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THE THERAPEUTIC POTENTIAL OF FRESH GOAT's MILK AGAINST PREMATURE OSTEOPOROSIS BY INHIBITING OF BIOMARKERS OF BONE RESORPTION IN UNTRAINED HEALTHY WOMEN

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ABSTRACT: The aim of this study was to (1) analyze the effect of fresh goat's milk intervention on serum Carboxyterminal Cross-Linked Telopeptide of type I Collagen (CTX) and calcium in untrained healthy women, therefore goat milk can be used for osteoporosis therapy, (2) examined the relationship between levels of calcium and CTX after the intervention of fresh goat's milk. The research design was a controlled randomized trial. Eighteen volunteers sedentary women were randomized into 2 equal groups (control, n=9, and trial, n=9), aged 18-19 years, healthy, and did not consume high calcium foods or drugs. The treatment group was treated with 250 ml/day of fresh goat's milk, given in the morning, for 110 days. Fasting morning serum calcium and CTX levels were measured before and after fresh goat milk intervention. The data were analyzed by the statistical t-test and linear correlation with the significance level of 5%. Untreated, both serum calcium and CTX levels in the trial and control group were not significantly different ($p>0.05$). Treated, serum calcium levels were higher ($p<0.05$) in the trial group than the control group. Serum CTX levels were lower ($p<0.05$) in the trial group than in the control group. There was a significant increase in calcium levels and the significant decrease of CTX levels after-treated in the trial group. Goat milk affects inhibiting the process of bone resorption in untrained healthy women.

INTRODUCTION: Physical inactivity or sedentary lifestyle has a role in the etiology and pathology of osteoporosis [1-3]. Increasing numbers of people with the sedentary lifestyle or physical inactivity significantly cause an increase in the population with chronic disease [1-3]. According to data from the Ministry of Health Republic of Indonesia in 2013, the number of population with physical inactivity in Indonesia is about 26.1 percent and the sedentary lifestyle (sitting time 3-5.9 hours per day) is 42% [4].

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The population with physical inactivity in Aceh, Indonesia is about 37.2% [4]. Physical inactivity causes about 10.3% of premature deaths and contributed about 18% as a cause of osteoporosis in Canada [5]. Osteoporosis is a silent disease that has a significant impact on the socio-economic and quality of life of patients and their families as well as government [6].

Osteoporosis is a metabolite bone disease characterized by changes in the microarchitecture of bone tissue and decreases of bone mass resulting in low levels of bone density, fragile and fractures [6-8]. The etiology of osteoporosis is very complex such as multiple genetic, hormonal, drugs, sedentary lifestyle and nutritional factors (chronic hypocalcemia) [6, 7]. An imbalance of bone remodeling causes osteoporosis, an imbalance

between the process of bone formation by osteoblasts and bone resorption by osteoclasts [1]. Abnormalities of bone turnover which is a process of bone resorption are higher than bone formation results in the onset of osteoporosis [6-9]. The increase of the activity of osteoclasts is lead to an increase of bone resorption [6-9]. Increased bone resorption results in disruption of the microarchitecture of the bone tissue and therefore not only the occurrence of Bone loss but also decreases the level of bone density [6-9]. Markers of bone resorption can be determined by analyzing the levels of Carboxyterminal Cross-Linked Telopeptide Collagen (CTX) [10-11]. CTX levels are elevated in patients with osteoporosis [10].

The process of bone remodeling is influenced by many factors including hormonal, mechanical stimulation, disease, and nutrition [9-11]. The balance between bone formation and resorption is regulated and influenced by a complex system such as cytokines, growth factors, sex hormones, and calcium [10, 11]. Chronic calcium deficiency is a risk factor for osteoporosis [12]. Consumption of 1200 mg of calcium daily may decrease the incidence of vertebral fractures in women with low calcium intakes [12]. Bone remodeling markers are influenced by diurnal variation and calcium intake [13].

Goat milk contains high calcium [14-15,] and it is expected to play a role in preventing and controlling osteoporosis through decreased bone resorption marker, CTX. How the effect of goat milk consumption to prevent osteoporosis by inhibiting bone resorption remains unexamined, therefore we conducted a study to analyze the effect of goat milk consumption on CTX levels and its association with serum calcium levels in untrained healthy women.

