

# The effect of raloxifene on left ventricular hypertrophy in postmenopausal women: A prospective, randomized, and controlled study

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## ABSTRACT

**Objective:** In healthy women, there is a progressive age-related increase in myocardial mass that is not seen in their male counterparts and occurs primarily in postmenopausal women. Raloxifene is a selective estrogen receptor modulator that has estrogenic actions on bone and the cardiovascular system. The aim of this study was to investigate the effect of raloxifene on myocardial hypertrophy in postmenopausal patients.

**Methods:** A total of 22 postmenopausal osteoporotic women were included in this open-label, randomized, prospective, controlled study. Patients were randomized into two groups: 11 of the patients (group 1) were treated with raloxifene 60 mg/day, and the other 11 patients (group 2) were defined as the control group. Quantitative 2-dimensional and M-mode echocardiographic examination was performed in all patients at the beginning and repeated at the end of the 6-month follow-up period. Left ventricle mass (LVM) and left ventricle mass index (LVMI) were calculated for all patients.

**Results:** The mean age of the patients was 57.2±3.9 years, and baseline clinical characteristics and echocardiographic parameters were similar between the two groups. After 6 months of raloxifene treatment, there was no difference in echocardiographic parameters of LVM and LVMI compared with the control group (201.2±25.9 gr vs. 169.7±46.2 gr, p=0.14 and 120.4±25.9 gr/m<sup>2</sup> vs. 105.5±26.3 gr/m<sup>2</sup>, p=0.195, respectively). There was also no significant difference in LVM and LVMI in the within-group analysis of both groups.

**Conclusion:** Raloxifene therapy does not affect myocardial hypertrophy in postmenopausal women after 6 months of treatment.

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**Keywords:** raloxifene, echocardiography, hormone replacement therapy, left ventricle mass, left ventricle hypertrophy

## Introduction

In postmenopausal women, left ventricular hypertrophy is common and is likely to be a strong cardiovascular risk factor compared with men, suggesting that estrogen has potential protective effects in the cardiovascular system (1). There are substantial gender differences in myocardial remodeling due to the influence of sex hormones. Left ventricular hypertrophy is associated with an increased risk of cardiovascular morbidity and mortality in women (1).

In the general population, there is a progressive age-related increase in myocardial mass in healthy women that is not seen in their male counterparts (2). These findings were confirmed in a healthy, non-obese, normotensive subset of the Framingham Heart Study (3). These studies demonstrate that the increase in myocardial mass occurs primarily in postmenopausal women.

Indeed, premenopausal women with essential hypertension have thinner posterior left ventricular walls, smaller left ventricular mass, and better cardiac function than age-matched men (4).

Elderly (postmenopausal) women with systolic hypertension or aortic stenosis have more concentric remodeling and better preserved left ventricular systolic function than their male counterparts both at rest and with exercise (5, 6). These data suggest that the female sex hormones estrogen and progesterone influence myocardial hypertrophy and myocardial remodeling by suppressing cardiac hypertrophy and preserving myocardial function.

Selective estrogen receptor modulators (SERMs) have been approved as hormone replacement therapy (HRT) to prevent osteoporosis and improve lipid profiles in postmenopausal women without producing uterine proliferation (7). Raloxifene is



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a second-generation SERM and exerts estrogen-agonistic effects on the cardiovascular system and bone (7). The beneficial effects of raloxifene on cardiovascular risks and events have been investigated in the MORE study, and it has been shown that raloxifene decreased the risk of cardiovascular events among the subset of 1035 women with increased cardiovascular risk at baseline, compared with placebo (8). However, in the RUTH study, raloxifene did not significantly affect the risk of coronary heart disease in patients with high risk for major coronary events based on established cardiovascular disease (9).

The knowledge about the effects of raloxifene on myocardial hypertrophy in postmenopausal women is scant in the literature, and we aimed to investigate the effect of raloxifene on myocardial hypertrophy in this study.

