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Raloxifene Does Not Modify Insulin Sensitivity and Glucose Metabolism in Postmenopausal Women

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Insulin sensitivity (Si), glucose tolerance, and lipid metabolism were investigated in osteopenic postmenopausal women before and after 6 months of treatment with raloxifene (60 mg/d) or placebo. In a group of women (n = 34), glucose metabolism was evaluated by means of an oral glucose tolerance test (75 g). In another group of women (n = 24), Si and peripheral glucose utilization not dependent on insulin were evaluated by means of a frequently sampled iv glucose tolerance test associated with the minimal model method. No metabolic modification was observed in women receiving placebo. Raloxifene did not significantly modify high density lipoprotein-cholesterol and triglycerides, whereas it significantly decreased low density lipoprotein (LDL) cholesterol (4.84 ± 0.34 mmol/liter *vs.* 3.83 ± 0.49 mmol/liter; $P = 0.014$) and LDL/high density lipoprotein cholesterol ratio (3.21 ± 0.31 mmol/liter *vs.* 2.46 ± 0.44 mmol/liter; $P = 0.012$). Fasting levels and responses to the oral glucose tolerance test of glucose, insulin, C-peptide, and C-peptide/insulin were not modified by raloxifene. Similarly, raloxifene did not modify Si (4.22 ± 4.1 *vs.* 5.13 ± 1.75), or insulin (0.025 ± 0.003 *vs.* 0.019 ± 0.002). The present data show that in osteopenic postmenopausal women raloxifene reduces LDL levels but does not modify insulin sensitivity and glucose metabolism. (*J Clin Endocrinol Metab* 87: 4117–4121, 2002)

RALOXIFENE IS A SELECTIVE estrogen receptor modulator, which is able to effectively reduce osteoporotic bone fractures (1–4). Raloxifene shows the unique capability to exert estrogenic effects on bone and antiestrogenic effects on endometrium and breast (1, 2). Indeed, women treated with raloxifene show a marked reduction in new diagnosis of breast cancer (5). Climacteric symptoms are not improved by raloxifene (2, 4), and for this reason, raloxifene is administered several years after the menopause. This is a period of life in which cardiovascular diseases increase exponentially (6). Among the cardiovascular risk factors, a main role is played by the alteration of glucose/insulin metabolism. Type II diabetes elevates three to seven times the woman's risk of coronary artery disease (7, 8), and heperinsulinemia/insulin resistance aggravates the influence of other risk factors (9–11). Glucose metabolism deteriorates with age (12, 13), consequently to a reduction in pancreatic β-cell responsiveness (14) and in peripheral glucose utilization (15). This age-related decline in glucose tolerance might be counteracted, at least in part, by the administration of estrogens in low to moderate doses. Indeed, estrogens exert neutral (16–21) or positive effect (20–25) on pancreatic β-cell responsiveness and on peripheral glucose utilization. Whether the same is exerted by raloxifene, which interacts with estrogen receptors, is presently unclear (26). Definition of this effect may furnish additional evidence (3, 27, 28) on the metabolic and cardiovascular impact of raloxifene in postmenopausal women.

Abbreviations: FSIGT, Frequently sampled iv glucose tolerance test; HDL, high density lipoprotein; LDL, low density lipoprotein; OGTT, oral glucose tolerance test; Sg, glucose utilization not dependent on insulin; Si, insulin sensitivity.

Materials and Methods

The study was performed in Caucasian osteopenic women, as diagnosed by a T score between –1 and –2.5, at a DEXA evaluation of the spine (L2-L4). Women were 56–60 yr of age, and gave their informed consent to the study, which had been previously approved by our local ethics committee and institutional review board. All women were in natural menopause for at least 3 yr. Levels of FSH were higher than 50 IU/liter, and those of estradiol lower than 73.4 pmol/liter (20 pg/ml). Women were free from medications, including hormone, for at least 6 months, and within 15% of the ideal body mass index. None of the subjects had a family or personal history of glucose or lipid alterations. Absence of glucose intolerance was confirmed at a baseline oral glucose tolerance test (OGTT). In the first 34 women enrolled into the study, the effect of raloxifene on glucose metabolism was investigated by an OGTT. In the following 24 women, the effect of raloxifene on insulin sensitivity (Si) and glucose utilization not dependent on insulin (Sg) was investigated by a frequently sampled iv glucose tolerance test (FSIGT) associated with the minimal model method (29). Investigations were performed before and after 6 months of treatment. During the 6 months, women were requested to not modify their lifestyle or dietary habit. Compliance with treatment was checked every 2 months by counting returned treatment pills. A woman was considered compliant and entered into the analysis when returned pills were less than 10%.

