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Short Communication

Effects of a long-term treatment with raloxifene on insulin sensitivity in postmenopausal women

A. Lasco · A. Gaudio · N. Morabito · M. Previti · A. Mileto · N. Frisina · D. Cucinotta

Department of Internal Medicine, University of Messina School of Medicine, Messina, Italy

Abstract

Aims/hypothesis. Our aim was to investigate the effect of long-term administration of raloxifene, a selective estrogen receptor modulator, on insulin sensitivity, glucose tolerance and plasma lipid concentrations in a group of postmenopausal women.
Methods. A total of 24 women with postmenopausal osteoporosis were consecutively enrolled and randomly assigned to take raloxifene, 60 mg/day for 12 months or placebo. At baseline and after 6 and 12 months, in each subject insulin sensitivity (M-index) was assessed by means of an euglycaemic hyperinsulinaemic clamp. Plasma concentrations of total cholesterol, triglycerides and HDL-cholesterol were also measured and glucose tolerance was evaluated.
Results. In the raloxifene-treated group, the M index decreased after 6 and 12 months with respect to the placebo group (−21%, p=0.042 and −23%, p=0.018, respectively). Neither fasting plasma glucose nor glucose tolerance changed in the raloxifene-treated group, compared to the placebo group. Low density lipoprotein cholesterol concentrations decreased at 12 months (−13%, p=0.047).
Conclusion/interpretation. A long-term treatment with raloxifene in osteoporotic, otherwise healthy postmenopausal women can reduce insulin sensitivity without affecting glucose tolerance. [Diabetologia (2004) 47:571–574]

Keywords Raloxifene · Insulin sensitivity · M-index · CAD · Postmenopausal

Coronary artery disease (CAD) is the leading cause of death among women in developed countries and its incidence increases substantially after menopause, probably because of the loss of estrogen protection.

Hormone replacement therapy, in population-based observational studies, reduces the risk of cardiovascular events, but other studies have shown that it exerts contrasting effects on CAD risk factors, including insulin resistance [1, 2] and CAD events [3].

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A. Lasco (✉)
Department of Internal Medicine,
University of Messina School of Medicine,
98100 Messina, Italy
E-mail: alasco@unime.it

Raloxifene is a selective estrogen receptor modulator, i.e. a class of drugs that have estrogen-antagonist effects on the breast and uterus and estrogen-agonist effects on bone mineral density. Raloxifene has been shown to reduce total- and low-density lipoprotein cholesterol plasma concentrations, to improve endothelium-dependent vasomotion and to increase nitric oxide concentrations [4]. Data on the possible effects of raloxifene on the insulin-glucose homeostasis are few and contrasting. In a 3-year large clinical trial raloxifene seems to increase the risk of new or worsening diabetes [5]. In contrast, insulin sensitivity has been reported as unmodified [6] or even improved [7, 8] after raloxifene treatment. Considering these data, we decided to better and specifically investigate the effect of long-term raloxifene administration on glucose metabolism and especially on insulin sensitivity in a group of postmenopausal women.

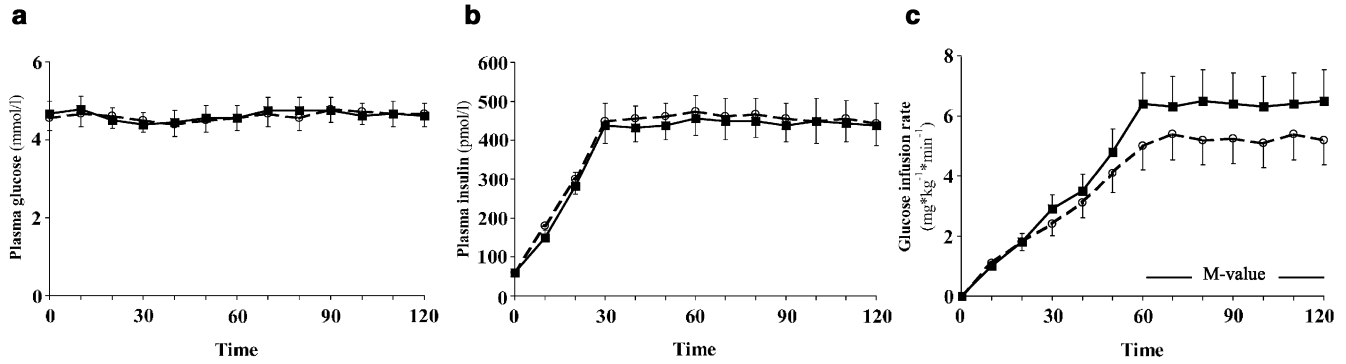

Fig. 1a–c. Steady-state plasma glucose (**a**) and insulin (**b**) and glucose infusion rate (**c**) during an hyperinsulinaemic euglycaemic clamp after 12 months of treatment with raloxifene (○) or with placebo (■). Data are shown as means ± SD

