Effect of Raloxifene on Serum Lipids for Type 2 Diabetic Menopausal Women with or without Statin Treatment

Mihoko Matsumura Tsuyoshi Monden Yuki Nakatani Hiroaki Shimizu
Nozomi Domeki Kazunori Yanagi Shiori Ikeda Yoshiaki Kawagoe Kikuo Kasai

Department of Endocrinology and Metabolism, Dokkyo Medical University School of Medicine, Mibu, Japan

Key Words

Raloxifene • Type 2 diabetes • Lipid • Low-density lipoprotein cholesterol

Abstract

Objective: Our aim was to investigate the effect of 1-year treatment with raloxifene, a selective estrogen receptor modulator, on plasma lipid profiles in Japanese postmenopausal type 2 diabetic patients. **Subjects and Methods:** A total of 43 Japanese women with postmenopausal osteoporosis and type 2 diabetes with serum low-density lipoprotein cholesterol (LDL-C) <3.59 mmol/l, serum triglyceride <1.68 mmol/l and serum high-density lipoprotein cholesterol (HDL-C) >1.03 mmol/l, who took 60 mg/day of raloxifene for 12 months, were enrolled. For analysis, they were divided into 2 groups: nonhyperlipidemia (n = 23) and hyperlipidemia treated with statin (n = 20). **Results:** Raloxifene treatment significantly induced a mean reduction in serum LDL-C from 2.90 to 2.36 and 2.67 mmol/l in the nonhyperlipidemia and statin-treated group, respectively. However, the reduction ratio of serum LDL-C showed a significant difference in the nonhyperlipidemia group (17%) compared to the statin-treated group (7%; p = 0.03). Although serum HDL-C showed an increase in both groups (from 1.45 to 1.58 vs. from 1.40 to 1.47 mmol/l), the increase ratio of serum HDL-C was not sig-

nificant between the two groups. Raloxifene administration showed 15% reduction in the nonhyperlipidemia group (p = 0.02) and 13% reduction in the statin-treated group (p = 0.02) of urinary N-telopeptide of type I collagen. No significant change in blood HbA_{1c} was observed in either group. **Conclusion:** The administration of raloxifene to type 2 diabetic women showed favorable efficacy on serum lipid profiles, particularly in patients without statin treatment.

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Introduction

Diabetes is a risk factor for fractures among older women [1], and more than 30% of diabetic patients take lipid-lowering drugs to prevent cardiovascular events [2]. It is well established that raloxifene (RLX), a benzothio-phenene-selective estrogen receptor modulator, which has estrogen-agonistic action on bone tissue, is widely used for the treatment and prevention of osteoporosis in postmenopausal women with or without diabetes [3]. Recently, the favorable effects of RLX on type 2 diabetes were described [4, 5]. It limited the progression of albuminuria [4], increased serum adiponectin levels in postmenopausal diabetic women [5] and had beneficial effects on lipid metabolism in several clinical trials [3, 6, 7]. How-

Table 1. Comparison of the baseline characteristics of the statin-treated and the nonhyperlipidemia group

	Without statin treatment	Statin-treated	p value
Number	23	20	
Age, years	69.5 ± 1.9	70.1 ± 2.5	0.82
BMI	22.5 ± 0.8	22.4 ± 0.7	0.90
Time since menopause, years	20.5 ± 2.1	22.5 ± 3.0	0.54
Systolic blood pressure, mm Hg	123 ± 4	127 ± 3	0.40
Diastolic blood pressure, mm Hg	72 ± 3	72 ± 3	0.84
LDL-C, mmol/l	2.90 ± 0.10	2.93 ± 0.13	0.84
HDL-C, mmol/l	1.46 ± 0.08	1.40 ± 0.12	0.63
LDL/HDL-C ratio	2.10 ± 0.13	2.33 ± 0.19	0.24
TG, mmol/l	1.23 ± 0.11	1.07 ± 0.11	0.23
Urinary NTx, nmol BCE/nmol Cr	54.3 ± 5.2	54.3 ± 4.5	0.99
Fasting plasma glucose, mg/dl	126.0 ± 13.1	129.1 ± 13.0	0.90
HbA _{1c} , %	6.6 ± 0.2	6.6 ± 0.2	0.93
Hypertension	8 (7)	7 (6)	0.77

Values are mean ± SE. BMI = Body mass index; BCE = bone collagen equivalents; Cr = creatinine. Figures in parentheses indicate numbers of patients treated with an angiotensin receptor blocker or an angiotensin-converting enzyme inhibitor.

ever, the effects of RLX on serum lipid profiles of patients taking HMG-CoA reductase inhibitors (statins), the most common lipid-lowering drugs, have not been clarified. Therefore, in this study, we retrospectively compared a statin-treated group with a group without statin treatment to examine the effects of RLX on serum lipid profiles in osteoporotic postmenopausal Japanese women with type 2 diabetes.