OGTT evaluation

An OGTT was performed in 34 subjects. Each woman was hospitalized at 0700 h, following a 12-h overnight fasting and a 3-d diet containing at least 200 g/d of carbohydrates. Women were maintained in bed rest. A polyethylene catheter was inserted in an antecubital vein and was kept patent by a slow infusion of saline solution. A glucose load of 75 g was given orally at 0900 h. Samples of arterialized blood, obtained by forearm warming, were collected at times −30, 0, 30, 60, 90, 120, and 180 min after glucose administration.

Each woman received 1 g/d of calcium and in a double blind fashion was randomized to receive for 6 months either placebo (n = 17) or 60 mg/d of raloxifene (n = 17).

FSIGT evaluation

A FSIGT was performed in 24 subjects. Each woman was hospitalized at 0700 h, following a 12-h overnight fasting and a 3-d diet containing at least 200 g/d of carbohydrates. Women were maintained in bed rest.

Two polyethylene catheters were placed in two antecubital veins, and were kept patent by a slow infusion of saline solution. One catheter was used for iv glucose or insulin administration and the other for blood collection. At 0900 h, glucose (0.3 g/kg) was injected over 1 min iv and was followed 20 min later by an iv insulin bolus (0.03 U/kg) (29). Samples of arterialized blood, were collected at time −5, −1, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, 20, 22, 23, 24, 25, 27, 30, 40, 60, 70, 80, 90, 100, 120, 160, and 180 min after glucose load.

Each woman received 1 g/d of calcium and in a double blind fashion was randomized to receive for 6 months either placebo (n = 12) or 60 mg/d of raloxifene (n = 12).

Assays

For both the OGTT and FSIGT investigations, blood samples were collected into heparinized glass tubes placed on ice. Blood was immediately centrifuged. An aliquot of plasma was immediately tested for glucose levels, whereas another aliquot was immediately frozen at −25 C until assayed. Glucose was determined by the glucose oxidase method. Insulin levels were assayed in all samples, in duplicate by RIA methods using commercial kits (Biodata, Guidonia Montecelio, Roma, Italy). Intraassay and interassay coefficients of variation of the assay were 6.2% and 7%, respectively, and sensitivity was 14.35 pmol/liter. C-peptide levels were analyzed in all the OGTT samples, and in the samples collected in the first 20 min of the FSIGT. Assays were performed in duplicate by commercial RIA kits (Biodata, Guidonia Montecelio). Intraassay and interassay coefficients of variation were 3.2% and 8.5%, respectively, and sensitivity was 33.1 pmol/liter. Circulating levels of lipids were evaluated in baseline fasting samples of the OGTT or FSIGT. Total cholesterol and triglycerides were measured by enzymatic methods (Olympus Italia SRL, Milan, Italy). High density lipoprotein (HDL) cholesterol was determined after precipitation with Peg 6000. Low density lipoprotein (LDL) was calculated with the formula of Friedewald *et al.* (30). To avoid interassay variability, samples of each subject were analyzed all together in the same assay.

Statistical analyses

Assuming that the difference induced by raloxifene was equal to 1 SD of the difference and setting type I error at 0.05 and type II error at 0.20, eight subjects were sufficient to detect a statistically significant modification in either the OGTT or FSIGT investigation.

