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The effect of chronic exercise on a biomarker of bone resorption in healthy adults

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A – Study Design, **B** – Data Collection, **C** – Statistical Analysis, **D** – Data Interpretation, **E** – Manuscript Preparation, **F** – Literature Search, **G** – Funds Collection

Summary **Background.** Long-term exercise contributes to the inhibition of osteoblast cell activity and to the decrease of bone resorption.

Objectives. The research objective was to analyze the chronic effect of regular, long-term physical activity and physical inactivity on carboxyterminal collagen cross-linking telopeptide levels (CTx) and calcium levels in healthy adults.

Material and methods. This study was a prospective cohort study. Fifty-four men and women, aged 17–26 years, were divided into 2 groups of 27 people each: exercise and non-exercise. This research was carried out from April 2015 to April 2016 at the Faculty of Medicine, Syiah Kuala University, Aceh, Indonesia. Bone resorption can be determined by measuring the carboxyterminal cross-linking telopeptide of collagen (CTx). The data were analyzed using Student's *t*-test and regression correlation analysis with a significance level of 5%.

Results. The highest levels of CTx were found in the non-exercise group; the lowest levels of CTx were in the exercise group (1.6 ng/mL and 0.30 ng/mL, respectively). This difference in CTx levels between groups was statistically significant (0.52 ± 0.22 ng/mL vs 0.72 ± 0.28 ng/mL; $p = 0.005$). Calcium was significantly higher in the exercise group than in the non-exercise one (9.67 ± 0.30 vs 9.01 ± 0.21 mg/dl; $p = 0.006$). There was a negative correlation between calcium levels and CTx in the exercise group ($r = 0.038$; $p = 0.001$).

Conclusions. Regular exercise led to lower CTx levels and increased calcium levels. The increase in calcium is an effect of the decrease in CTx in healthy adults. Regular exercise decreases bone resorption and increases bone calcium deposition in healthy adults. Regular exercise has the potential to prevent and treat osteoporosis non-pharmacologically.

Key words: exercise, calcium, bone resorption, adult.

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Background

Physical exercise plays a role in bone turnover and in the prevention of osteoporosis [1, 2]. Long-term physical inactivity is a risk factor for osteoporosis [3–5], a chronic bone disease characterized by a reduction in bone mass, the progressive destruction of bone tissue microstructure and, in consequence, a high risk of fracture [6, 7]. Osteoporosis occurs due to bone turnover disorders in the process of bone remodeling [8–10]. Bone resorption is performed by osteoclasts, while bone formation is performed by osteoblasts [11–14]. In osteoporosis, bone resorption is higher than bone formation [15, 16]. Bone formation and resorption are simultaneous during bone tissue remodeling [14, 17, 18–20]. The process of remodeling takes place continuously throughout the life of a human being [10, 14, 19, 20]. Bone mass or bone density is influenced by the balance of bone resorption and formation processes from the activity of bone remodeling [9, 13, 18, 19]. Changes or disruptions in the bone remodeling process give rise to an imbalance between the resorption and bone formation processes [21–24], which form the basis for almost all metabolism disorders of the bone and the pathogenesis of osteoporosis [7, 25, 26].

Osteoporosis generally occurs in people over 50 years of age, but a sedentary lifestyle or physical inactivity is a trigger or a risk factor for osteoporosis in young adults, which is called premature osteoporosis [26, 27]. The process of bone loss in women is progressive, starting from the age of 30–40 years [28, 29]. The risk of osteoporosis is higher in women than in men: women are four times more at risk of osteoporosis than men [6, 30]. Epidemiological data show that 1 in 4 Indonesian women are at the risk of developing osteoporosis at the age of 50–80 years [31]. This is likely influenced by the physically inactive lifestyle of the population of Indonesia [31]. The Indonesian Minister of Health stated that the number of people who are physically inactive in Indonesia in 2013 was 26.1 percent of the total population [31].

Osteoporosis is associated with aging, but the presence of risk factors such as physical inactivity causes early-onset osteoporosis [26, 32–34]. Osteoporosis is characterized by a decrease in bone mineral density and an increase in bone resorption compared with bone formation [21]. Bone density decreases progressively and continuously throughout one's lifetime, and physical inactivity accelerates this decrease [8–10]. The level of bone resorption activity by osteoclasts can be measured by examining the levels of C-telopeptide (CTx) [35–38]. CTx level is a bone resorption biomarker and a marker of osteoclast cell activity [38, 39]. CTx levels can be measured using urine and blood serum samples [40]. CTx is one of the laboratory markers used to determine the risk of developing osteoporosis [39, 41]. We hypothesize that there is a long-term effect of physical activity on bone resorption; therefore, we studied the chronic effects of moderate-intensity physical activity (gymnastics) on bone resorption.