Subjects and Methods

Forty-three type 2 diabetic postmenopausal women with osteoporosis, who had undergone 1-year 60 mg/day RLX treatment at Dokkyo Medical University Hospital and who met the following criteria, were analyzed: serum low-density lipoprotein cholesterol (LDL-C) <3.59 mmol/l, serum triglyceride (TG) <1.68 mmol/l, serum high-density lipoprotein cholesterol (HDL-C) >1.03 mmol/l before the initiation of RLX treatment, no changes in medications during the past 3 months, no administration of thiazolidine or other lipid-lowering drugs such as fibrates, nicotinic acid or cholestimide, no administration of androgen, calcitonin, bisphosphonates, estrogen, progesterone, corticosteroid and vitamin D, no history of coronary disease, congestive heart failure or stroke, attending the diabetes education program in our hospital once a year, and outpatients. Medications known to influence lipid metabolism were neither added nor withdrawn during the study. All patients gave informed consent to be included in this study. The study was performed according to the guidelines of the Declaration of Helsinki. We divided patients into two groups: one group (n = 20) had received HMG-CoA reductase in-

hibitor (statin) treatment for at least 6 months (5 mg/day atorvastatin, n = 4; 10 mg/day atorvastatin, n = 6; 10 mg/day simvastatin, n = 5; 10 mg/day pravastatin, n = 5) before administration of RLX and continued the same amount of statin during the study; the other group (n = 23) had taken no antihyperlipidemic agents. The clinical profiles of the subjects at baseline are shown in table 1. The concentration of urinary N-telopeptide of type I collagen (NTx) was measured with an ELISA kit (Osteomark, Inverness Medical Professional Diagnostics, Princeton, N.J., USA). Serum TG was measured by the free glycerol reductase method using glycerol kinase and lipoprotein kinase (Roche Diagnostics Co. Ltd., Tokyo, Japan). Serum HDL-C was measured by a direct method using cholesterol oxidase and cholesterol esterase (Dai-ichi Pure Chemicals Co. Ltd., Tokyo, Japan). Serum LDL-C was calculated using Friedewald's equation [8]. Blood HbA_{1c} levels were determined by high-performance liquid chromatography (Hi-auto A_{1c}, HA8150; Arkray Inc., Kyoto, Japan).

Statistical Analysis

All data were analyzed with JMP7. The results are presented as mean ± SE. To compare the two groups, we carried out an unpaired t test or Mann-Whitney U test for continuous variables, and the χ^2 test or Fisher test for qualitative variables. Two-tailed p values less than 0.05 were considered significant.

Results

After the RLX treatment, serum LDL-C decreased from 2.90 to 2.36 (17%) and 2.67 mmol/l (7%) in the non-hyperlipidemia group and the statin-treated group, respectively (table 2); the difference in reduction between

Fig. 1. Effects of RLX on urinary NTx, LDL-C, HDL-C, TG and HbA_{1c} in diabetic women with and without statin treatment. Results are presented as the median percent change from baseline. Values are mean $\pm$ SE. * $p < 0.05$ versus the nonhyperlipidemia group.

Table 2. Lipid profiles and parameters of postmenopausal women with diabetes and osteoporosis at baseline and 1 year after RLX treatment

	Without statin treatment		Statin-treated	
	before	after	before	after
Systolic blood pressure, mm Hg	123 $\pm$ 4	124 $\pm$ 5	123 $\pm$ 3	126 $\pm$ 4
Diastolic blood pressure, mm Hg	72 $\pm$ 2	73 $\pm$ 3	72 $\pm$ 3	73 $\pm$ 2
BMI	22.5 $\pm$ 0.8	22.4 $\pm$ 0.6	22.4 $\pm$ 0.7	22.6 $\pm$ 0.8
LDL-C, mmol/l	2.90 $\pm$ 0.10	2.36 $\pm$ 0.11*	2.93 $\pm$ 0.13	2.67 $\pm$ 0.08*
HDL-C, mmol/l	1.46 $\pm$ 0.08	1.58 $\pm$ 0.09*	1.40 $\pm$ 0.12	1.47 $\pm$ 0.13*
LDL-C/HDL-C ratio	2.10 $\pm$ 0.13	1.62 $\pm$ 0.14*	2.33 $\pm$ 0.19	1.99 $\pm$ 0.15*
TG, mmol/l	1.23 $\pm$ 0.11	1.24 $\pm$ 0.12	1.07 $\pm$ 0.11	1.13 $\pm$ 0.11
Fasting plasma glucose, mg/dl	126.0 $\pm$ 13.1	126.4 $\pm$ 12.9	129.1 $\pm$ 13.2	127.0 $\pm$ 12.0
HbA _{1c} , %	6.6 $\pm$ 0.2	6.5 $\pm$ 0.2	6.6 $\pm$ 0.2	6.6 $\pm$ 0.2
Urinary NTx, nmol BCE/nmol Cr	54.3 $\pm$ 5.2	44.9 $\pm$ 4.7*	54.3 $\pm$ 4.5	44.3 $\pm$ 3.9*

