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Original Research Article

Effects of raloxifene use on cardiovascular disease risk determinants in postmenopausal women

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ABSTRACT

Background: Raloxifene is a selective estrogen receptor modulator (SERM) that binds to estrogen receptors with high affinity, acting as an estrogen agonist or antagonist in a tissue-specific manner. This study aimed to evaluate the effect of raloxifene on various cardiovascular risk determinants in postmenopausal women and to compare these effects with those in a control group.
Methods: The study was conducted as a prospective, open, matched case-control study at Gazi University Hospital. A total of 100 postmenopausal women were included. Fifty postmenopausal women with osteoporosis received 60 mg of raloxifene daily. The other fifty healthy postmenopausal women in the control group received no treatment. After one year, changes in cardiovascular risk markers compared to baseline values were evaluated in both the treatment and control groups. The plasma determinants evaluated included total cholesterol, LDL, HDL, triglycerides, lipoprotein (a), Apo A, Apo B, homocysteine, hs-CRP, and fibrinogen. Carotid intima-media thickness, an important radiologic indicator of cardiovascular risk, was also measured and compared between the groups.
Results: After the study, raloxifene was found to decrease levels of total cholesterol, LDL, homocysteine, and fibrinogen, but it did not affect HDL, triglyceride, Apo B, lipoprotein (a), and hs-CRP levels. There were no differences between the baseline values of the groups or the values of the control group after the study period. In the control group, there was a significant increase in carotid intima-media thickness compared to baseline values, while no such difference was observed in the raloxifene group.
Conclusions: Raloxifene caused favorable changes in many biochemical and radiologic cardiovascular risk determinants compared to the control group. Further clinical studies are needed to determine whether these effects are associated with cardiovascular protection.

Keywords: Cardiovascular disease, Menopause, Postmenopausal, Raloxifene

INTRODUCTION

In the early twentieth century, women's lifespans rarely extended beyond menopause. Today, however, one-third of a woman's lifespan consists of the postmenopausal period. Therefore, the quality of life during this time has become a very important and justified expectation.[1,2] The main problems that postmenopausal women face during this period include cardiovascular disease (CVD), osteoporosis, loss of cognitive function, urogenital atrophy, and malignancies.[3] Cardiovascular disease (CVD) is the leading cause of death in our country, as it is worldwide.[4] The fact that this disease, which is less common in women than in men during the premenopausal period, approaches similar rates with men after menopause suggests that estrogen has a protective effect before menopause.[5]

The concept of hormone replacement therapy (HRT), which holds great promise for addressing all these menopausal problems, emerged in the 1970s based on observational studies.[6] It wasn't until the 2000s that

randomized controlled trials on this subject were concluded, sparking significant controversy.[7] At the time of this study, the consensus was that hormone replacement therapy (HRT) should not be used for primary or secondary prevention of cardiovascular disease (CVD). Its primary indication was for treating vasomotor and urogenital atrophic symptoms, with treatment recommended for the shortest duration and lowest effective dose.[8,9]

These results have prompted the medical community to explore various treatment alternatives. The ideal agent would ideally harness the beneficial effects of estrogen on bone, arteries, and the brain, while mitigating its undesirable effects on the breast and endometrium. This concept sparked significant interest in 1998 with the advancement of selective estrogen receptor modulators (SERMs) from the laboratory to pharmaceutical development.[10,11]

SERMs are synthetic, non-steroidal agents that bind strongly to estrogen receptors, acting either as agonists or antagonists depending on the target tissue.[12] Those approved for human use are tamoxifen, toremifene, clomiphene and raloxifene. Tamoxifen is a SERM indicated for the treatment and prevention of breast cancer; toremifene for the treatment of breast cancer; clomiphene for the treatment of infertility; raloxifene for the treatment and prevention of postmenopausal osteoporosis.[13,14] The potential cardioprotective effect of raloxifene, initially discovered through extensive osteoporosis studies, has prompted the scientific community to conduct research focusing on cardiovascular disease as a primary outcome.[14]

The aim of this study was to evaluate the impact of raloxifene on various cardiovascular risk factors known to be crucial in the development of cardiovascular disease (CVD) in postmenopausal women. We examined serum lipids and lipoproteins including total cholesterol (TC), LDL, HDL, triglycerides (TG), Apo A, Apo B, and Lp (a) to assess dyslipidemia, which plays a significant role in the atherosclerotic process. Inflammatory markers such as hs-CRP were also analyzed, along with fibrinogen as a hemostatic factor. Carotid intima-media thickness (IMT) was evaluated as a radiological indicator of homocysteine and coronary atherosclerosis.

