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ORIGINAL ARTICLE

Insulin sensitivity during postmenopausal hormone replacement with transdermal estradiol and intrauterine levonorgestrel

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Background. The study was devised to measure the effect of intrauterinely delivered levonorgestrel and transdermal estradiol on insulin sensitivity in postmenopausal women and compare this effect with that induced by transdermal estradiol alone.
Methods. An open, prospective, comparative study of healthy postmenopausal women without earlier use of hormone replacement therapy. The estrogen therapy group consisted of eight hysterectomized women, who used a transdermal patch delivering a daily dose of 50 μg of estradiol continuously for 6 months. The estrogen-progestin therapy group consisted of 13 women with an intact uterus, who received a simultaneous combination of a transdermal patch and a levonorgestrel (20 μg/day) intrauterine system for the same length of time. Fasting plasma concentrations of glucose, insulin and C-peptide and an insulin tolerance test were used to measure glucose metabolism and insulin sensitivity.
Results. Neither therapy changed the fasting plasma levels of glucose, insulin or C-peptide. Transdermal estrogen improved insulin sensitivity by 22%, as measured by an insulin tolerance test, while a small increase of 3.6% was observed using the combination therapy.
Conclusions. Transdermal estradiol improves insulin sensitivity in healthy postmenopausal women. Combining intrauterine levonorgestrel to transdermal estradiol reverses this effect. This combination does not, however, seem to induce insulin resistance.

Key words: insulin sensitivity; intrauterine; levonorgestrel; transdermal estrogen

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Epidemiologic studies suggest that postmenopausal estrogen replacement therapy is associated with an overall reduction of 50% in the risk of cardiovascular disease (1–3). The addition of progestin to estrogen therapy does not appear to attenuate this cardioprotective effect (4, 5) and may even result in a more beneficial physiologic profile than the use of estrogen alone (6).

Abbreviations:
ANOVA: analysis of variance; BMI: body mass index; CV: coefficient of variance; E_2: estradiol; FSH: follicle stimulating hormone; ITT: insulin tolerance test; MPA: medroxyprogesterone acetate; NS: nonspecific; SE: standard error; s.d.: standard deviation.

The cardioprotective effect of estrogen depends on several mechanisms. Estrogen replacement therapy improves arterial function through direct endothelium- and calcium-dependent mechanism (7, 8). It also induces beneficial changes in lipids and lipoproteins (9), in coagulation and fibroninolysis (10–12) and in glucose and insulin metabolism (13).

Elevated plasma insulin concentrations are suggested to be an independent risk factor for coronary heart disease (14, 15), although some controversy exists (16, 17). Menopause is associated with a reduced pancreatic insulin secretion response and reduced insulin elimination. There

is a progressive increase in insulin resistance (18, 19) and hence circulating insulin levels with increasing age in postmenopausal women, which may be counteracted by estrogen replacement therapy. In a cohort study, which was controlled for confounding factors such as age and obesity, women on oral estrogen therapy had lower levels of insulin and no evidence of impaired glucose tolerance as compared with those who did not take estrogen (13). In another cohort study, current users of oral estrogen had lower levels of fasting serum glucose and insulin than nonusers (6). Postmenopausal replacement therapy with transdermal estradiol has not been associated with any major impact on glucose metabolism (20, 21) or shown to exert a beneficial effect (22–24).

Progestins increase pancreatic insulin secretion but, in contrast to estrogen, they also increase insulin resistance. There are observations of attenuating effect of oral progestins on insulin sensitivity when given cyclically with oral (13, 22, 25) or transdermal estrogen (23). Insulin sensitivity is unaffected, however, by the addition of cyclic transdermal norethisterone acetate to continuous transdermal estradiol (25).

A new method of postmenopausal hormone replacement therapy is to combine transdermal estrogen with a levonorgestrel intrauterine system. Intrauterinely administered levonorgestrel has been proven to effectively protect the endometrium from the proliferative action of estrogen and to produce amenorrhea (26).

