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Insulin Resistance Is Increased by Transdermal Estrogen Therapy in Postmenopausal Women with Cardiac Syndrome X

A.R. Assali[a, b] Z. Jabara[b] Z. Shafer[b] A. Solodky[c] I. Herz[c] E. Sclarovsky[c]
B. Strasberg[c] S. Sclarovsky[c] M. Fainaru[b]

[a]Cardiology Division, University of Texas Medical School and Hermann Hospital, Houston, Tex., USA;
[b]Lipid Research Laboratory, Department of Medicine A, [c]Cardiology Department, Rabin Medical Center, Beilinson Campus, Petah-Tiqva, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

Key Words
Insulin resistance · Estrogen replacement therapy · Cardiac syndrome X

Abstract
Estrogen has been reported to have both short- and long-term effects on the cardiovascular system. However, it remains to be examined how short-term transdermal estrogen therapy (TET) affects insulin sensitivity (SI) in patients with cardiac syndrome X (CSX), who are characterized by elevated insulin resistance. SI was assessed in a randomized, double-blind, placebo-controlled crossover study by minimal model analysis in seven postmenopausal women with CSX treated by TET. SI decreased by 32 ± 8.3%, from 5.94 ± 1.14 at baseline to 3.61 ± 0.40 [$(10^{-4} \times min^{-1})/(\mu U/ml)$] during TET ($p = 0.03$). Time to the onset of symptoms increased from 414.2 ± 51.0 s at baseline to 450.0 ± 53.2 s ($p = 0.04$). We conclude that TET increases SI in postmenopausal women with CSX. This effect is unrelated to the beneficial anti-ischemic effects on exercise duration.

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This study was performed to fulfill the requirements for internal medicine certification in Israel for Z.J.

Introduction

Cardiac syndrome X (CSX) describes patients with angina-like chest pain, noninvasive tests suggestive of myocardial ischemia and angiographically normal epicardial coronary vessels. Several pathophysiological theories have been put forward to explain this syndrome, including endothelial dysfunction and decreased coronary vasodilator reserve [1, 2]. Since most patients with CSX are postmenopausal women, a possible link to estrogen deficiency has been postulated [3]. Recently, it has been shown that transdermal estrogen therapy (TET) lessens angina and myocardial ischemia in postmenopausal women with coronary artery disease [4] or CSX [5, 6]. The possible mechanism could be an improvement in endothelial function [6, 7].

Insulin resistance (IR) is one of the newly recognized risk factors for coronary artery disease. IR is associated with atherogenic dyslipidemia, hypertension, procoagulant state and glucose intolerance [8–11]. It is believed that IR has a key role in this constellation, which is common in persons who develop premature coronary heart disease [8]. Furthermore, CSX was recently reported to be associated with IR [12–14].

Since TET is associated with improvement in both the clinical symptoms and vasomotor function in CSX pa-

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Prof. M. Fainaru
Lipid Research Laboratory, Department of Medicine A
Rabin Medical Center, Petah Tiqva 49 100 (Israel)
Tel. +972 3 937 7101, Fax +972 3 923 1019
E-Mail mfainar@post.tau.ac.il

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tients, it may be expected that such beneficial effects may be associated with an improvement in insulin sensitivity (SI) and a decrease in insulin levels. To our knowledge, the short-term effects of TET on SI in postmenopausal women with CSX have not been directly investigated. This prospective, randomized, double-blind, placebo-controlled crossover study was thus designed to examine whether short-term TET affects IR.

Patients and Methods

Subjects

Seven nondiabetic postmenopausal women aged 49–60 years who suffered from CSX were studied. The subjects fulfilled all the following inclusion criteria: (1) menopause >6 months of duration; (2) typical anginal chest pain; (3) evidence of myocardial ischemia as assessed either by ECG changes during angina (ST segment depression >1 mm or T wave inversion on at least two consecutive leads) or by positive exercise test results, and positive thallium-201 scintigraphy for stress-induced regional uptake abnormalities and (4) normal results on coronary arteriograms within 6 months of the study. All patients underwent a clinical gynecological examination including a vaginal ultrasound examination and a Papanicolaou smear. Those with a history of malignancy, thromboembolism, previous cardiac disease (infarction, valvular or cardiomyopathy), diabetes mellitus, hypertriglyceridemia (triglyceride >250 mg/dl), liver disease or detectable abnormalities on physical examination or laboratory testing were excluded. Patients with hypertension and ventricular hypertrophy (septum or posterior wall thickness >12 mm) were also excluded. No patient was receiving estrogen replacement therapy. All women received accurate information about the study protocol and gave written consent. The study was approved by the hospital Ethics Committee.