Responses of glucose, insulin, and C-peptide observed during the OGTT and in the first 20 min of the FSIGT, were reported as absolute values and as area under the curve, calculated by the trapezoid method and expressed in arbitrary units (picomoles/liter × minutes; AUC). To have an index of hepatic insulin clearance, the C-peptide/insulin ratio of absolute and integrated responses to glucose challenges was calculated (20, 23). Glucose and insulin values obtained during the FSIGT were used to calculate Si (31, 32) and Sg, by a computerized algorithm (MINMOD). Si is expressed in international units $\times 10^{-4}$/min × μU/ml, and Sg in international units $\times 10^{-4}$/min.

Statistical analysis of the results was performed by the *t* test for paired data. Two-way ANOVA for repeated measures (treatment × time, with subjects as replicates) was also used to evaluate differences on glucose, insulin C-peptide or C-peptide/insulin ratio to the OGTT or first 20 min of the FSIGT. All the results are expressed as the mean ± SE.

Results

At the baseline OGTT no subject showed an impaired glucose tolerance. There were four dropouts in the OGTT evaluation group and three dropouts in the FSIGT evaluation group. Accordingly, calculations of the OGTT results were performed in 30 women (14 placebo and 16 raloxifene), and those of the FSIGT results in 21 women (11 placebo and 10 raloxifene). General characteristics and lipid modifications of the women allocated to the OGTT or FSIGT investigations are presented together (Table 1). There was no significant difference in the clinical parameters of women allocated to

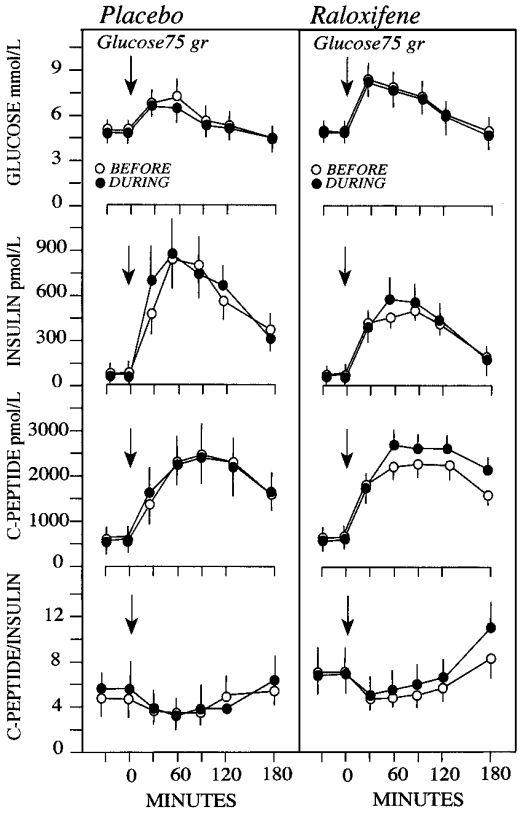

FIG. 1. Mean (±SE) glucose, insulin, C-peptide, C-peptide/insulin responses to an OGTT observed in postmenopausal women prior (*open circles*) and after (*closed circles*) 6 months of placebo (on the *left*; n = 14) or raloxifene at the dose of 60 mg/d (on the *right*; n = 16). *Arrows* indicate time of glucose administration.

TABLE 1. Mean (±SE) characteristics of women treated for 6 months with placebo (n = 25) or raloxifene (60 mg/d; n = 26)

	Placebo		Raloxifene	
	Before	During	Before	During
Age (yr)	57.2 ± 0.5		57.7 ± 0.4	
BMI (kg/m^2)	25.1 ± 1.0	24.8 ± 0.9	23.2 ± 0.6	23.1 ± 0.7
HDL-ch (mmol/liter)	1.59 ± 0.1	1.55 ± 0.1	1.69 ± 0.14	1.73 ± 0.76
LDL-ch (mmol/liter)	4.96 ± 0.51	4.94 ± 0.37	4.84 ± 0.34	3.83 ± 0.49[a]
LDL/HDL (mmol/liter)	3.20 ± 0.05	3.17 ± 0.04	3.21 ± 0.31	2.46 ± 0.44[a]
Triglycerides (mmol/liter)	0.98 ± 0.07	0.92 ± 0.02	1.24 ± 0.13	1.12 ± 0.13

[a] $P < 0.02$ *vs.* before.