The risk factor of osteoporosis is lower in active people than in non-exercising or sedentary people [3, 26, 42–44]. Physical activity can stimulate the formation of bone by osteoblast cells and can inhibit bone resorption by osteoclast cells [44, 45]. Several scientific studies mention that the activity of osteoclasts and bone resorption is higher in people who exercise than in those who do not [1, 42, 43, 46, 47]. Increased bone resorption is characterized by elevated serum CTx levels, which is the primary focus of our research. Physical activity is also reported to induce osteogenesis and stimulate osteoblast cell activity, thereby increasing bone quality [5, 48]. Therefore, we examined calcium levels in order to correlate them with CTx levels in groups of exercising and non-exercising subjects. Physical activity or exercise such as playing football can increase bone density in men aged 35–40 years and in women aged 35–40 years [49–51].

Objectives

The aim of this study was to analyze the relationship between CTx and calcium levels in exercising and non-exercising people. This study can be used as a baseline for further research to ensure that the exercise as a non-pharmacological therapy for osteoporosis.

Materials and methods

Study design

This study was an observational study using a prospective cohort. The examination of CTx levels and blood calcium levels was done once (after 10 months of gymnastics). It was conducted from April 2015 to April 2016 at the Faculty of Medicine, Syiah Kuala University, Aceh, Indonesia. This study was a preliminary study and the data were collected in a database for further research. Total population sampling was used.

Participants

This study used two groups of participants: non-professional athlete volunteers for the experimental group (exercise group) and sedentary volunteers as a control group (non-exercise group). The experimental group was given exercise as a treatment. The research participants were healthy men and women, 18–26 years old, who did not take calcium or vitamin D supplements, did not have a high-calcium diet, were non-smokers and did not drink alcohol or coffee. The total number of subjects was 54 people, divided into 2 groups, namely: the exercise group (n = 27; men, n = 18 and women, n = 9) and the non-exercise group (n = 27; men, n = 10 and women, n = 17). The non-exercise group criteria were no regular physical activity for more than 6 months.

Aerobic exercise

The subjects in the experimental group were given aerobic exercise (gymnastics), a frequency of 2 times per week, a duration of 30–60 minutes per time, for a period of 10 months. The gymnastics were performed from April 2015 until February 2016. All participants followed the study protocol to complete the study and none of them withdrew or dropped out of the study. Aerobic exercise (gymnastics) was performed every Wednesday and Sunday morning starting at 08.00–09.00 a.m. The physical exercise program consisted of (1) a warm-up for 5–10 minutes by marching, (2) core aerobic exercise for 40 minutes and (3) a cool-down for 5–10 minutes. The subjects were tested for bone resorption after 10 months of the gymnastics program. The examination consisted of measuring the levels of calcium and CTx.

Laboratory tests

The measurement of calcium and carboxyterminal cross-linking telopeptide collagen (CTx) levels was performed using serum blood samples. The measurement of serum calcium levels and blood CTx levels were performed one time at the end of the exercise intervention. Calcium levels were measured using the O-cresolphthalein complexone method. The measurement of CTx was performed by the electrochemiluminescence immunoassay (ECLIA) method using a Cobas–Roche reagent.

Ethical consideration

The treatment in this study was approved by the medical and health ethics committee of the Faculty of Medicine, Syiah Kuala University (304/KE/FK/2015). All volunteer participants signed a written informed consent form.

Statistical analysis

The data are presented as averages with standard deviation (mean ± SD). Statistical analysis was done using Statistical Product and Service Solutions (SPSS) 16.0 software for Windows. Data analysis was carried out using the Mann–Whitney test, independent sample t-test and simple linear regression test. A significance level of 5% was used. The Mann–Whitney test was done in order to compare the characteristics of the participants between the exercise and non-exercise groups. The unpaired t-test analysis was used to compare differences in calcium and CTx levels between the 2 study groups and to compare the effect of exercise or no exercise on bone resorption. The simple linear regression test was performed to analyze the relationship between calcium level and CTx level among the 2 groups.