Study Protocol

The study was conducted using a prospective, randomized, double-blind crossover design. After a 4-week run-in phase, the patients were randomly assigned, in a double-blind manner, to receive 17-beta-estradiol or placebo for 4 weeks; then they crossed over to the alternative treatment for 4 weeks. 17β-estradiol was administered in the form of self-adhesive cutaneous patches (Estraderm TTS, Ciba Pharmaceuticals), providing a cutaneous absorption rate of 50 μg/24 h. The estrogen and placebo patches were identical in appearance, and all patches were changed every 3 days. Compliance with the study medication was confirmed by the measurement of plasma 17β-estradiol concentrations. The subjects were studied at baseline and at the end of each treatment period, i.e. after 4 and 8 weeks.

Exercise Testing

Symptom-limited exercise testing was performed using the Bruce protocol. A 12-lead ECG and blood pressure were recorded at baseline, at the end of each exercise stage, at the onset of chest pain and at 1-mm ST segment depression during exercise, at peak exercise and during recovery.

Measurements and Analysis

17β-estradiol concentrations were quantified by enzyme-linked immunoassay (Diagnostic Products Coropration, Los Angeles, Calif., USA). Plasma lipid levels were determined by enzymatic methods (Boehringer, Mannheim) after a 12-hour overnight fast. SI was assessed by an insulin-enhanced, frequently sampled intravenous glucose tolerance test (FSIGT) using minimal model analysis [15]. The FSIGT was conducted after an overnight fast and 30 min of recumbency. An intravenous line was inserted into each antecubital vein. Glucose (0.3 g/kg) and insulin (0.03 U/kg) were injected intravenously in one arm at 0 and 20 min, respectively, and blood samples from the other arm were collected for glucose and insulin determination at –5, –1, 2, 4, 6, 8, 10, 12, 14, 16, 19, 22, 23, 25, 27, 30, 40, 50, 60, 90, 120 and 180 min. blood glucose was determined by the glucose-oxidase method (Boehringer, Mannheim) and serum insulin by radioimmunoassay (Sorin, Biomedica).

Statistical Analysis

Data are presented as mean ± SEM. Repeated-measures analysis of variance (ANOVA) was used to compare the different periods, and the Pearson correlation coefficient was used to study the degree of association between changes in SI and weight. A p value of 5% or less was considered significant.

Results

All seven patients had a positive exercise test at baseline. All patients were stable during the study period. Four patients were randomly assigned to initial treatment with 17β-estradiol patches. The baseline characteristics of the patients are shown in table 1. There was a slight, statistically nonsignificant increase in body weight (1.56 ± 2.25%) with TET.

Metabolism

The results of metabolic tests are presented in table 1. The mean baseline serum estradiol level was 111.3 ± 28.3 pg/ml. Serum estradiol increased significantly by 100 ± 19% ($p = 0.01$) during TET. Fasting blood levels of glucose, insulin and serum lipids did not change significantly during the two treatment periods. Serum triglyceride tended to increase during TET, but this increase did not reach statistical significance. The SI index decreased by 32 ± 8.3%, from 5.94 ± 1.14 at baseline to 3.61 ± 0.40 [$(10^{-4} \times min^{-1})/(\mu U/ml)$] during TET ($p = 0.03$). There was a negative correlation between changes in SI and changes in weight during estradiol therapy ($r = -0.33$, $p < 0.05$). SI did not change significantly during placebo therapy.

Exercise Time and ST Segment Depression

The results from exercise testing are presented in table 2. TET significantly prolonged the exercise duration

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Table 1. Weight and metabolic parameters (mean ± SEM) at baseline and after placebo or estrogen replacement therapy

	Baseline (n = 7)	Placebo (n = 7)	TET (n = 7)
Body weight, kg	74.7 ± 4.4	74.9 ± 4.3	75.7 ± 4.2
Estrogen level, pg/ml	111.2 ± 28.3	111.3 ± 11.2	216.0 ± 52.2*
Fasting glucose, mg/dl	85.3 ± 6.3	85.7 ± 5.1	85.2 ± 4.3
Fasting insulin, μU/ml	15.6 ± 1.6	14.1 ± 1.2	15.4 ± 1.4
SI index, $[(10^{-4} \times min^{-1})/(\mu U/ml)]$	5.94 ± 1.14	6.19 ± 0.81	3.61 ± 0.40**
Serum cholesterol, mg/dl			
Total	231.6 ± 19.3	224.1 ± 9.5	226.1 ± 12.5
HDL	56.7 ± 6.0	51.9 ± 4.2	54.4 ± 4.3
LDL	146.1 ± 12.8	139.6 ± 7.9	145.3 ± 10.0
Lp(a)	42.6 ± 9.8	37.0 ± 6.0	41.6 ± 7.6
Serum triglyceride, mg/dl	142.6 ± 19.9	149.7 ± 29.1	165.3 ± 29.8

* p = 0.01, ** p = 0.03. HDL = High-density lipoprotein; LDL = low-density lipoprotein; Lp(a) = lipoprotein(a).