Apart from the type and dose of progestin, the attenuation of glucose metabolism induced by progestin may also depend on the method of administration. We therefore designed a prospective, open study to determine the effect of intrauterine levonorgestrel in combination with continuous transdermal estradiol on insulin sensitivity. In addition, we compared its effect on the changes induced by transdermal estradiol alone.

Material and methods

Twenty-one healthy, volunteer postmenopausal women seeking help for their climacteric symptoms were recruited into the study. Those with an intact uterus were required to have had amenorrhea for at least 12 months but less than 5 years. Exclusion criteria were a history of malignancy of any kind, a history of thromboembolism, a history of gestational diabetes or diabetes, and a history of earlier postmenopausal hormonal replacement therapy. Approval for the study was obtained from the ethical committee of Oulu University and the patients gave their informed consent.

All patients underwent a clinical gynecological examination including a vaginal ultrasound examination and a Papanicolaou smear. An endometrial biopsy was obtained in women with an intact uterus to exclude endometrial pathology. The postmenopausal status was confirmed by an elevated serum FSH concentration (>24 U/L).

Unopposed estrogen is contraindicated in women with an intact uterus, and therefore no randomization was performed in this study. Those eight women who had undergone hysterectomy for benign gynecological diseases earlier, formed the estrogen therapy group. They received transdermal estradiol via a patch releasing 50 μg of estradiol per day, which was changed twice a week (Estraderm TTS®, Novartis, Stein, Germany). The estrogen therapy was continued for 6 months. The estrogen-progestin therapy group consisted of thirteen women with an intact uterus. After a one-month period of transdermal estrogen (Estraderm TTS®) a levonorgestrel intrauterine system releasing 20 μg of levonorgestrel per day (Levonova®, Leiras Oy, Turku, Finland) was inserted into the uterine cavity. This combination therapy continued for 6 months.

An insulin tolerance test (ITT) was carried out on each patient before any hormonal therapy and after 1, 2, 3 and 6 months of therapy. After a 12-h overnight fast, a 16-gauge butterfly needle (Venflon 2®, Ohmeda AB, Helsingborg, Sweden) was placed in an antecubital vein for blood sampling. A basal blood sample was drawn, and the plasma was separated with centrifugation and frozen for later measurement of fasting plasma glucose, insulin and C-peptide. Following this, a bolus of 0.1 U/kg body weight of regular human insulin (Actrapid®, Novo Nordisk, Bagsvaerd, Denmark) was given intravenously to an antecubital vein in the contralateral antebrachium. Blood samples were obtained at −15, −5, 0, 3, 6, 9, 12, 15, 20 and 30 minutes after the insulin injection to determine blood glucose concentrations as described by Bonora et al. (27). One hundred ml of 10% glucose was given intravenously at 30 minutes to arrest the

Table I. The age, BMI and the baseline values of plasma glucose, insulin and C-peptide of the patients, mean (s.d.)

	Estrogen therapy group	Estrogen-progestin therapy group
Age, years	50 (47–54)[1]	50.7 (45–58)[1]
BMI, kg/m^2	24.9 (2.4)	25.9 (2.8)
Plasma glucose, mmol/L	4.5 (0.5)	4.5 (0.5)
Plasma insulin, mU/L	8.6 (4.5)	7.8 (4.2)
Plasma C-peptide, μg/L	1.9 (0.7)	1.8 (1.0)

[1] median (range).