TABLE 2. Integrated values (units × minutes; AUC) of glucose, insulin, C-peptide, and C-peptide to insulin ratio during an OGTT (75 g) observed in postmenopausal women before and after 6 months of placebo (n = 14) or raloxifene (60 mg/d; n = 16)

	Placebo		Raloxifene	
	Before	During	Before	During
Glucose (mmol/liter)	1,075 ± 46	983 ± 42	1,204 ± 60	1,164 ± 49
Insulin (pmol/liter)	97,863 ± 21,842	110,897 ± 24,227	69,980 ± 6,946	71,182 ± 8,750
C-peptide (pmol/liter)	279,867 ± 82,429	314,934 ± 80,676	352,439 ± 25,507	399,815 ± 41,249
C-peptide/insulin	3.2 ± 0.8	3.3 ± 0.9	5.8 ± 0.5	6.4 ± 0.6

placebo or raloxifene, although serum triglycerides tended to be higher in the raloxifene group. Circulating levels of estradiol were less than 13 pg/ml and were not modified by placebo or raloxifene treatment. Body mass index did not vary during both treatments. Administration of placebo did not modify levels of HDL cholesterol, LDL cholesterol, LDL/HDL cholesterol and triglycerides. Administration of raloxifene did not modify levels of HDL cholesterol and triglycerides but significantly decreased LDL-cholesterol (P = 0.014) and the LDL/HDL cholesterol ratio (P = 0.012).

OGTT evaluation

At baseline, women randomly assigned to placebo had fasting insulin levels higher ($P < 0.01$) and response of C-peptide/insulin to the OGTT lower ($P < 0.05$) than women allocated to raloxifene.

During placebo, no modification was observed in fasting glucose (4.64 ± 0.19 mmol/liter *vs.* 4.96 ± 0.12 mmol/liter), insulin (95.1 ± 10.1 pmol/liter *vs.* 103.6 ± 15.2 pmol/liter), C-peptide (549.9 ± 126.3 pmol/liter *vs.* 516 ± 178 pmol/liter), or C-peptide/insulin (5.5 ± 0.9 *vs.* 4.76 ± 1.1). Similarly, absolute (Fig. 1) or integrated (Table 2) responses to the OGTT of glucose, insulin, C-peptide, and C-peptide/insulin did not vary during the placebo treatment.

Treatment with raloxifene did not modify fasting levels of glucose (4.99 ± 0.2 mmol/liter *vs.* 4.98 ± 0.15 mmol/liter), insulin (62.1 ± 4.2 pmol/liter *vs.* 62.4 ± 4.9 pmol/liter), C-peptide (528 ± 66.6 pmol/liter *vs.* 551.5 ± 72.2 pmol/liter), and C-peptide/insulin (7.7 ± 0.7 *vs.* 8.6 ± 0.8.). Similarly, absolute (Fig. 1) or integrated (Table 2) responses to the OGTT of glucose, insulin, C-peptide, and C-peptide/insulin were not modified by the 6-month treatment with raloxifene.

FSIGT evaluation

At baseline, no difference was observed between women allocated to raloxifene or placebo in fasting values or responses to the FSIGT.

Placebo did not modify fasting levels of glucose (5.01 ± 0.3 mmol/liter *vs.* 4.98 ± 0.3 mmol/liter), insulin (70.8 ± 4.1 pmol/liter *vs.* 65.8 ± 4.9 pmol/liter), C-peptide (270.1 ± 53.4 pmol/liter *vs.* 263.7 ± 55.6 pmol/liter), and C-peptide/insulin (3.80 ± 0.4 *vs.* 3.97 ± 0.6). Absolute (Fig. 2) and integrated (Table 3) responses of glucose, insulin, C-peptide, and C-peptide/insulin in the first 20 min of the FSIGT, were not modified by placebo. Similarly, administration of placebo did not modify Si (4.30 ± 1.4 *vs.* 4.43 ± 2.1) or Sg (0.023 ± 0.002 *vs.* 0.021 ± 0.002) values (Fig. 3)