Table 2. Hemodynamic responses during exercise stress test (mean ± SEM) at baseline and after placebo or estrogen replacement therapy

	Baseline (n = 7)	Placebo (n = 7)	TET (n = 7)
Exercise duration to symptoms, s	414.2 ± 51.0	398.2 ± 52.9	450.0 ± 53.2*
Maximal ST segment depression, mV	3.3 ± 0.45	3.0 ± 0.68	1.33 ± 0.39**
Peak heart rate, beats/min	157.8 ± 6.0	151.8 ± 5.6	155.0 ± 6.3
Peak systolic blood pressure, mm Hg	174 ± 6.3	164 ± 9.1	171 ± 4.7
Peak diastolic blood pressure, mm Hg	92 ± 6.8	88 ± 4.9	93 ± 5.3
Rate-pressure product (mm Hg × beats/min) × 10^2	275 ± 19.7	253 ± 16.6	266 ± 14.7

* p = 0.04, ** p = 0.003.

and time to the onset of symptoms from 414.2 ± 51.0 s at baseline to 450.0 ± 53.2 s (p = 0.04), as well as reducing the mean total ST segment depression during exercise (3.3 ± 0.45 versus 1.33 ± 0.39 mm; p = 0.003). No significant difference was noted in heart rate, blood pressure or rate-pressure product among the three examinations.

Discussion

The results of this study show that in postmenopausal women with CSX, TET increases IR by 32%. This deterioration in IR is unrelated to the short-term beneficial effect on exercise time and ST segment depression.

Hyperinsulinemia is detected frequently in patients with CSX [12–14], suggesting that a metabolic disorder may play a role in the pathogenesis of the cardiac syndrome. However, the link between microvascular dysfunction and hyperinsulinemia is still elusive. Recently, it has been shown that TET lessens angina and myocardial ischemia in postmenopausal women with CSX [5]. On the other hand, the effects of menopause and estrogen replacement therapy on IR are controversial. In two studies [16, 17] using the hyperinsulinemic euglycemic clamp technique, no significant change in SI was found with either oral estrogen therapy or TET. Cagnacci et al. [18] found that TET (50 μg/day) improved IR (measured by oral glucose tolerance test), while oral conjugated estrogen (25 mg/day) had no effects. In a later study, using FSIGT, these same investigators [19], along with others [20], did not find any effect on SI by TET. Kimmerle et al. [21] recently reported that SI decreased when higher doses of oral estradiol/norethisterone acetate were used.

To our knowledge, the short-term effects of TET on SI in postmenopausal women with CSX have not been directly investigated. The reason for the negative impact of TET on IR in women with CSX as we observed in the present study is not known. We can only speculate as to

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the mechanism. One possibility may be the mild increase in body weight seen during TET. We found a significant negative correlation between weight gain and change in SI during TET. In a recent study [Assali et al., in preparation], we found that even minor changes in body weight have a major impact on IR. A second possibility is that this group of patients with increased baseline IR has a different response to estrogen replacement therapy than postmenopausal women without cardiac syndrome X.

Clinical Implications

The clinical significance of our findings remains to be investigated. This deterioration in IR provides a possible mechanistic correlate to the results of pooled analysis of short-term randomized clinical trials [22] and the recently published HERS trial [23], which showed a tendency for an increased rate of coronary events in women with coronary disease who were assigned to estrogen plus medroxyprogesterone acetate. Although these findings cannot be generalized to all forms of estrogen therapy, studying the effects of hormone therapy on newly discovered coronary risk factors may provide useful information regarding the mechanism of therapy-mediated risk reduction.

Limitations of the Study

The main limitations of our study are: (1) only seven patients were investigated; however, the negative iompact of TET on SI was evident even with this small number and (2) we concentrated only on the immediate effects of estrogen.

Conclusion

TET increases IR in postmenopausal women with cardiac syndrome X. This effect is unrelated to the beneficial anti-ischemic effects on exercise duration.

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