Table II. The plasma levels (mean, s.d.) of insulin, glucose and C-peptide during transdermal estradiol therapy alone (E group) and combined with intrauterine levonorgestrel (E–P group)

	Plasma insulin, mU/L		Plasma glucose, mmol/L		Plasma C-peptide, ug/L	
	E group	E-P group	E group	E-P group	E group	E-P group
0 months	8.6 (4.5)	8.4 (5.7)	4.5 (0.5)	4.6 (0.5)	1.9 (0.7)	1.7 (0.9)
1 months	7.5 (2.4)	7.5 (4.2)	4.6 (1.0)	4.5 (0.6)	1.6 (0.5)	1.8 (0.9)
2 months	7.6 (1.8)	6.6 (3.2)	4.4 (0.5)	4.6 (0.6)	1.7 (0.5)	1.8 (0.8)
3 months	7.2 (2.1)	7.0 (2.6)	4.4 (0.4)	4.6 (0.6)	2.0 (0.9)	1.9 (0.9)
6 months	9.0 (4.0)	7.9 (4.2)	4.5 (0.6)	4.6 (0.6)	2.3 (1.5)	2.0 (1.0)

fall in plasma glucose. The plasma glucose disappearance rates were calculated from the glucose concentrations at the 3- to 15-min period following intravenous insulin injection.

Serum estradiol (E_2) was measured using reagents purchased from Sorin Biomedica (Saluggia, Italy). The intra-assay coefficient of variance (CV) was 4.2%, the range of measurements 0.02–3.7 nmol/L and the reference range for postmenopausal women <0.20 nmol/L. Blood glucose concentration was determined by glucose dehydrogenase catalyzing method (Granutest®, Diagnostica, Merck, Darmstadt, Germany). The normal range in fasting whole blood ranges from 3.9 to 5.6 nmol/L. Serum insulin concentrations were determined with radioimmunoassay purchased from Pharmacia AB, Uppsala, Sweden (Phadeseph®). The intra-assay CV was 8.0, 4.4 and 4.4% for insulin target values of 20.4, 42.4 and 79.1 mU/L and mean fasting levels for healthy individuals lie below 20 mU/L. The cross reactivity with C-peptide is<0.1% by weight. Serum C-peptide concentrations were determined with a radioimmunoassay purchased from EURO/DPC Ltd, United Kingdom. The intra-assay CV was 3.4, 3.0 and 5.3% for C-peptide target values of 0.89, 7.9 and 14.22 µg/L and the interassay CV was 10.0, 1.9 and 7.2% for C-peptide target values of 0.90, 8.85 and 15.38 µg/L. The reference range was 0.8 to 4 µg/L.

The Student's *t* test for independent variables was used to test the significance of the difference between the two study groups in the baseline concentrations of glucose, insulin and C-peptide. A two-way analysis of variance (ANOVA) for repeated measurements was used to test the significance of the change in glucose, insulin and C-peptide concentrations from baseline to 12 months within and between the two study groups. During ITT, the glucose disappearance rate was described by the slope of the regression analysis of the fall in glucose over time. This regression line, which is based on the least squares, was obtained from the 3- to 15-min period, when the decline in glycemia is linear over time. To detect differences in the mean glucose disappearance rates within and between the study groups, a two-way ANOVA was used. The relationship between body mass index (BMI) and insulin was performed using a linear regression model. The values of insulin were transformed by the natural logarithm. A p value<0.05 was considered as statistically significant.

Results

There was no difference between the two study groups with respect to age, BMI or the baseline values of insulin, glucose or C-peptide of the patients at the baseline (Table I). All the patients were within 20% of their ideal body weight. There was a positive correlation at the baseline between BMI

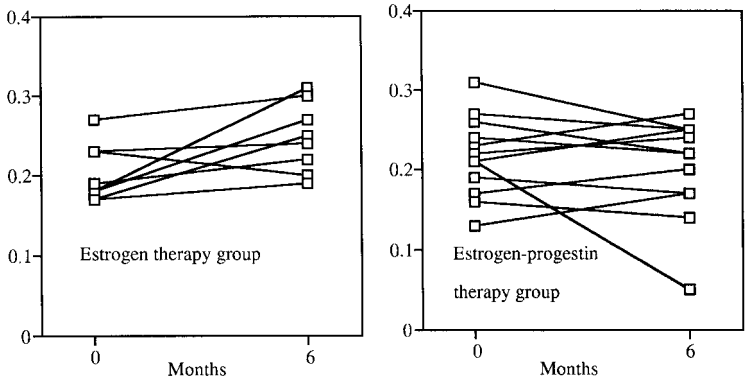

Fig. 1. The change in the constant of the slope of the regression line between 3 and 15 minutes after intravenous insulin injection in the patients at the baseline and after 6 months of therapy with transdermal estradiol alone or combined with intrauterine levonorgestrel.