Raloxifene did not modify fasting levels of glucose (4.8 ± 0.17 mmol/liter *vs.* 4.8 ± 0.2 mmol/liter), insulin (76.4 ± 13.5 pmol/liter *vs.* 65.7 ± 5.3 pmol/liter), C-peptide (230.0 ± 77.6 pmol/liter *vs.* 250.2 ± 33.6 pmol/liter), and C-peptide/insulin (3.52 ± 0.9 *vs.* 3.8 ± 0.6). Absolute (Fig. 2) or integrated responses (Table 3) of glucose, insulin, C-peptide, and C-peptide/insulin ratio evaluated during the first 20 min of the FSIGT were not modified by raloxifene.

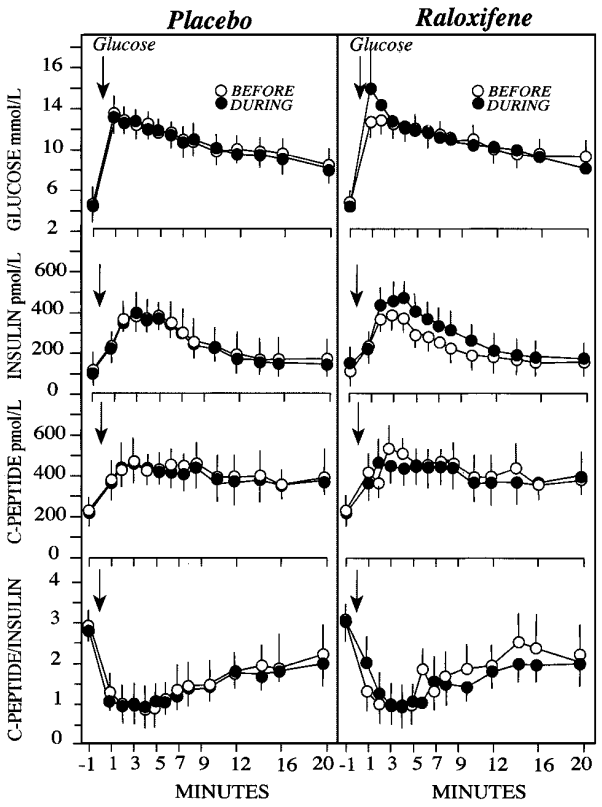

FIG. 2. Mean (±SE) glucose, insulin, C-peptide, C-peptide/insulin responses to an iv glucose tolerance test observed in postmenopausal women at baseline (*open circles*) and after 6 months of treatment (*closed circles*) with placebo (on the *left*; n = 11) or 60 mg/d of raloxifene (on the *right*; n = 10). *Arrows* indicate time of glucose administration.

Administration of raloxifene did not modify Si (4.22 ± 4.1 *vs.* 5.13 ± 1.75), and Sg (0.025 ± 0.003 *vs.* 0.019 ± 0.002) values (Fig. 3).

Discussion

In osteoporotic postmenopausal women, raloxifene does not modify cardiovascular risk factors as PAI or C-reactive protein (27, 28) and reduces fibrinogen (27), homocysteine (28), and LDL (3, 27). The present study, performed in osteopenic but otherwise healthy postmenopausal women,

TABLE 3. Integrated values (units × minutes; AUC) of glucose, insulin, C-peptide, and C-peptide to insulin ratio during first 20 min of a FSIGT observed in 10 postmenopausal women before and after 6 months of placebo (n = 11) or raloxifene (60 mg/d; n = 10) administration

	Placebo		Raloxifene	
	Before	During	Before	During
Glucose (mmol/liter)	205.1 ± 15.0	198.5 ± 12.5	219.9 ± 10.0	228.7 ± 11.1
Insulin (pmol/liter)	4980 ± 685	4888 ± 470	5063 ± 797	5275 ± 794
C-peptide (pmol/liter)	6430 ± 1380	6123 ± 1668	6763 ± 1403	7248 ± 1598
C-Peptide/insulin	1.3 ± 0.5	1.26 ± 2.5	1.6 ± 0.3	1.4 ± 0.3