METHODS

The study was conducted from January 2002 to January 2005 at Gazi University Faculty of Medicine, Department of Obstetrics and Gynecology, with the support of the Department of Biochemistry and the Department of Radiology. It was designed as a prospective, matched case-control study. Fifty women who visited the menopause outpatient clinic were selected for the study group and started on raloxifene hydrochloride treatment due to a diagnosis of postmenopausal osteoporosis. Concurrently, 50 healthy postmenopausal women attending the same clinic were included as the control group. The study protocol received approval from the ethics committee (Ethics Committee Approval No: **, Date: **). All participants provided written informed consent in accordance with the ethical principles outlined in the Declaration of Helsinki.

Before starting treatment, all women underwent a gynecological examination, PAP smear, transvaginal ultrasound (USG), breast examination, mammography, bone mineral density (BMD) measurement using dual-energy X-ray absorptiometry (DEXA), as well as assessments of blood pressure, body mass index (BMI), liver function, kidney function, thyroid function, and a complete blood count. Women with systemic diseases that may affect cardiovascular disease risk (such as type 2 diabetes, hypertension, familial dyslipidemia, obesity), smokers, those with known cardiovascular disease, and those using hormone replacement therapy (HRT), tibolone, antiresorptive agents, statins, or antihypertensive medications in the past year were excluded from the study. Additionally, women with a history or suspicion of gynecologic malignancy, endometrial thickness >4 mm, history of thromboembolic disease, cerebrovascular disease, amenorrhea for less than 2 years, or vasomotor symptoms were also excluded.

Although raloxifene has been used in the literature for treating and preventing osteoporosis, its use in Turkey is approved only for osteoporosis treatment by the Ministry of Health. Therefore, the study group started on raloxifene consisted of women classified as osteoporotic according to World Health Organization (WHO) criteria (bone mineral density T score at the femoral neck or lumbar vertebrae $\leq$ -2.5).[15] Since it would be unethical to withhold medication from osteoporotic patients, the control group consisted of women with normal BMD measurements (bone mineral density T score at the femoral neck or lumbar vertebrae >-1).

The study group used raloxifene hydrochloride, 1*1 tablet (60 mg) at any time of the day. In contrast, the control group received recommendations for exercise and a calcium-rich diet. All women underwent biochemical and radiological evaluations before and 12 months after the study. TC, LDL, HDL, TG, Lp (a), Apo A, Apo B, homocysteine, hs-CRP and fibrinogen were analyzed.[16] Carotid IMT was measured before and 1 year after the study.

Serum TC, HDL and triglyceride levels were measured enzymatically with an autoanalyzer (ABBOTT, Aeroset System). LDL level was calculated by the Friedewald formula (TC- triglyceride /5- HDL). Apo A, Apo B and Lp (a) were determined by immunonephelometric method (Beckman, immage). Homocysteine was determined by HPLC (high-performance liquid chromatography system, Chronosystems, Munich, Germany). Fibrinogen was determined by Clauss clotting technique. hs-CRP was

determined by immunonephelometric method (Beckman, immage).

B-mode ultrasound (USG) was used to measure carotid intima-media thickness (IMT). Patients were positioned supine with their head turned opposite to the side being measured and extended. Carotid IMT was defined as the distance between the anterior edge of the luminal echo and the anterior edge of the media/adventitia echo. Measurements were taken at the common carotid artery, 10 mm proximal to the carotid bulb, and the mean of five measurements was recorded. Results are reported as mean ± SD in centimeters.[17] Logic 7 (GE, Milwaukee, WI) USG system and 7-1O MHz linear transducer were used.

Statistical analyses were conducted using the t-test and chi-square test in the SPSS software (Version 1.0, Inc., Chicago, IL, USA). Pre- and post-study values within each group were analyzed using paired t-tests for dependent groups, while between-group comparisons were analyzed using independent t-tests for independent groups. A significance level of $p<0.05$ was considered statistically significant.

RESULTS

Descriptive patient characteristics

Table 1 shows the descriptive characteristics of the patients in both the study and control groups before the study. The study included 100 women aged 45-79 years (mean age 58.91±7.09 years). The duration of postmenopausal status ranged from 2 to 32 years (mean 11.25±6.32 years). There were no statistically significant differences between the groups in terms of age, years since menopause, type of menopause, BMI, blood pressure, or exercise status. All patients were non-smokers and did not consume alcohol. These characteristics ensured a precise matching between the study and control groups.

Table 1: Descriptive patient characteristics of the patients who participated in the study.

Parameters		Study group (n=50)	Control group (n=50)	P value
Age (year)		59.56±7.06	58.26±7.14	0.362
Postmenopausal period (year)		11.20±6.23	11.30±6.47	0.937
Menopause type (%)	Natural	86	84	1.000
	Surgical	14	16	
BMI (kg/m^2)		25.2±3.1	24.8±1.9	0.420
Blood pressure	Systolic (mmHg)	127±16	126±18	0.460
	Diastolic (mmHg)	78±10	81±9	0.684
Exercise per week (n)		3.2±2.5	4.1±1.7	0.735

Table 2: Changes in examined cholesterol profile values of groups (Mean±SD).