## Methods

This study was designed as a prospective-randomized-controlled study according to the CONSORT statement, and institutional review board approval was obtained from the Ethics Committee of Başkent University. Subjects were recruited from the Menopause Clinic of the Department of Obstetrics and Gynecology. All postmenopausal [at least 12 months elapsed from the last spontaneous menstrual bleeding, and each participant exhibited a serum follicle-stimulating hormone (FSH) level >40 U/L and an estradiol (E2) level <30 pg/mL] and osteoporotic [T-score for femoral neck or lumbar spine bone mineral density (BMD) measurements  $\leq 2.5$  standard deviation (SD) according to the results of dual-energy x-ray absorptiometry] women with endometrial thickness  $\leq 5$  mm in ultrasound imaging were evaluated for the study. Exclusion criteria were defined as: history of gynecologic malignancy, ischemic heart disease, heart failure, hypertrophic cardiomyopathy, aortic stenosis, thromboembolism, abnormal liver function, renal dysfunction, epilepsy, severe migraines, non-treated thyroid dysfunction, and patients treated with hormone therapy during the 3 months before the initiation of the study. A total of 22 postmenopausal osteoporotic women (age range, 51-70 years) were included in the study. A table of randomly generated numbers was used for randomization. Patients were randomized into two groups: group 1 (n: 11) was treated with raloxifene 60 mg/day, and group 2 (n: 11) was defined as the control group; all of the patients received 600 mg calcium daily + 400 IU vitamin D, an over-the-counter product. All subjects signed an informed consent form.

Hypertension was defined as systolic blood pressure  $\geq 140$  mm Hg, diastolic blood pressure  $\geq 90$  mm Hg, or both or the use of antihypertensive medication for the study purpose according to the 2013 guidelines of the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC) task force for the management of arterial hypertension (10). Diabetes was defined as fasting glucose level >126 mg on at least 2 occasions or current use of anti-diabetic agents (11). Patients who were currently smoking cigarettes were considered smokers. BMI

was calculated as weight (kilogram or kg) divided by height (meter or m) squared ( $\text{kg}/\text{m}^2$ ).

## Echocardiographic examination

All patients underwent an echocardiographic examination, including quantitative 2-dimensional and M-mode echocardiographic examination by means of an echocardiography unit with a 3.5-MHz transducer (Siemens Acuson Sequa c256, Munich, Germany). Echocardiograms were obtained by the same cardiologist after each patient was placed in the left lateral decubitus position. To reduce bias, the cardiologist was blinded to the patient groups. Measurements for M-mode-guided calculation of left ventricular mass (LVM) were taken in the parasternal short-axis view and were recorded at the papillary level. Left ventricular internal dimensions at end-diastole (LVIDd) and septal (SWTd) and posterior wall thickness at end-diastole (PWTd) were measured. LVM was calculated by the American Society of Echocardiography (ASE)-recommended formula (12)  $\text{LVM}(\text{g}) = 0.8 \times \{1.04 \times [(LVIDd + PWTd + SWTd)^3 - (LVIDd)^3] + 0.6$  and standardized to body size by dividing the raw LVM by body surface area as left ventricular mass index (LVMI). A second echocardiographic evaluation was conducted after the sixth month of the treatment, and all measurements were repeated.

## Statistical analysis

The statistical package SPSS (Statistical Package for the Social Sciences, version 17.0, SSPs Inc, Chicago, Ill, USA) was used for statistical analyses. Continuous variables are expressed as mean  $\pm$  SD. All continuous variables were checked with Kolmogorov-Smirnov normality test to show their distributions. Continuous variables with normal distributions were compared using the unpaired student t-test. Continuous variables with abnormal distributions were compared using the Mann-Whitney U test. The chi-square test was used for categorical variables. P values of less than .05 were considered statistically significant. Changes in the echocardiographic measurements from baseline to those recorded at the end of the sixth month of the study were evaluated by means of the paired-sample t-test.

## Results

The mean age of the two groups was  $57.8 \pm 4.5$  vs.  $56.6 \pm 3.4$  years ( $p=0.494$ ). Gravity and parity of the patients were not different between the groups ( $p=0.897$  and  $p=0.627$ , respectively). Baseline laboratory parameters and clinical features were similar in both groups (Table 1). All patients completed the follow-up period of 6 months.