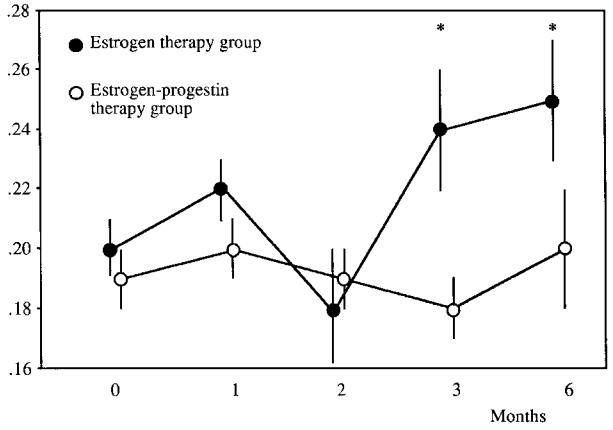

Fig. 2. Mean (SE) constant of the slope of the regression line between 3 and 15 minutes after intravenous insulin injection, $*p<0.05$ between the study groups.

and fasting insulin levels ($p=0.011$) but not with BMI and fasting glucose levels ($p=0.754$).

During the 6-month therapy the mean (s.d.) circulating E_2 levels increased significantly in women using transdermal estrogen therapy from 0.07 (0.05) to 0.16 (0.05) nmol/L and in women using transdermal estrogen combined with a levonorgestrel intrauterine system from 0.05 (0.03) to 0.16 (0.11) nmol/L. There were no differences between the two therapy groups at the baseline or endpoint of the study.

During the study period, there were no significant changes in the fasting levels of plasma glucose, insulin or C-peptide in either group. No significant differences were observed between the two study groups at any point of the study (Table II).

The plasma glucose disappearance rate increased in 6/8 women, remained the same in one and decreased in one woman using transdermal estrogen. However, this value decreased in 8/13 women and increased in 5/13 using transdermal estrogen with levonorgestrel intrauterine system (Fig. 1). The mean plasma glucose disappearance rate increased in the estrogen therapy group ($p=0.013$) but not in the estrogen-progestin therapy group (NS). There was a significant difference between the two study groups ($p=0.015$), and the difference was mainly observed after 3 months of treatment (Fig. 2).

Discussion

Fasting blood levels of glucose, insulin or C-peptide were not modified by replacement therapy with transdermal estrogen alone or transdermal estrogen combined with a levonorgestrel intrauterine system (Table II). These measures are not helpful methods to demonstrate insulin resistance in postmenopausal women as Lindheim et al. earlier pointed out (1993). There have been contradictory results, however, on the decreasing effect which transdermal estradiol has on fasting plasma insulin levels with the same dose we used (24).

The positive correlation between BMI and fasting insulin levels, which we observed, is a known phenomen. Several obesity-associated life style factors, such as physical activity, alcohol or cigarette consumption contribute little additional information to the prediction of carbohydrate metabolism (28).

The liver extracts approximately 50% of the insulin delivered to it on the first pass. This extracted fraction of secreted insulin is modified by such circumstances as fasting or insulin administered. Proinsulin is enzymatically converted to equimolar quantities of insulin and C-peptide, which are secreted simultaneously from the pancreatic beta cell. As hepatic extraction of C-peptide is negligible, the plasma level of C-peptide can be used to assess pancreatic insulin secretion. We did not find any significant changes in plasma C-peptide concentrations with our study combinations.