Parameters		Baseline	1 year after treatment	P value
Total cholesterol (mg/dl)	Case	221.64±34.21	199.98±29.50	>0.001
	Control	217.62±36.33	219.34±38.50	0.775
LDL cholesterol (mg/dl)	Case	135.84±29.98	121.98±26.36	0.001
	Control	133.96±33.71	130.12±34.16	0.457
HDL cholesterol (mg/dl)	Case	63.26±12.73	62.60±12.04	0.590
	Control	61.86±14.52	59.94±14.98	0.174
Triglyceride (mg/dl)	Case	115.86±63.48	117.02±49.02	0.906
	Control	121.88±63.80	134.00±65.65	0.133
Lipoprotein(a) (mg/dl)	Case	24.71±25.02	26.46±30.50	0.550
	Control	33.56±26.28	30.04±30.13	0.381
Apo A (mg/dl)	Case	124.26±24.44	140.63±47.79	0.009
	Control	135.34±26.12	141.98±44.53	0.346
Apo B (mg/dl)	Case	108.72±24.48	105.70±26.55	0.418
	Control	116.18±24.19	109.06±30.16	0.136
Homocysteine (umol/l)	Case	12.07±3.50	10.82±2.74	0.042
	Control	12.01±2.84	11.47±3.81	0.417
hs-CRP (mg/dl)	Case	0.39±0.44	0.34±0.35	0.473
	Control	0.40±0.45	0.27±0.22	0.106
Fibrinogen (mg/dl)	Case	202.00±110.71	161.58±90.89	0.031
	Control	257.41±192.42	209.67±128.95	0.131
Carotid IMT (cm)	Case	0.80±0.39	0.86±0.43	0.161
	Control	0.72±0.11	0.76±0.13	0.045

Table 2 presents the laboratory and measurement results of both groups at baseline and after 1 year.

Laboratory results

There was no statistical difference between the baseline values of lipids and lipoproteins, but there was a significant decrease in TC (p=0.000), LDL (p=0.001) and increase in Apo A (p=0.009) at the end of the first year in raloxifene-treated patients. HDL (p=0.590), Apo B (p=0.418), Lp (a) (p=0.550) and triglycerides (p=0.906) did not change. In the control group, no statistically significant change was observed in any lipid and lipoprotein compared to baseline (Figure 1). In homocysteine evaluation, there was no difference between baseline values, and the significant decrease in the raloxifene group (p=0.042) was not observed in the control group (p=0.417) after 1 year of use (Figure 2). There were no intra- and inter-group differences in hs-CRP at baseline and at the end of the first year (Figure 2).

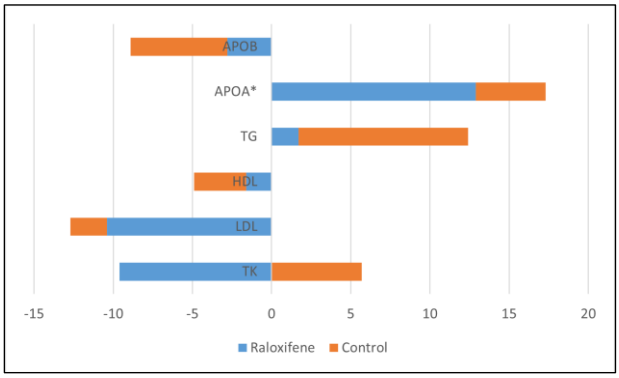

Figure 1: Changes in lipids and lipoproteins in the study group and control group.
*p<0.05 (significant according to baseline value)

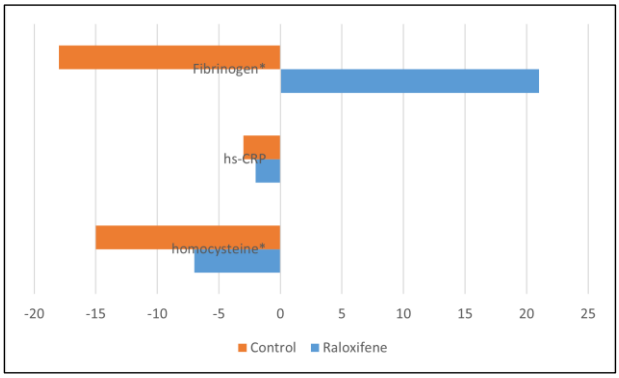

Figure 2: Fibrinogen, hs-CRP and homocysteine changes in the study group and control group.
*p<0.05 (significant according to baseline value)

There was a significant decrease in fibrinogen level in the raloxifene group after 1 year of use (p:0.031). There was no significant difference between baseline values (p:0.383) and in the control group (p:0.131) (Figure 2).

