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Raloxifene has favourable effects on metabolic parameters but has no effect on left ventricular function in postmenopausal women

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ABSTRACT

In this prospective randomized study, we investigated the effect of raloxifene on the echocardiographic parameters of left ventricular diastolic and systolic function and on blood levels of lipids, homocysteine, and lipoprotein (a) in postmenopausal osteoporotic patients and compared the results with those treated with risedronate. A total of 44 women were included in the study. Patients were randomized into two groups. Twenty-two patients received raloxifene 60 mg/day (group 1), and 22 patients received risedronate 5 mg/day (group 2; the control group). All patients underwent quantitative two-dimensional pulsed wave Doppler and tissue Doppler echocardiography. Levels of fasting total-C, HDL-C, LDL-C, triglycerides, homocysteine, and lipoprotein (a) were measured. All echocardiographic and biochemical parameters were assessed at the beginning of the study and after the 6-month follow-up. Demographic characteristics and baseline metabolic and echocardiographic parameters were similar in the two groups. After 6 months of the therapy, serum levels of total-C, LDL-C, and homocysteine decreased significantly ($P = .04$, $P = .02$, $P = .008$, respectively) in the treated group when compared with the control group. All echocardiographic measurements except a wave from level of basal interventricular septum were similar in the two groups both before and after 6 month of therapy. In the control group, a wave from level of basal interventricular septum increased significantly ($P = .019$). In conclusions raloxifene may decrease serum levels of total-C, LDL-C, and homocysteine in postmenopausal osteoporotic patients and raloxifene therapy seems to have no significant effect on left ventricular systolic and diastolic function.

1. Introduction

Cardiovascular disease (CVD) and osteoporotic fractures are major health problems and the primary causes of morbidity and mortality in postmenopausal women [1]. The postmenopausal period is associated with unfavourable changes in the lipid profile [2,3]. Lipoprotein (a) [Lp(a)] and homocysteine (hcy) have also been found to play role in the development of coronary heart disease (CHD) [4,5]. Although observational studies published during the 1990s pointed out that the use of estrogen plus progestogen therapy decreased the risk of CVD in postmenopausal women [6,7], the recent randomized clinical trials proved that neither estrogen therapy nor estrogen plus progestogen therapy provide cardiovascular protection; instead they might even increase the risk of CVD in postmenopausal women [8–10].

Raloxifene, a second-generation selective estrogen receptor modulator (SERM), exerts estrogen-agonistic effects of on cardiovascular system and bone [11–13] and estrogen-antagonist effects on the breast and uterus [14–16]. Although many aspects of the cardiovascular effects of raloxifene have been studied, the effect of raloxifene on cardiac function, including echocardiographic parameters, has not been well studied. To our knowledge, no study has used pulsed wave Doppler (PWD) and tissue Doppler echocardiography (TDE) to examine the effect of raloxifene on left ventricular diastolic function.

This prospective randomized study was designed to investigate the effects of raloxifene on echocardiographic parameters of left ventricular diastolic and systolic functions using PWD and TDE and on blood levels of lipids, hcy and Lp(a) in the postmenopausal osteoporotic patients, after 6 months of therapy.

2. Methods

2.1. Patients and protocol

A total of 44 postmenopausal osteoporotic women (age range, 51–70 years) were included in this prospective controlled study. All

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women had a T-score for femoral neck or lumbal spine bone mineral density (BMD) measurements ≤2.5 standard deviation according to the results of dual-energy X-ray absorptiometry. According to the World Health Organization definition, postmenopausal osteoporosis is defined as a BMD of at least 2.5 standard deviation below that of the average bone mineral density of a young adult. Subjects were recruited from the Menopause Clinic of the Department of Obstetrics and Gynecology. In all subjects, at least 12 months had elapsed from the last spontaneous menstrual bleeding, and each participant exhibited a serum follicle-stimulating hormone level greater than 40 U/L and an estradiol (E_2) level less than 30 pg/mL. The investigation was conducted according to the principles outlined in the Declaration of Helsinki. The local ethics committee approved the study protocol, and all patients gave written informed consent. Exclusion criteria were endometrial thickness of >5 mm, history of gynecologic malignancy, ischemic heart disease, thromboembolism, diabetes mellitus, non-treated thyroid dysfunction, or treatment with lipid-lowering and antihypertensive medication or hormone therapy during the 6 months before the initiation of the study.

Patients were randomized by computer-generated numbers into two groups as follows: group 1 ($N = 22$) consisted of patients treated with raloxifene 60 mg/day (Evista, Lilly Company, Istanbul, Turkey), and group 2 ($N = 22$) consisted of patients treated with risedronate 5 mg/day (Actonel, Aventis Pharma, Istanbul, Turkey). Group 2 served as the controls, since ethics committee insisted that the control osteoporotic patients had to receive an antiresorptive treatment. Patients in both groups received 600 mg daily calcium + 400 IU Vit D (Cal-D-Vita, Roche, Istanbul, Turkey) an over-the-counter product.

