



The effect of detraining following an endurance training program on bone metabolism markers in asthmatic men

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Abstract

Background: This study investigated the impact of a 3-week detraining period, followed by 10 weeks of aerobic training, on the serum levels of osteocalcin and alkaline phosphatase (ALP) in asthmatic males.

Methods: Thirty adult males with asthma were randomly divided into experimental and control groups. The experimental group engaged in a 10-week aerobic training program, which included running sessions 3 times per week for 30-60 minutes each, maintaining a target heart rate range of 55%-75% of their maximum heart rate (HRmax). In contrast, the control subjects did not participate in any exercise activities during the study period. Fasting blood samples were obtained at baseline, after aerobic training, and after detraining to measure the levels of osteocalcin and ALP in both groups.

Results: The 10-week aerobic training program led to a significant increase in levels of osteocalcin and ALP in the experimental group, but following the detraining period, these variables returned to their pre-training levels.

Conclusion: The effectiveness of continuous aerobic training on bone formation markers in asthmatic patients will disappear after a relatively short period of detraining. This evidence emphasizes the lack of stopping aerobic exercise in the presence of inhaled corticosteroids with the aim of improving bone metabolism in asthmatic patients.

Introduction

Previous studies have indicated that patients with asthma and chronic pulmonary obstruction, especially those who have been treated with corticosteroids for a long time, are at increased risk for osteoporosis (1). In addition, 30% to 50% of lung patients have osteoporosis of the vertebrae and femur (2). There is evidence that the risk of vertebral and non-vertebral fractures in asthmatic patients is 2.6 and 1.4 times higher than in healthy individuals (3), and asthmatic patients who take oral or inhaled corticosteroids have the lowest levels of bone density and a double risk of osteoporosis compared to those patients who have no history of corticosteroid use (3). Osteoporosis is commonly known as the "silent disease" and the most common metabolic bone disease (4,5). During life, young bones are replaced with worn bones. This process is achieved by the destruction or reabsorption of bone by osteoclast cells on the one hand and the formation of new bone tissue by osteoblasts on the other. This cycle continues throughout life (6). Numerous factors (such as clinical disorders, including hyperthyroidism and elevated serum cortisol, gastrointestinal disorders, genetics, aging, and detraining) affect this phenomenon, and in some way, the serum or plasma levels of these indicators affect bone reabsorption or formation, which is often associated with a decrease in bone density and osteoporosis (7,8). Alkaline phosphatase (ALP) and osteocalcin are bone metabolism biomarkers that can be used to determine bone changes (9). Alkaline phosphatase is an enzyme derived from bone and liver that shows the activity of osteoblast cells and bone formation (10). Osteoblasts are a rich source of ALP, and their serum levels indicate osteoblast osteogenesis (11). Osteocalcin is a 49-amino acid protein that is specifically secreted by osteoblasts and is a high-performance hormone that is released into the bloodstream (12).

The degree of bone formation can be estimated based on the osteocalcin level (9). Physical activity as one of the important determinants of bone mass and its role in skeletal tissue health and bone mass growth has been proven many times (13). Exercise has both a direct and indirect osteogenic effect on skeletal tissue and can increase bone density by altering the balance between bone formation and reabsorption (14). Among the benefits of physical activity are the effects of mechanical loading due to physical activity, which has become a clinical issue and basic research. A variety of training methods, including treadmill running, jumping, aerobic and resistance training, have a variety of mechanisms in activating bone cells (15). Accordingly, bone biomarkers seem to be of particular importance in determining the bone's metabolic response to exercise. Many studies have been conducted to investigate the effects of exercise on changes in biomarkers associated with bone formation and reabsorption. However, the results have been inconsistent and diverse among different studies. As in the study of Alghadir et al, aerobic exercise increased the levels of