MATERIALS AND METHODS:

Participants: The design of this study was a controlled randomized trial. Participants were 18 untrained healthy women, aged 18-19 years. The inclusion criteria were healthy, not physical exercise regularly (exercise less than twice per week), not drinking coffee, not drinking alcohol, not smoking, non-calcium supplements, not taking vitamin D supplements, not consuming goat's milk or cow's milk regularly, not undergoing hormonal therapy. Exclusion criteria were injured, osteoporosis or other bone diseases. The subjects were randomized into two equal groups (the control group, n=9, and the trial group, n=9).

Treatment and Laboratory Procedures: The trial group was treated with 250 ml of fresh goat milk, given every morning, and given for 110 days. Fresh goat milk was tested for safety levels to consume. The examination of calcium and CTX levels is performed before and after therapy. Fasting serum calcium levels was measured using the O-cresolphthalein complex one method. Normal serum calcium levels are 9.2-11.0 mg/dL (age 5-20 years). Fasting serum CTX level was measured using Electrochemiluminescence Immunoassay (ECLIA) method. Normal serum CTX level is 0.016-0.584 ng/mL.

Statistical Analysis: The statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) Version 16.0 Chicago, IL., USA). The data was using t-test with a significance level of 5%. Independent sample t-test ($p<0.05$) was conducted to analyze the differences in the levels of calcium and CTX before and after treated in each group. Analysis of paired sample t-test was performed to determine differences in the levels of calcium and CTX before and after treated between the two groups.

Ethical Approval: The Research Ethics Committee approved the implementation of this research, Faculty of Medicine, Syiah Kuala University, Banda, Aceh, Indonesia with the letter number is 304/KE/FK/2015. All participants were volunteers and signed a written informed consent.

RESULTS:

Participants Characteristics: Characteristics of participants such as anthropometric and blood pressure as shown in **Table 1**. There was no difference in age, weight, height, Body Mass Index (BMI), systolic and diastolic between the control and trial groups.

Differences of Serum Calcium and CTX Levels between Control and Trial Groups: Table 2 shows that there was no significant difference in serum calcium levels before therapy (untreated, $p=0.07$) and after therapy (treated, $p=0.36$) between the two groups.

This study also showed that there was no significant difference (p=0.08) of serum CTX levels untreated between the two groups. We observed a significant difference (p=0.01) of serum CTX levels after therapy between the two groups. These results indicate that there is a significant decrease in serum CTX levels after regular consumption of fresh goat milk.

The Effects of Fresh Goat Milk Intervention on Calcium and Carboxyterminal Cross-Linked Telopeptide Collagen (CTX) in the Control and Trial Groups: Table 3, showed that the average serum calcium levels increased significantly in the trial group (p=0.00), whereas serum CTX levels decreased significantly (p=0.00), after the intervention with fresh goat's milk. Unlike the control group, the average value of the serum calcium level was not increased significantly (p=0.06), as well as the average of CTX levels also did not change (p=0.16) after the intervention period. This study suggests that regular consumption of fresh goat milk increases calcium levels and decrease CTX levels in untrained healthy women.

TABLE 1: SAMPLE CHARACTERISTICS BETWEEN THE CONTROL AND TRIAL GROUPS

Characteristics	Groups	n	Mean ± SD	p-value
Age (year)	Control	9	18.77 ± 0.44	1.000
	Trial	9	18.78 ± 0.44	
Weight (kg)	Control	9	57.05 ± 1.02	0.254
	Trial	9	51.78 ± 8.60	
Height (cm2)	Control	9	154.11 ± 2.66	0.863
	Trial	9	154.33 ± 2.69	
BMI (kg/cm2)	Control	9	23.99 ± 3.93	0.257
	Trial	9	21.80 ± 3.98	
Systolic (mmHg)	Control	9	112.22 ± 9.71	0.250
	Trial	9	101.11 ± 9.28	
Diastolic (mmHg)	Control	9	75.56 ± 5.27	0.077
	Trial	9	70.00 ± 7.07	

* Significance at the level of error of 5% (p<0.05).