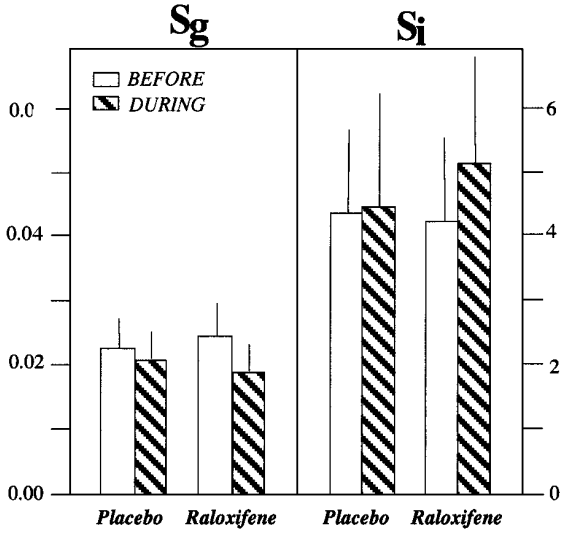

FIG. 3. Mean (±SE) glucose utilization not dependent on insulin (Sg) and dependent on insulin (Si) observed in postmenopausal women at baseline (*open bars*) and after 6 months of treatment (*hatched bars*) with placebo (on the *left*; n = 11) or raloxifene at the dose of 60 mg/d (on the *right*; n = 10). Sg is expressed in international units × 10^{-4}/min and Si in international units × 10^{-4}/min × μU/ml.

confirms the capability of raloxifene to reduce levels of LDL and LDL/HDL ratio.

Glucose metabolism deteriorates with age (12–15), and this effect can possibly be slowed by estrogen administration (20–25). Indeed, transdermal estradiol has been reported to increase pancreatic β-cell responsiveness (C-peptide), to enhance insulin clearance, mainly from the liver (C-peptide/insulin ratio) (20, 22), and to improve Si (21, 25). This latter effect has not been confirmed in other studies (17–19, 20, 23). In comparison to transdermal, oral estrogens do not seem to affect pancreatic β-cell responsiveness and insulin clearance (20). Oral estrogens improve Si (22, 24, 25), although this effect has not been always documented (16–18). Modifications of glucose metabolism similar to those induced by oral estrogens have been reported with tibolone whose administration increases Si (33). Herein it was investigated whether the effect of raloxifene on pancreatic β-cell responsiveness, insulin clearance, and Si resembles that of estrogens. Raloxifene is administered orally, and modifications, mainly on Si, similar to those induced by oral estrogens (20, 22, 24, 25, 33) were expected. In a previous report, focused on the modification of the GH/IGF-I axis, a beneficial effect of raloxifene on Si was suggested on the basis of an improved insulin/glucose ratio observed in two fasting blood samples (26). Those data are not herein confirmed with the use of a method more appropriate to investigate Si (31, 32). Indeed, in the present study raloxifene did not modify insulin-dependent and insulin-independent glucose utilization. Similarly, raloxifene did not affect pancreatic β-cell responsiveness and insulin clearance evaluated during the OGTT. These data are in accordance with a recent publication reporting a neutral effect of raloxifene on glucose control of diabetic women (34).

We cannot exclude that the 6-month administration of raloxifene was too short to induce metabolic modifications. However, it was sufficient to induce the expected changes in lipoprotein levels, and in previous studies, to document, estrogen-induced modifications of glucose metabolism (16, 21–25, 33). The statistical power of the study was calculated on the basis of previous results with estrogens (20–22, 24, 25, 33). Raloxifene failed to significantly influence glucose metabolism, but trends of modifications were not negative. Eventual consolidation or magnification of these trends in larger clinical trials might result in the documentation of a minimal positive effect of raloxifene on glucose-insulin metabolism.

In conclusion, the present data indicate that the cardiovascular risk of osteopenic postmenopausal women is not likely to be influenced by raloxifene through modifications in glucose/insulin metabolism.

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