biomarkers of bone formation, including ALP, in healthy men and women (16). However, other studies have shown that ALP levels do not change after a period of moderate-intensity aerobic exercise (17,18), and a biomarker of bone formation decreases after high-intensity interval training (19). Ashizawa et al reported that resistance training in sedentary men caused a significant increase in osteocalcin levels after exercise (20). In the studies by Kristofferson et al (21) and Whipple et al (22), the level of osteocalcin and bone-specific ALP did not change after resistance and aerobic training. Fernandez et al found that resistance training improved osteocalcin levels in obese women (23). Alipour and Eizadi investigated the effects of a 3-month exercise program involving treadmill sessions lasting 40-60 minutes, with an intensity range of 55%-75% of the participants' maximum heart rate (HRmax). They observed that a regular aerobic exercise program resulted in a significant increase in serum osteocalcin levels. However, they did not observe a significant change in serum ALP levels (24). On the other hand, the effects of detraining on osteoporosis indices are less visible. Some contradictory findings on the effect of detraining following regular exercise on other hormonal components can be seen in other healthy or sick populations. Abbaszadeh et al examined a period of detraining after 16 weeks of aerobic exercise on the serum levels of calcitonin and parathyroid hormone in middle-aged women with osteopenia. They observed a decrease in calcitonin and an increase in parathyroid hormone after a period of inactivity (25). On the other hand, Kim et al showed that 12 weeks of resistance training increased markers of bone metabolism; osteocalcin and ALP in healthy young men (followed by 6 weeks of inactivity) had no effect on markers of bone metabolism (9). However, it is not clear whether the effects obtained through exercise are maintained, reduced, or lost when the exercise is stopped. Therefore, considering the anti-osteoporotic effects of exercise, its strong effects on hormones affecting bone, and the importance of preventing osteoporosis, it can be assumed that aerobic exercise is effective in preventing osteoporosis in asthmatic patients. Considering the conflicting findings in the existing literature and the limited evidence specific to asthmatic patients, this study aimed to assess the impact of a 3-week detraining period following an endurance training program on indicators of bone formation, specifically osteocalcin and ALP levels, in asthmatic patients.

Methods

Thirty adult males with asthma (aged 35 and 45), who were receiving treatment with inhaled corticosteroids, were enrolled in this quasi-experimental study. They met the inclusion criteria and voluntarily participated in the study. The criteria for diagnosing asthma were measuring respiratory volumes (the forced expiratory volume in 1 second [FEV1]/forced vital capacity [FVC] ratio) by the spirometry test (Vitalograph model, made in Italy) and examining clinical manifestations by

an allergist. The patients had mild to moderate asthma, characterized by asthma symptoms typically occurring no more than once a day. These patients were prescribed inhaled steroids to be taken once or twice daily. All individuals were advised to refrain from consuming tea, coffee, and other respiratory tract stimulants for approximately 4 hours prior to spirometry testing. Then, the participants were randomly assigned to either the experimental group ($n = 15$) or the control group ($n = 15$). The experimental group engaged in a 10-week aerobic training program consisting of 3 sessions per week, followed by a 3-week period of detraining. The control group did not engage in any specific training.

The use of inhaled corticosteroids for at least 3 years is the main inclusion criteria. The subjects are non-athletes, as they have not participated in any regular training program in the last 6 months. The subjects also did not have a defined diet during the last 6 months, and their weight fluctuation was less than 1 kg during this period. History of diabetes, kidney disease, cancer and seizures, and other chronic diseases are also excluded from the study.

Next, the experimental group performed a course of aerobic exercise for 10 weeks and 3 sessions per week, and the control group did not participate in exercise during this period and continued their normal life pattern. Each training session lasted for 30 to 60 minutes in the form of 10 minutes of warm-up and stretching exercises, and then the main stage of the activity was performed in the form of running on a flat surface without slope in the range of 75%-55% of HRmax and finally 10 minutes of cooling. Exercise intensity was controlled based on the percentage of maximal heart rate using a polar pacemaker. To determine the effect of detraining on dependent variables, all subjects underwent a 3-week period of detraining. This situation continued for the control group as well.