The baseline echocardiographic parameters were similar, and ejection fraction was normal in both groups ( $p=0.835$ ). There was no significant within-group changes in echocardiographic parameters of LVM and LVMI at the end of the 6-month follow-up period in both groups (group 1:  $p=0.919$  and  $p=0.915$ , respectively; group 2:  $p=0.194$  and  $p=0.147$ , respectively). Also, these echocardiographic parameters (LVM and LVMI) did not differ

**Table 1. Baseline clinical characteristics and laboratory parameters of the groups**

Characteristics	Group 1 (n:11)	Group 2 (n:11)	P
Age, years	57.8±4.5	56.6±3.4	0.494
Diabetes mellitus, n (%)	2 (18.2)	0	0.138
Hypertension, n (%)	5 (45.5)	3 (27.3)	0.375
Smoking, n (%)	4 (36.4)	1 (9.1)	0.127
Gravida, n	3.0±1.6	2.9±1.6	0.897
Parity, n	1.5±0.7	1.7±1.0	0.627
BMI, (kg/m <sup>2</sup> )	25.1±2.5	24.8±2.4	0.817
Hemoglobin (g/dL)	13.5±1.2	13.7±1.4	0.819
Creatinine (mg/dL)	0.8±0.3	0.9±0.2	0.632
Total-C (mg/dL)	226.3±39.6	213.0±43.4	0.462
LDL-C (mg/dL)	144.4±28.6	132.8±33.7	0.392
HDL-C (mg/dL)	54.5±11.1	57.2±16.7	0.657
Triglyceride (mg/dL)	135.8±74.1	118.0±47.0	0.511
CRP	3.0±3.3	1.4±1.4	0.176
Antihypertensive therapy			
ACEI/ARB, n (%)	3 (27.3)	1 (9.1)	0.524
Beta-blocker, n (%)	4 (36.4)	2 (9.1)	0.635
CCB, n (%)	1 (9.1)	1 (9.1)	0.524
<small>ACEI - angiotensin-converting enzyme inhibitor; ARB - angiotensin receptor blocker; BMI - body mass index; CCB - calcium channel blocker; CRP - C-reactive protein; HDL-C - high-density lipoprotein cholesterol; LDL-C - low-density lipoprotein cholesterol; Total-C - total cholesterol. Independent t-test and Mann-Whitney U-test for baseline characteristics. Parametric values given as mean±standard deviation</small>			

between the raloxifene group compared with control group at baseline and the 6<sup>th</sup> month ( $p=0.14$  and  $p=0.195$ , respectively). The other echocardiographic parameters were also similar in the between- and within-group analyses at the end of the study (Table 2).

## Discussion

In this prospective, randomized, controlled study, we studied the association between raloxifene use and LVMI determined by echocardiography in postmenopausal women, and we did not find any effect of raloxifene on left ventricle hypertrophy in the 6-month follow-up period.

It is known that estrogen receptors are present in the myocardium (13), and there are controversial data in the literature about the effect of HRT on LVM and LVMI. In contrast with our study, Lim et al. (14) showed that women who were using HRT for more than 10 years had a significant reduction in septal and posterior left ventricular wall thickness when compared with controls. In an autopsy study, Olivetti et al. (15) demonstrated that myocyte number and volume are better preserved in women than in men. This intriguing study is supported by findings that estrogen may be important in the activation of the antiapoptotic

AKT (protein kinase B) kinase in the heart (16). Thus HRT, and particularly estrogen, positively affects myocardial hypertrophy and remodeling, and this mechanism seems to be the most plausible explanation for the improved survival with HRT in women with advanced heart failure (17).

However, some studies were consistent with our findings. Snabes et al. (18) examined the effect of E2 replacement therapy on cardiac structure and function in healthy postmenopausal women, and they found that E2 replacement therapy, which results in physiological serum concentrations, does not affect cardiac structure or function in normal postmenopausal women after 12 weeks of treatment. In a prospective, controlled study, Kessel et al. (19) studied the short- and intermediate-term effects of low-dose HRT on echocardiographic parameters of cardiac function in healthy postmenopausal women, and they did not find any clinically relevant differences in M-mode, quantitative 2-dimensional, and Doppler echocardiographic parameters within 15 months of 17 beta-estradiol and dydrogesterone treatment. Recently, Schwarz et al. (20) analyzed the association between HRT and either LVMI, determined echocardiographically, in a cross-sectional study, and they did not find any significant associations with LVH after full adjustment. However, all of these studies were performed by using non-selective estrogens or did not consider what the patients were treated with.