Values are mean $\pm$ SE. * $p < 0.05$ versus baseline. BMI = Body mass index; BCE = bone collagen equivalents; Cr = creatinine.

the two groups was statistically significant ($p < 0.05$; fig. 1). Serum LDL-C showed a significant decrease ($p < 0.05$) in the control group compared to the statin-treated group after 1 year of RLX administration (fig. 1). Serum HDL-C increased from 1.45 to 1.58 mmol/l (8%), in the nonhyperlipidemia and from 1.40 to 1.47 mmol/l (6%) in the statin-treated group (table 2), and the difference between values before and after RLX administration was statistically significant ($p < 0.05$) but that between the two groups was not. However, the ratio of LDL-C/HDL-C was significantly more reduced in the nonhyperlipidemia group (from 2.10 to 1.62; 22.4%) than in the statin-treated

group (from 2.33 to 1.99; 12.0%, $p < 0.05$). There was no significant change or difference in serum TG in either group (table 2, fig. 1). No change or difference was observed in blood HbA_{1c} in both groups.

Urinary NTx decreased by 15% in the nonhyperlipidemia group ($p < 0.05$) and by 13% in the statin-treated group ($p < 0.05$; table 2), and no significant difference in urinary NTx was observed between the two groups (fig. 1).

Discussion

It is clear that RLX reduces serum LDL-C levels [3, 6, 7]; however, many diabetic elderly patients are under antihyperlipidemic therapy [9]. Our findings showed that the reduction of serum LDL-C levels by RLX was greater in the group without statin treatment than the statin-treated group. There are reports [10, 11] that coadministration of RLX and statins for 3 months showed a more significant reduction in serum LDL-C than each individual treatment but our results indicated that RLX had less effect on lowering serum LDL-C levels in the statin-treated patients. Probable explanations for the difference between our results and previous ones [10, 11] are: our treatment period was 1 year, statin treatment of more than 6 months could stimulate LDL-C receptor expression, and variations in doses and types of statins were given to our patients. In addition, there was no correlation between the change of serum LDL-C levels and change of urinary NTx levels (data not shown), suggesting that effects of RLX on lipid profiles might differ from the effects of RLX on bone metabolism.

Another characteristic of this study was the elevation action of serum HDL-C. Our findings indicated a significant increase in serum HDL-C in both groups. Serum HDL-C did not show a significant change by RLX administration in large-scale studies of western women [3, 6, 7, 12]; however, a few small-scale studies indicated a significant increase in HDL-C by RLX administration [13].

Compared to these trials, serum HDL-C has shown an upward trend in clinical studies from Asian countries such as Taiwan [14] and Korea [15], suggesting that serum HDL-C elevation by RLX treatment may be influenced by ethnicity. The possibility could not be excluded that dietary education on diabetes, exercise and antihypertensive treatment such as renin-angiotensin blockers affected the improvement of lipid profiles in the study.

Our observation of no significant change of difference in blood HbA_{1c} confirmed the findings of a previous study [16]. Recent studies have shown that the ratio of LDL-C/HDL-C is associated with regression of coronary atherosclerosis [6, 17]. Draper et al. [6] suggested that RLX treatment improved the ratio of LDL-C/HDL-C. Our findings were consistent with their results, but a significantly greater reduction in the LDL/HDL ratio was observed in the group without statin treatment than in the statin-treated group. These findings suggest that the effects of RLX on reducing serum LDL-C may reflect on the change of LDL-C/HDL-C ratio between the two groups.

Conclusion

The administration of RLX to type 2 diabetic women showed favorable efficacy on serum lipid profiles, particularly in patients without statin treatment.

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