TABLE 2: DIFFERENCES IN CALCIUM AND CTX LEVELS BEFORE AND AFTER THERAPY BETWEEN THE CONTROL GROUP AND TRIAL

Variable	Data	Group	n	Mean ± SD	t-test	p-value
Calcium (mg/dl)	Untreated	Control	9	9.08 ± 0.20	1.91	0.073
		Trial	9	8.91 ± 0.18		
	Treated	Control	9	9.26 ± 0.43	0.92	0.367
		Trial	9	9.40 ± 0.32		
CTX (ng/mL)	Untreated	Control	9	0.78 ± 0.34	1.85	0.082
		Trial	9	0.55 ± 0.15		
	Treated	Control	9	0.69 ± 0.18	2.77	0.001*
		Trial	9	0.35 ± 0.16		

* Significance at the level of error of 5% (p<0.05).

TABLE 3: THE EFFECT OF FRESH GOAT MILK THERAPY ON CALCIUM AND CTX LEVELS IN THE CONTROL AND TRIAL GROUPS

Variable	Group	Group	n	Mean ± SD	t-test	p-value
Calcium (mg/dl)	Control	Untreated	9	9.08 ± 0.20	3.87	0.060
		Treated	9	9.26 ± 0.43		
	Trial	Untreated	9	8.91 ± 0.18	4.85	0.001*
		Treated	9	9.40 ± 0.32		
CTX (ng/mL)	Control	Untreated	9	0.78 ± 0.34	1.51	0.168
		Treated	9	0.69 ± 0.18		
	Trial	Untreated	9	0.55 ± 0.15	4.02	0.004*
		Treated	9	0.35 ± 0.16		

* Significance at the level of error of 5% (p<0.05).

DISCUSSION: The results of this study indicate that regular goat milk consumption increases serum calcium levels and decreases CTX levels. Therefore goat milk is useful for reducing bone

resorption in untrained healthy women. Bone metabolism occurs continuously, balanced between growth and bone resorption [16, 18]. Bone metabolism activity is known by examination of bone turnover markers (BTM) [16-18]. BTM is a biomarker of bone formation or osteoblastic activity and biomarkers of bone resorption or osteoclastogenesis [16-18]. Bone formation markers are C-terminal propeptide of type-I procollagen (PICP), the bone alkaline phosphatase (BSAP), and osteocalcin (OC), the N-terminal propeptide (PINP). Markers of the bone resorption of the C-terminal telopeptide (CTX), the N-terminal telopeptide (NTX), pyridinoline (PYD) and deoxypyridinoline (DPD), and matrix-metalloproteases (MMP) -generated (CTXMMP or ICTP) type I collagen Fragments, tartrate-resistant acid phosphatase 5b isoform (TRAP-5b) is an enzyme secreted by the osteoclasts, namely, receptor activator of nuclear factor NF-κB ligand (RANKL), an osteoclast regulatory proteins produced by osteocytes, osteoblasts, and immune system cells [16-18].

Calcium plays a role in the process of bone formation [19-20]. Chronic calcium and vitamin D deficiency is the risk factor for osteoporosis [19-20]. Osteoporosis results in decreased bone mass and strength [19-20]. The cause of decreased mass and bone strength is the failure to reach the peak of bone mass growth, excessive bone resorption by osteoclast, and bone formation disorders by osteoblasts [19-20]. Osteoporosis usually occurs in the menopause women, but some risk factors such as the physical inactivity or sedentary lifestyle, lack of exposure to sunlight and low intake of calcium induce premature osteoporosis in young women [6, 7].

Consuming high of calcium and vitamin D foods is preventing premature osteoporosis [18-21]. Goat milk contains high calcium and vitamin D [14, 15, 22-24]. Calcium plays a role in maintaining the strength and density of bone [19-21]. The consumption of goat's cheese is more to increase the cortical bone mass when compared with the consumption of calcium tablets in the same dose [24]. Goat milk contains medium-chain triglycerides (MCT), an important factor that plays a role in the absorption of calcium and phosphorus [23-24]. A study has shown that milk consumption decreases of CTX levels in metabolic syndrome women [25]. Our study also found that consumption of fresh goat milk regularly was decreased CTX levels in sedentary healthy women. How the mechanism of goat's milk in increasing serum calcium levels and lowering CTX levels is still not fully understood. We are continuing this research.

CONCLUSION: We conclude that consuming fresh goat milk increases serum calcium levels and lowers serum CTX levels in untrained healthy women. Goat milk inhibits bone resorption; therefore it is useful for preventing and inhibiting osteoporosis.

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CONFLICT OF INTEREST: None of the authors declared conflicts of interest in this study.

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