Results

Subject characteristics

The sample size calculation is based on total population sampling. The sample size for the non-exercise group consisted of the entire nursing student class of 2015. The sample size for the exercise group was composed entirely of non-professional athletes in the Syiah Kuala University dormitories. All athletes were willing to volunteer as research subjects. The total study population of 54 people consisted of 27 people in the exercise group (male, n = 18 and female, n = 9) and 27 people in the non-exercise group (male, n = 10 and female, n = 17). An overview of the participants' characteristics, including age (years), body weight (kg), height (cm^2), Body Mass Index (BMI = kg/cm^2) and blood pressure (mm Hg) are presented in Table 1. As seen in Table 1, there were significant differences in BMI between the males and females in the exercise group ($p < 0.05$).

Table 1. Characteristics of participants in both groups

	Group	Gender		p
		Male	Female	
Age (years)	exercise	24.39 ± 3.05	23.56 ± 3.00	0.71
	non-exercise	18.80 ± 0.42	18.71 ± 0.47	0.28
Weight (kg)	exercise	60.28 ± 6.54	57.56 ± 7.16	0.35
	non-exercise	59.60 ± 6.09	52.52 ± 9.18	0.88
Height (cm^2)	exercise	168.52 ± 158.77	158.77 ± 2.27	0.09
	non-exercise	164.50 ± 2.59	153.71 ± 2.26	0.98

Table 1. Characteristics of participants in both groups				
	Group	Gender		p
		Male	Female	
BMI (kg/cm^2)	exercise	21.19 ± 1.76	22.87 ± 3.19	0.001*
	non-exercise	22.08 ± 2.78	22.21 ± 3.61	0.92
Systolic (mm Hg)	exercise	120.11 ± 7.18	119.11 ± 7.18	0.57
	non-exercise	100 ± 9.42	108 ± 10.74	0.94
Diastolic (mm Hg)	exercise	80.17 ± 4.71	79.44 ± 3.90	0.40
	non-exercise	69.00 ± 7.37	74.71 ± 7.17	0.59

* Significant at the level of 5% ($p < 0.05$).

Comparison of calcium and C-telopeptide (CTx) levels in the 2 groups

The highest levels of calcium were found in the exercise group (10.60 mg/dL), whereas the lowest levels of calcium were found in the non-exercise group (0.31 mg/dL). Figure 1 shows that as many as 74.07% (20 people) of the non-exercise group had hypocalcemia and the remaining 25.93% (7 people) had normal calcium levels; there was no hypocalcemia in the exercise group. All of the exercise subgroups had normal calcium levels, defined as 9.2–10.6 mg/dL.

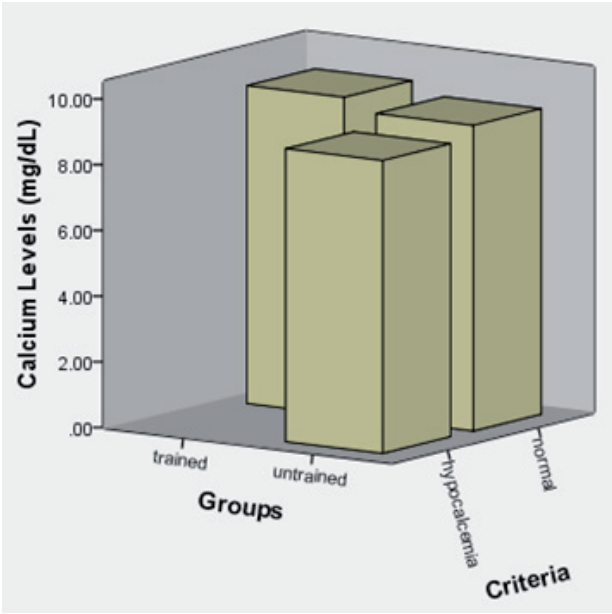

Figure 1. The number of hypocalcemic patients in the exercise and non-exercise groups

The lowest levels of CTx were in the exercise group (0.30 ng/mL), whereas the highest levels of CTx were in the non-exercise group (1.66 ng/mL). A normal CTx level is < 0.573 ng/mL and a CTx level of ≥ 0.573 ng/mL is considered a risk. Figure 2 shows that the number of subjects with normal levels of CTx among the exercise group was higher (55.55%) than the non-exercise group (29.63%). There were more subjects with CTx levels in the risk category in the non-exercise group (70.37%) than in the exercise group (44.55%). This study shows that regular physical activity of a moderate intensity can reduce bone resorption, which may prevent or reduce the risk of premature osteoporosis.

Table 2 shows that the mean serum calcium levels were significantly higher in the exercise group than in the non-exercise group ($p < 0.05$). We found that the mean levels of CTx were significantly lower in the exercise group than in the non-exercise group ($p < 0.05$). There was a significant difference in calcium and CTx levels among the 2 groups ($p < 0.05$). We also found that the rate of bone resorption was higher in the non-exercise group than in the exercise group. These results indicate that moderate-intensity exercise (gymnastics) inhibits bone resorption and that exercise has the potential for a preventative and therapeutic effect of osteoporosis. Analysis of the independent sample *t*-test found that there were significant differences between serum CTx levels and calcium levels in the 2 study groups ($p < 0.05$).