The golden standards for measuring insulin sensitivity *in vivo* are the euglycemic and hyperglycemic glucose clamp techniques. These tests require a significant amount of time, work and accurate equipment. Insulin tolerance test has been demonstrated to be a reliable method to test insulin action *in vivo*. The insulin-induced glucose decrease leads to a counterregulatory response and this, in turn, slows the glucose disappearance rate from the plasma. This counterregulatory response, however, takes at least 15–20 minutes to occur after insulin injection (29). Plasma glucose disappearance rate calculated from the plasma glucose concentrations during the first 15 minutes of the test correlates well with the ratio of glucose metabolized to plasma insulin concentrations during steady state euglycemic or hyperglycemic clamp studies. ITT is particularly suitable for studies which include serial evaluations of insulin sensitivity (27).

The increase in glucose disappearance rate means improvement in insulin sensitivity. Lindheim et al. (1993) (22) observed that insulin sensitivity increased 24% with an oral daily dose of 0.625 mg of conjugated equine estrogen measured by ITT. Combining cyclical medroxyprogesterone acetate (MPA) to estrogen therapy attenuated insulin sensitivity from the baseline by 17%. Transdermal estradiol in a daily dose of 100 μg increased the glucose disappearance rate by 13.2% while therapy with a combination of transdermal estradiol and cyclical oral MPA decreased the value by 3.8% (23). This is in accordance with our

present finding of a 22% increase in insulin sensitivity with a daily dose of 50 μg of transdermal estradiol measured with the glucose disappearance rate from plasma. The same dose of 50 μg/day of transdermal estradiol improved glucose metabolism in another study in which an oral glucose tolerance test was performed (24).

The ITT was first carried out monthly to determine how soon the possible alterations in insulin sensitivity will appear after beginning hormone replacement therapy. The effect of hormonal replacement on insulin sensitivity rose during the first months of therapy, and the change was still pronounced after 6 months of therapy (Fig. 2). An earlier study using the hyperinsulinemic euglycemic clamp technique (21) did not find any significant change in insulin action on glucose disposal during 12 weeks of therapy with oral or transdermal estrogen. Transdermal estrogen induced, however, a more pronounced suppression of nonesterified free fatty acid concentration than oral estrogen during the clamp. This suggests an improvement in insulin action on lipid metabolism during transdermal estrogen therapy (21).

In our study, the combination of transdermal estradiol and a levonorgestrel intrauterine system induced practically no change in insulin sensitivity as measured by ITT. Non-oral levonorgestrel counteracted the beneficial effect of estrogen on insulin sensitivity, as the glucose disappearance rate improved by only 3.6% compared to a 22% improvement with transdermal estrogen alone. Our combination, however, did not induce insulin resistance as did a combination of cyclical oral levonorgestrel of 0.075 mg/day and oral continuous conjugated equine estrogen in a daily dose of 0.625 mg. The measurements were performed during the estrogen-alone phase and during the estrogen-progestin phase and showed that insulin resistance was associated with the addition of progestin (25). In addition, oral norgestrel for contraception in a daily dose of 0.075 mg in fertile aged women produced an abnormal glucose tolerance test in 10.1% of the women after 6 months and in 15.5% after one year of therapy (30).

One of our patients (with a BMI of 26.9) in the estrogen-progestin group had a fasting glucose level above the normal range at the baseline and no change was observed during the study. The fasting plasma insulin level was nearly abnormal at the baseline (19.6 mU/L) but decreased during the therapy to a normal value of 12.3 mU/L at the end of the study. Her plasma C-peptide values remained above normal throughout the study, however, indicating a faster insulin clearance rate during the estrogen-progestin treatment. The plasma glucose disappearance rate decreased during the study treatment indicating an increase in insulin resistance.

In conclusion, the present findings confirm that hormone replacement therapy with transdermal estradiol tends to improve insulin sensitivity as measured with the glucose disappearance rate during ITT. This improvement may be attenuated by intrauterine levonorgestrel. It seems, however, that levonorgestrel administered intrauterinely does not induce insulin resistance when combined with transdermal estradiol.

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