USG measurement

The ultrasound examination of IMT showed no difference between the groups before treatment (p=0.391). However, a statistically significant increase was observed in the control group after 1 year (p=0.045), while no significant change was found in the raloxifene group after 1 year (p=0.161).

DISCUSSION

Based on the results of our study, raloxifene at a daily dose of 60 mg had a positive impact on the serum lipid profile and other significant intermediate determinants of CVD. These results align well with previous research.[18-20]

Clinical trials have demonstrated that raloxifene reduces TC and LDL by 8-12%, with this effect starting in the third month and persisting for 4 years.[18,20,21] In our study, raloxifene led to a significant decrease in total cholesterol (TC) and LDL levels after 1 year, whereas these levels remained unchanged in the control group with similar baseline values. This effect is believed to be linked to raloxifene's mechanism of inhibiting LDL oxidation in vitro.[22] Studies examining the impact of raloxifene on HDL levels report varying results. While the Euralox (European Raloxifene Trial) study found a significant increase in HDL; the MORE study and studies by Walsh et al and Delmas et al did not observe statistically significant changes.[20,21] Similar to these two studies, no change was found in HDL in our study.

The effects of raloxifene on TG are controversial. Nickelsen et al reported a decreasing effect on TG levels, while Walsh et al. suggested no significant change in TG levels.[20] In our study, we observed a slight increase that was not statistically significant, similar to the results of the MORE study.[18] Studies have indicated that raloxifene reduces Lp (a), although not to the extent seen with hormone replacement therapy (HRT), Mijatovic et al even reported a decrease of up to 30% with a dose of 150 mg raloxifene.[23,24] However, the effect of raloxifene on Lp (a) was not significant in our study. We speculate that the 60 mg dose used in our study may be lower compared to other studies we reviewed. It is well-established that serum concentrations of Apo B and Apo A are important determinants of CVD.[25] Walsh et al found an increase in Apo A and a decrease in Apo B in women using raloxifene.[20] Similarly, we observed a significant increase in Apo A levels in our study, whereas the slight decrease in Apo B was not statistically significant. Consistent with other studies, we also noted a significant reduction in fibrinogen levels, which we investigated as a hemostatic factor playing a crucial role in atherogenesis.[24] Similar to the study by Cushman et al which was widely reported in the literature, HRT was found to increase hs-CRP.[26] However, we did not observe a significant change in hs-CRP levels in our study, which aligns with the results of Walsh et al.[20]

IMT is considered an indicator of carotid wall structure and is an important marker of atherosclerosis.[27] CVD and carotid IMT have been shown to be closely related.[28] In the literature, studies of HRT with carotid IMT have yielded different results.[29,30] In our study, compared to the control group with similar baseline values, an increase was observed in carotid IMT after 1 year in the control group, whereas this increase was not observed in the raloxifene group. These results suggest that the increase observed in the control group may be attributed to aging, while raloxifene prevented this increase. Furthermore, the exclusion of factors such as hypertension, obesity, diabetes, and smoking, which affect carotid IMT, is crucial in demonstrating the specific effect of raloxifene.

The literature indicates that raloxifene influences risk factors associated with atherosclerotic disease. In our study, multiple known determinants were simultaneously assessed in both the patient and control groups, while other significant risk factors were excluded through precise matching. The absence of statistical differences between the groups in any of the baseline determinants greatly enhanced this matching. Consequently, raloxifene is believed to exhibit multiple anti-atherogenic effects.[31-33]

Raloxifene reduces total cholesterol (TC), LDL, and homocysteine levels similar to hormone replacement therapy (HRT), but unlike HRT, it does not lead to an increase in triglycerides (TG) and hs-CRP.[19,32] Moreover, it's worth noting that HRT) does not exhibit a beneficial effect on HDL levels. Numerous clinical studies have demonstrated that raloxifene also influences risk factors associated with atherosclerotic disease. In our study, multiple well-known determinants were simultaneously assessed in both the patient and control groups, and other significant risk factors were excluded through precise matching. The absence of statistical differences between the groups in any of the baseline determinants greatly contributed to this matching.

This study has few limitations. Although the study design was prospective, it was not randomized and was an open-label study. Additionally, one reason for not administering any medication in the control group is the recognition of the powerful placebo effect.

CONCLUSION

Although the effect of raloxifene on the venous system is generally similar to that of HRT, based on clinical data and our study results, it can be inferred that raloxifene has a neutral or slightly positive effect on the arterial system and, consequently, on atherosclerotic events. In the postmenopausal period, the desired pharmacological effects should include corticosteroids that suppress the immune system without inducing bone loss, androgens with anabolic effects that do not cause masculinization or worsen lipid profiles, progestins that induce endometrial atrophy without causing fluid retention, and medications that increase mineral density without leading to hypercalcemia. Randomized controlled studies on these topics are needed.

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