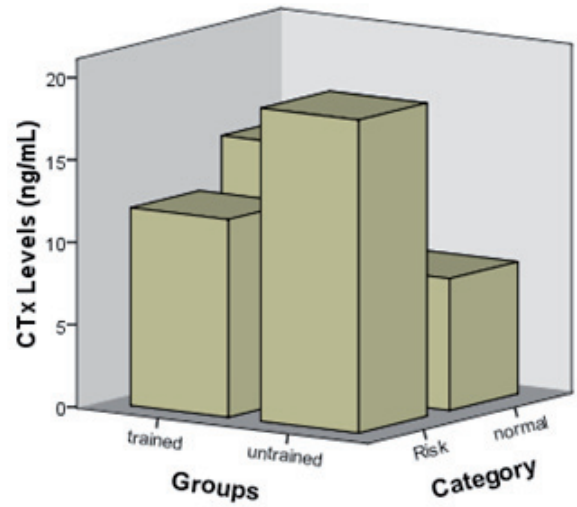

Figure 2. The category of serum CTx levels in the 2 study groups

Table 2. Differences in calcium levels and CTx levels among the 2 study groups			
	Exercise	Non-exercise	p
Calcium	9.674 ± 0.30	9.014 ± 0.21	0.006*
CTx	0.529 ± 0.22	0.727 ± 0.28	0.001**

* Significant at the level of 5% ($p < 0.05$).

The relationship between calcium and C-telopeptide (CTx) in the study groups

Figure 3 shows that there was a negative correlation between calcium level and CTx level in the exercise group ($r = 0.051$ and $p = 0.001$). These results indicate that serum CTx level is inversely related with serum calcium levels, which means that elevated CTx levels will cause a decrease in calcium in people who do little exercise or that an increased calcium level will lead to decreased levels of CTX in active people.

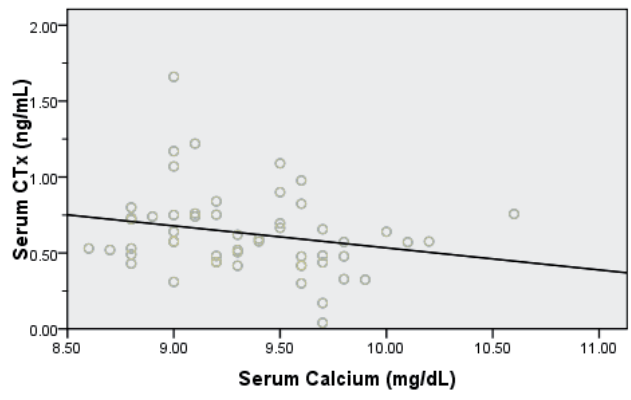

Figure 3. Scatter plot of the correlation between serum calcium level and CTx level in the exercise group

Discussion

The level of carboxyterminal collagen cross-linking telopeptide (CTx) is one of the laboratory tests used to measure bone resorption and to predict the risk of osteoporosis [37, 39, 41, 52–54]. The CTx molecule consists of four isoforms, namely: the native a-L isoform, the b-L isoform – also known as CrossLaps – the a-D isoform and the b-d isoform. CTX levels are measured from a sample of urine (isoforms a and b) or serum (isoform b only) [11, 55, 56]. CTx level provides an overview of the activity of osteoclasts and is a biomarker for bone resorption [55]. Measurement of CTx level is also one way to detect the process of bone loss early on [37, 39, 41, 52–54]. CTx is the result of the decomposition of bone collagen that is released into the circulation. Examination of CTx level is a very specific method for assessing the cellular response of bone loss rates [17, 57]. CTx levels are also useful for monitoring the use of oral antiresorption drugs in osteoporosis patients. The measurement of CTx levels is performed using a sample of urine or blood serum [11, 58, 59]. CTx levels are influenced by circadian rhythms and are higher in the morning [37, 53, 54, 60].

In this study, we found that regular exercise decreases CTx levels and inhibits bone resorption by osteoclasts. Regular exercise increases serum calcium levels [43]. Physical inactivity or a sedentary lifestyle increase the levels of CTx and reduce the calcium deposits in bone [24, 61–64]. These results suggest that physical inactivity increases bone resorption and increases the risk factor for osteoporosis. Physical inactivity is a risk factor for early-onset osteoporosis [6, 7, 65, 66]. This study strengthens the scientific grounds for the use of exercise as a non-pharmacological therapy for patients with osteoporosis. Exercise also prevents premature osteoporosis and is a therapy for osteoporosis.