To measure bone formation indices, blood sampling was performed in 3 stages, before the study, 48 hours after the last training session, and after 3 weeks of detraining in both groups. The blood sampling was conducted after a 10 to 12-hour overnight fast, between 8 and 9 o'clock in the morning. Each participant was seated in a resting position, and 5 mL of blood was drawn from the vein of their left hand. The samples were immediately centrifuged to separate the serum and stored at -80°C until the variables were measured. Participants were asked to avoid strenuous physical activity for 48 hours before each test. To measure serum osteocalcin by enzyme-linked immunosorbent assay (ELISA), an Austrian Biovendor kit (osteocalcin ELISA is an enzyme immunological test) was used. The coefficients of in-group and out-group changes and osteocalcin sensitivity were 1.3% and 5.1% and 0.5 ng/mL, respectively. Alkaline phosphatase was measured by the photometric method using a kit (Pars Azmoun Company, Tehran, Iran) using an autoanalyzer (RA-100, Canada). The coefficients of in-group and out-group changes and measurement sensitivity for ALP were 1.06 and 0.85 and 3 international units per liter, respectively.

The Shapiro-Wilk test was used to ensure the normal distribution of data. The independent t test was used to compare data in pretest conditions between the 2 groups. After collecting data in response to the training and detraining programs, all variables were compared by analysis of variance (ANOVA), repeated measures test, and least significant difference post hoc test. Also, the paired t test was used to determine the in-group changes between the 2 conditions before and after the test in each group. All statistical analyses were performed using SPSS version 22 (SPSS Inc, Chicago, IL, USA). P values less than 0.05 were considered statistically significant.

Results

Based on the statistical findings of the independent t test, no significant difference was observed in the baseline levels of each of the biochemical variables between the control and experimental groups ($P < 0.05$).

Serum osteocalcin and ALP levels in each of the sampling steps in the groups are summarized in (Table 1). Considering the significant level of the interaction effect of time and group, it is concluded that detraining and endurance exercises do not affect the levels of osteocalcin ($F = 2.34$; $P = 0.132$) and ALP ($F = 3.068$; $P = 0.073$) in asthmatic patients. However, when the in-group changes were performed by the paired t test, the results showed that serum osteocalcin levels increased significantly in response to 10 weeks of aerobic exercise in the experimental group ($P = 0.028$), while there was no significant change in the control group. ($P = 0.352$).

Table 1. Levels of Osteocalcin and Alkaline phosphatase in each of the sampling stages in the 2 groups

Variable	Alkaline phosphatase (IU/L)		Osteocalcin (ng/mL)	
	Control group	Experimental group	Control group	Experimental group
Pretest	50 \pm 238	41 \pm 236	2.82 \pm 29.4	3.54 \pm 28.9
Posttest	42 \pm 232	44 \pm 250	2.90 \pm 29.1	2.62 \pm 31.1
Detraining	38 \pm 227	52 \pm 242	3.35 \pm 28.3	3.61 \pm 28.6

Also, when the in-group changes of ALP were performed by the correlated test, the results showed that the levels of ALP increased significantly in response to 10 weeks of aerobic exercise in the experimental group ($P = 0.033$), while there was no significant change in the control group ($P = 0.441$).

These findings suggest that although 10 weeks of aerobic exercise leads to an increase in serum osteocalcin and ALP in asthmatic patients treated with inhaled corticosteroids, its levels after 3 weeks of detraining return to pre-exercise conditions.

