Azad University with this code: 139.237.

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