Calcium homeostasis is affected by exercise intensity [67, 68]. Strenuous exercise, such as an ultramarathon, affects calcium metabolism through a significant reduction of urine calcium for the 3 days following a race [69]. Calcium is the important mineral needed in order to inhibit collagen breakdown [25, 67, 70]. Long-term strenuous exercise triggers an increase in the hormone paratyroid and CTx [71]. Ingesting a high-calcium supplement prevents the increase of CTX in athletes who exercise strenuously. This study was a preliminary study that is useful for providing scientific evidence of the long-term effects of physical exercise on bone formation and bone resorption. Research shows that physical activity has a positive impact on bone resorption [72]. Moderate-intensity exercise is beneficial for bone resorption because it can support homeostasis between the production of osteoclastogenic cytokines and antiosteoclastogenic cytokines [72]. Research in sedentary women has shown that the bone density level of the tibia increased by about 2–3% after 14 weeks of football therapy (football performed 1 hour per session, 2 times per week) [73]. A study found that swimming is beneficial to bone health because it increases bone turnover, strength and bone structure compared to being sedentary [74]. A longitudinal study showed that school-aged children who performed gymnastics for 8–12 months showed an increase in bone density [75]. Research on elderly males found that playing recreational football (4 months) increased osteogenic activity, resulting in increased bone turnover and anabolic effects which eventually resulted in increased bone formation [76].

The intensity of exercise also affected the rate of bone resorption [77]. High-intensity exercise and strenuous exercise causes more bone resorption and therefore has the potential to decrease bone density and cause osteoporosis in athletes [77]. Markers of bone turnover and bone mass in the feet of sedentary middle-aged women who played football (15 weeks) increased after the intervention; therefore, football stimulates the osteogenic process, while high-intensity swimming did not change the levels of bone formation and absorption [78]. Resistance training regularly has the effect of reducing serum CTx levels in older adults [1]. Women who perform strenuous, intense exercise showed an increase in serum CTx levels compared with control patients [79]. A clinical trial of 50 premenopausal women showed that submaximal-intensity aerobic exercise for 2 months decreased serum CTx levels and decreased bone resorption [46].

The impact of physical activity on bone resorption differs between acute effects and chronic effects. Welsh et al. studied the short-term influence of moderate-intensity exercise on bone resorption [80]. They found that markers of bone resorption increased after 32 hours of running on a treadmill for 30 minutes with an intensity of 60% of maximum heart rate in sedentary males aged 20–35 years [80]. Herrmann et al. found that CTx levels increased after anaerobic exercise in men, but there was no change in women. A study in 25 female athletes doing endurance exercises found that their CTx levels were higher than those of the controls [79]. Serum CTx was also higher in a group of runners than in rowers, swimmers or a control group [81].

Eliakim et al. examined the effect of chronic physical exercise on bone resorption in 44 boys aged 15–17 years [82]. The 44 boys were divided into 2 groups (physical activity of 2 hours a day for 5 weeks, and physical inactivity) [82]. They found that there was a decrease in markers of bone resorption in the physical exercise group [82]. Woitge et al. mentioned that low bone resorption levels were characterized by a significant decrease in urine CTx after four weeks of continuous aerobic exercise in healthy sedentary men [83]. Mohr et al. found no change in bone formation and resorption and found that CTx was unchanged after intermittent, long-term swimming at submaximal or high intensity for 15 weeks, but there was an increase in bone turnover markers after football training for 15 weeks in sedentary middle-aged women [78]. Solarz et al. examined 50 professional football players and physically inactive men and found no differences in CTx levels between the groups [84].

Limitations of the study

There were some limitations of the study, including the small sample size and the imbalance between males and females, and the fact that calcium and CTx levels were measured only once (after intervention). Calcium and CTx levels should be examined before and after intervention in both groups.

Conclusions

In conclusion, long-term aerobic exercise increases serum calcium levels and lowers CTx levels in healthy young adults. There was a negative correlation between calcium and CTx levels in the exercise group. There was an increase in serum calcium levels, which will cause a decrease in CTx levels in the exercise group. Bone resorption is more active in the non-exercise group than in healthy, exercising adults. Physical activity acts as a preventative measure of early-onset osteoporosis in young adults.

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Tables: 2
Figures: 3
References: 84

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