Selective estrogen receptor modulators bind to and alter estrogen receptor function by inhibiting the binding of endogenous estrogens and can be conveniently divided into different categories (21). Tamoxifen is the prototype of SERMs, and it has been shown that tamoxifen can cause severe dilated cardiomyopathy in animal models (22, 23). Raloxifene is a second-generation SERM that is used for the same indication but has a different mechanism of action by comparison with tamoxifen. Conversely, raloxifene increases myocyte contraction and was not associated with an increased risk of heart failure (24, 25). However, the knowledge in the literature about the effect of raloxifene on myocardial hypertrophy is scant.

Two studies performed with raloxifene were consistent with our study. In a mouse model, Westphal et al. (26) showed that raloxifene did not reduce myocardial hypertrophy but improved cardiac function in ovariectomized mice. Similarly, Vogelvang et al. (27) performed two studies with a follow-up period of 2 years. They found significant within-group changes in some parameters (LVMI, aortic peak flow velocity, and aortic velocity integral) from baseline, but interestingly, the same changes occurred in the placebo group; so, they found no effect on echocardiographic parameters of left ventricular systolic function within 2 years of raloxifene treatment in healthy postmenopausal women. In our study, we also did not find any effect of raloxifene treatment on LVM and LVMI, but unlikely, we did not find any difference in within-group echocardiographic parameters. A small number of our patients were hypertensive and diabetic, and the distribution was similar between groups. Antihypertensive and antidiabetic treatment of patients during follow-up was unchanged, and all

**Table 2. Two-dimensional and M-mode echocardiographic measurements**

Variable	Group 1 (n=11)		Group 2 (n=11)		P <sup>a</sup> value	P <sup>b</sup> value	P <sup>c</sup> value	P <sup>d</sup> value
	Baseline	6 month	Baseline	6 month				
Ejection fraction, %	56.2±4.9	57.6±3.7	56.6±5.1	57.0±4.5	0.437	0.785	0.835	0.726
SWTd, mm (2-D)	1.01±0.15	1.03±0.16	0.92±0.12	0.92±0.12	0.858	1.0	0.101	0.78
PWTd, mm (2-D)	0.98±0.14	1.01±0.15	0.93±0.11	0.95±0.11	0.397	1.0	0.323	0.117
SWTd, mm (M-mode)	1.01±0.12	1.04±0.13	1.00±0.11	0.95±0.11	0.432	0.89	0.855	0.68
PWTd, mm (M-mode)	1.01±0.08	1.03±0.14	0.99±0.07	0.95±0.11	0.796	0.211	0.389	0.15
ASE LVM, gr	199.8±24.6	201.2±49.6	183.8±21.9	169.7±46.2	0.919	0.194	0.124	0.14
ASE LVMI, gr/m <sup>2</sup>	119.6±11.3	120.4±25.9	115.3±10.9	105.5±26.7	0.915	0.147	0.379	0.195

ASE - American Society of Echocardiography; LVM - left ventricular mass; LVMI - left ventricular mass index; PWTd - posterior wall thickness at end-diastole; SWTd - septal wall thickness at end-diastole  
a. Paired sample t-test for within-group differences in group 1  
b. Paired sample t-test for within-group differences in group 2  
c. Independent t-test for baseline levels; group 1 vs. group 2  
d. Independent t-test for 6-month levels; group 1 vs. group 2

patients' blood pressure and blood glucose values did not change significantly. Therefore, the possible effect of these factors on LVH was neglected during the study.

### Study limitations

The small number of the subjects and the short follow-up period were the major limitations of our study.

### Conclusion

Based on our results, we may conclude that raloxifene therapy has no effect on left ventricle hypertrophy in healthy postmenopausal women. But, there is still a need for larger and long-term studies to draw firm conclusions.

**Conflict of interest:** None declared.

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