Discussion

The findings of the present study indicate the beneficial effects of aerobic exercise on bone formation indices in asthmatic patients. Ten weeks of endurance exercise with 3 sessions per week led to a significant increase in serum osteocalcin and ALP as 2 indicators of bone formation in asthmatic patients. Although the response of osteocalcin or other markers that determine bone density or formation to exercise has been less studied in asthma patients, their response in some other healthy or sick populations to various exercise programs has been reported many times. The findings are more or less contradictory and heterogeneous. Tartibian et al (2009) reported an increase in parathyroid hormone and ALP after 9 weeks of aerobic exercise (26). Zargar et al (2016) reported a significant increase in ALP after 12 weeks of aerobic exercise in obese adult men (27). Contrary to these findings, Alev et al (2013) reported that 2 months of sub-maximal aerobic exercise did not alter serum ALP levels in inactive women compared with controls (17). In the study by Akgül et al, a period of swimming training did not result in a change in bone density, osteocalcin, and ALP in swimmers aged 10 to 22 years (28). Although these findings have been reported in non-asthmatic populations, they are somewhat consistent with the findings of the present study. In general, the contradictory findings of studies examining the effects of exercise on bone metabolism suggest that several factors, including the type of exercise (such as weight bearing), age, sex, genetic characteristics, nutrition, and hormonal status, mediate the effects of exercise on skeletal tissue (29). Based on scientific evidence, the type of activity is one of the most important factors that can affect the response of biomarkers of bone formation and reabsorption to exercise (30,31). According to the Wolf law, the process of bone regeneration depends directly on the mechanical pressures on the bone (32). Accordingly, due to the mechanical stresses of weight-bearing activities, participation in such activities can lead to improved levels of bone biochemical markers, while these osteogenic adaptations do not occur with non-weight-bearing exercises, such as swimming (33). The mechanisms by which exercise can alter bone metabolism are not fully understood. However, some regulators of bone metabolism, such as osteoprotegerin (OPG) as an inhibitor of osteoclast production and receptor activator of NF- κ B ligand (RANKL) as the strongest stimulator of osteoclastogenesis, may play a key role (34). It has been suggested that mechanical stresses on the bone may have a direct effect on osteoblasts and an indirect effect on osteoclasts. Indirect osteoclast response increases OPG expression and decreases RANKL expression, which in turn leads to a decrease in the number of osteoclasts (35).

In the present study investigating the potential impact of long-term corticosteroid use on bone metabolism, it was observed that serum osteocalcin levels were not significantly affected by aerobic exercise in patients using inhaled corticosteroids. This is because inhaled corticosteroids enter the bloodstream and have some negligible side effects, though they are the most effective and available drug intervention to control asthma (36). Inhibition of airway inflammation by corticosteroids reduces airway hyperresponsiveness and controls asthma symptoms. Glucocorticoids penetrate the cytoplasm through the cell membrane and bind to their receptors in the cytoplasm (37). There is only 1 form of corticosteroid receptor called GR α that accepts glucocorticoids in the cytoplasm. Their entry into the airways activates or inhibits some genes associated with asthma due to their function (38). However, using high doses over long periods of time has adverse systemic effects, including bone diseases, such as rachitism, osteoporosis, and bone necrosis. Corticoids have destructive effects on the function and survival of osteoblasts and osteocytes and the maintenance or prolongation of osteoclasts associated with metabolic bone disease. Osteoporosis caused by corticosteroids is associated with some abnormalities, such as fractures of the spine and neck of the femur (39). Glucocorticoids reduce the process of osteoblastogenesis, increase osteoblast cell death, and decrease their ability to form bone (40,41). In summary, there is evidence of impaired bone metabolism and osteoporosis following long-term use of inhaled steroids, especially in asthmatic patients. On the other hand, despite some contradictory evidence, the review of evidence points to some kind of effectiveness of exercise on the process of bone formation or improvement of bone metastasis markers in healthy or sick populations. Some of them have also supported the beneficial effects of exercise in this regard on asthmatic patients. Unfortunately, there is currently no study available that directly addresses the question of whether the effectiveness of inhaled corticosteroids persists after discontinuing exercise in asthmatic patients. The duration for which the effectiveness can be maintained remains unknown. However, the findings of the present study indicated the instability of the effectiveness of aerobic exercise after 3 weeks of detraining. In other words, regular and continuous aerobic exercise leads to increased serum osteocalcin and ALP levels in asthmatic men, but after 3 weeks of detraining, it returns to pre-exercise conditions. This

evidence has not been reported in asthmatic patients but in some healthy populations or other patients by other researchers

Conclusion

Relatively long-term aerobic exercise leads to the improvement of bone formation markers in asthmatic patients treated with inhaled corticosteroids, but the effectiveness of these exercises will disappear after a relatively short period of detraining. This evidence emphasizes that aerobic exercise should not be discontinued to improve bone metabolism in asthmatic patients treated with inhaled corticosteroids.

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Ethical statement

The present study is taken from the master's thesis approved by the Islamic Azad University of Qaemshahr. Written informed consent was taken from all participants, and the study received approval from ethics committee (Code: 10721435972006).

Conflicts of interest

The authors declare that there is no conflict of interest.

Author contributions

The contributions of the authors have been the same.

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