2.2. Echocardiographic examination

Before randomization, all patients underwent echocardiography. A second echocardiographic evaluation was conducted after the sixth month of treatment, and all measurements were repeated. All echocardiographic examinations, including quantitative two-dimensional echocardiography, PWD echocardiography, and TDE, were performed by means of an Acuson Sequa 256 echocardiography unit with a 3.5-MHz transducer after each patient had been placed in the left lateral decubitus position.

Quantitative two-dimensional measurements included left ventricular end-diastolic and end-systolic volume and the derived parameters of stroke volume and ejection fraction. Left ventricular end-diastolic volume and end-systolic volume were determined via the Simpson formula from apical 4-chamber views.

The left ventricular diastolic filling pattern was recorded via PWD from the apical position with the sample volume situated between the mitral leaflet tips. The peak velocities of early (E) and late (A) diastolic filling, their ratio (E/A), and the deceleration time of the E wave (EDT) were measured. The isovolumic relaxation time (IVRT) was measured from the closure spike of the aortic valve to the onset of mitral inflow.

We performed TDE at the level of the basal interventricular septum and the mitral annular level of the lateral wall. The measured TDE parameters were as follows: early diastolic maximal velocity (e wave), the deceleration time of the e wave (eDT) late diastolic maximal velocity (a wave), systolic maximal velocity (s wave), and IVRT. All measurements were performed and recorded by one investigator who was blinded to the patients' treatment groups.

2.3. Lipid, homocysteine, and Lp(a) measurement

Levels of fasting total-C, HDL-C, and TG were determined by the colorimetric method with a Cobas Mira Plus autoanalyzer (Roche Diagnostics, Mannheim, Germany). LDL-C levels were calculated by the formula of Friedwald (1972). Lp(a) was quantified by the immunoturbidimetric method in a Roche/Hitachi 912 autoanalyzer. The fasting hcy concentration was measured with an AxSYM hormone autoanalyzer (Abbott Laboratories, Abbott Park, IL, USA) via the microparticle enzyme immunoassay method. All biochemical parameters were assessed twice, once at the beginning of the study and again at the end of sixth month of the study.

2.4. Statistical analyses

The statistical package SPSS (Statistical Package for the Social Sciences, version 9.0, Chicago, IL, USA) was used for statistical analyses. A sample size analysis before the study commencement was performed. We assumed that raloxifene may cause hemodynamic differences of 15–20% between baseline and post-treatment and standard deviations of 15% in stroke volume, ejection fraction and tissue Doppler measurements. To have an 80% power of detecting a difference with a significance level of 5%, we calculated that 18 subjects to be recruited into each arm of the study. Continuous variables are expressed as the mean ± S.D. Continuous variables were compared with the independent sample t-test. The χ^2-test was used for categorical variables. P-values of less than .05 were considered statistically significant. In each group, changes in the levels of homocysteine, total-C, LDL-C, HDL-C, Lp(a), and TG and echocardiographic measurements from baseline to that recorded at the end of the sixth month of the study were evaluated by means of the paired-sample t-test.

3. Results

All patients completed the study period. Demographic characteristics of the groups were similar (Table 1). No differences were detected in the baseline levels of total-C, HDL-C, LDL-C, TG, hcy and Lp(a) levels between two groups (Table 2). After 6 months of the therapy, the serum levels of total-C, LDL-C, and hcy ($P = .04$, $P = .02$, $P = .008$, respectively) was significantly lower in study group compared with control group. In the follow-up, the decrease in serum levels of total-C, LDL-C, hcy and increase in TG levels ($P = .01$, $P < .001$, $P < .001$, $P < .01$, respectively) were statistically significant in the raloxifene-treated group. However, in the control group, all lipid parameters, Lp(a) and hcy levels were similar at the end of the study compared to the basal values (Table 2).

All echocardiographic measurements were similar in the two groups before randomization. Two-dimensional and pulsed Doppler measurements were also similar in the two groups at follow-up, and no significant alteration was observed in any of these parameters during follow-up period ($P > .05$) (Tables 3 and 4). All TDE measurements were similar in the two groups at follow-up (Table 5). At the end of the study, TDE measurements in raloxifene-treated group did not change from the baseline values ($P > .05$) (Table 5), meanwhile TDE parameters of the control group (except for a wave from the level of the basal interventricular septum) did not change from the baseline values. However, only late diastolic

Table 1
Descriptive characteristics of the study groups at baseline

Characteristic	Group 1 ($n = 22$)	Group 2 ($n = 22$)	P-value
Age (year)	59.5 ± 4.4	57.3 ± 4.8	.49
Body mass index (kg/mg^2)	25.1 ± 1.8	25.0 ± 2.0	.89
Duration of amenorrhoea (year)	9.5 ± 4.0	7.9 ± 4.4	.63
Gravida (n)	3.0 ± 1.6	3.0 ± 1.7	.90
Parity (n)	1.6 ± 0.8	1.7 ± 1.0	.61