Materials and methods

Subjects. A total of 24 women with postmenopausal osteoporosis, never treated with hormonal replacement therapy, who met the inclusion criteria and gave their informed consent, were consecutively enrolled and randomly assigned to two different treatment groups: 12 women (mean age 56.5±3.9 years, mean amenorrhea duration 10.3±3.4 years, BMI 25.2±2.0) were treated with raloxifene, 60 mg/day at 21:00 hours for 12 months; the other 12 women (mean age 55.8±3.7 years, mean amenorrhea duration 10.5±3.2 years, BMI 24.9±1.7) received an identical placebo tablet. Randomisation was done by using a computer-generated system. Inclusion criteria were: amenorrhea duration of more than 5 years; a BMI less than 29; normal glucose tolerance during a 75-g OGTT (WHO criteria); bone mineral density evaluated by a dual energy X-ray densitometer (Hologic QDR 4500, Bedford, Mass., USA) at lumbar and femoral level below −2.5 SD T-score; no evidence of other chronic illness than osteoporosis; no acute disease in the month preceding the enrolment. Study drug and placebo were given to each patient in boxes containing 90 tablets, i.e. the supply for a 3-month period. To check compliance with the medication tablets, patients were asked to bring these boxes at each 3-month control visit, when the remaining tablets were counted. During these control visits, a complete clinical examination and routine laboratory tests, including a side effects or adverse events check, were carried out. All patients took a calcium and cholecalciferol supplement containing 1 g of elemental calcium and 800 IU cholecalciferol in the evening at meal time. They were also encouraged to maintain their usual diet during the study period.

The study protocol was approved by the Ethics Committee of the University of Messina School of Medicine and it has been carried out in accordance with the Declaration of Helsinki.

Methods. After the enrolment and before starting treatment, in each subject insulin sensitivity was assessed by means of the euglycaemic hyperinsulinaemic clamp technique, according to [9]. Briefly, after an overnight fast in each subject a 2-h euglycaemic hyperinsulinaemia was established with a primed constant infusion of regular insulin. To suppress hepatic glucose production, the target clamped insulin concentration was 70 to 80 μU/ml, achieved with an infusion rate of 1 mU*kg body weight^{-1}*min^{-1}. Basal glucose concentrations were maintained by means of a variable 20% glucose infusion. Plasma glucose and insulin were sampled every 10 min; glucose was immediately measured with a Beckman Glucose Analyser 2 (Beckman Instruments, Milan, Italy), while aliquots of plasma were stored for subsequent insulin radioimmunoassay (Diagnostic Products Corporation, Los Angeles, Calif., USA). The glucose infusion rate required to maintain euglycaemia, expressed as mg*kg^{-1}*min^{-1} and calculated during the second hour of the clamp, was used as insulin sensitivity index (M index).The euglycaemic clamp was carried out by an operator who was not aware of the patient's treatment and was repeated in each woman after 6 and 12 months, i.e. in the middle and at the end of the study period. Metabolic parameters during the 12-month clamp are depicted in Fig. 1.

Fasting plasma concentrations of total-cholesterol, triglycerides (enzymatic methods, Roche Diagnostics; Milan, Italy) and HDL-cholesterol (after plasma precipitation with dextran-magnesium) were also measured. LDL-cholesterol was indirectly estimated by means of the Friedewald formula. BMI was calculated as weight (Kg) divided by height (m) squared. An OGTT was also repeated at 6 and 12 months.

Statistical analysis. Statistical analyses were done by using the StatSoft release 4.5. All values were expressed as means ± SD. The comparison of the changes between treated and control patients was evaluated by ANOVA for repeated measures and then by Student's *t* test for unpaired observation. Pearson's correlation coefficient was calculated to test the relation between two variables. A two-tailed *p* value of less than 0.05 was considered significant.

Results

Biochemical parameters evaluated during the treatment period are reported in Table 1. Baseline values were not different in the two groups. In the raloxifene-treated group, M index values decreased compared with the placebo group after 6 (−21%, p=0.042) and 12 months (−23%, p=0.018). During the study period there were no significant differences between groups in fasting plasma glucose, triglycerides, and total- and HDL-cholesterol concentrations. LDL-cholesterol concentrations decreased after 12 months (−13%, p=0.047) in raloxifene-treated group compared with the placebo-treated group. BMI did not change significantly from baseline to the end of the study in neither group. Glucose tolerance during OGTT was still normal in all subjects at 6 and 12 months. No correlations were found between metabolic parameters and clinical

Table 1. Characteristics of raloxifene- and placebo-treated patients

	Raloxifene-treated patients			Placebo-treated patients		
	Baseline	6 months	12 months	Baseline	6 months	12 months
M index ($mg*kg^{-1}*min^{-1}$)	6.3±1.3	5.3±1.2[a]	5.2±1.1[a]	6.5±0.9	6.4±1.3	6.4±1.2
Fasting plasma glucose (mmol/l)	4.70±0.56	4.69±0.48	4.58±0.71	4.89±0.57	5.08±0.61	4.80±0.48
Total-cholesterol (mmol/l)	5.25±0.75	5.01±0.64	4.99±0.60	5.15±0.81	5.11±0.71	5.26±0.78
HDL-cholesterol (mmol/l)	1.13±0.19	1.18±0.21	1.29±0.17	1.05±0.21	1.11±0.24	1.16±0.26
LDL-cholesterol (mmol/l)	3.69±0.61	3.18±0.59	3.12±0.52[a]	3.56±0.64	3.48±0.61	3.58±0.56
Triglycerides (mmol/l)	1.16±0.14	1.21±0.11	1.27±0.12	1.17±0.18	1.15±0.13	1.18±0.15
BMI (kg/m^2)	25.2±2.0	25.1±1.9	24.8±1.5	24.9±1.7	24.8±1.8	24.7±1.8

Data are expressed as means ± SD
[a] $p<0.05$ vs placebo group

variables such as age, BMI and menopausal duration in the two groups, neither at the beginning nor at the end of the study. No relevant side effects were recorded; only one patient developed leg cramps with raloxifene, but they spontaneously disappeared. The compliance of each patient with treatment was apparently high, since the number of the unused pills given back at each visit was never greater than 8, i.e. less than 10% of the original supplies (mean ± SD: 4±2 pills).

Discussion

Our results show that treatment with raloxifene for 12 months in osteoporotic, otherwise healthy post-menopausal women can reduce insulin sensitivity, assessed by means of the euglycaemic clamp method, but it does not modify fasting plasma glucose and glucose tolerance. We also observed in the raloxifene-treated subjects a significant reduction of LDL cholesterol plasma concentrations that is in accordance with previous reports [4].

Published data concerning the effect of raloxifene on glucose or insulin metabolism are few and contrasting. In the Multiple Outcome of Raloxifene Evaluation (MORE) randomised trial of 7705 postmenopausal women with osteoporosis, a significantly higher number of women in the raloxifene group (1.2%) reported new or worsening diabetes, compared with the participants in the placebo group (0.5%, $p=0.009$) [5]. In a subsequent ancillary study of the same MORE trial, a small group of non-diabetic women underwent an evaluation of insulin sensitivity, indirectly estimated by means of fasting plasma insulin and insulin to glucose ratio. Whereas plasma glucose was similar, fasting insulin and insulin to glucose ratio were lower in patients using raloxifene (60 or 120 mg/day) compared with those treated with placebo, thus indirectly suggesting a better insulin sensitivity in the former group [7].

In our study we used the euglycaemic clamp technique, that is considered the gold standard method to evaluate insulin resistance [7], and we observed that long-term raloxifene administration slightly but significantly reduces peripheral sensitivity to insulin, without affecting glucose homeostasis. This finding is different from what was observed in the above mentioned study [7], but it has been shown that the insulin to glucose ratio does not correlate with the measurement of insulin sensitivity during the euglycaemic insulin clamp [10]. Our data are also in contrast with those from two recent reports where raloxifene (60 mg/day) resulted in no changes in insulin sensitivity [8] or improvements in gluco-insulinaemic homeostasis [6] respectively. These differences could be due to the different methods of assessment of insulin sensitivity and the shorter duration of raloxifene treatment (12 weeks) used by these studies compared to ours. On the other hand, our study has some limitations, i.e. the small number of subjects and the lack of a double-blind design.

In conclusion, in a group of osteoporotic, otherwise healthy women a 12-month raloxifene treatment is associated with a reduced insulin sensitivity, and with lower LDL cholesterol plasma concentrations, but not with modification of plasma glucose concentrations and tolerance. The clinical relevance of these findings is not known and we cannot exclude that, in subjects at high risk for diabetes or after a longer term treatment (i.e. >12 months), this reduced insulin sensitivity can eventually lead to an impairment of glucose tolerance or to an overt diabetes.

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