Ischemic Heart Disease Risk in Postmenopausal Women
Effects of Estrogen Use on Glucose and Insulin Levels

Elizabeth Barrett-Connor and Markku Laakso

We report the fasting and post-challenge plasma insulin and glucose levels in 469 nondiabetic postmenopausal women from the Rancho Bernardo cohort according to the current use of estrogen replacement therapy. In these older women, the use of noncontraceptive estrogen was not associated with impaired glucose tolerance. Estrogen-treated women had lower levels of insulin than women who were not taking estrogen; these differences were not explained by age, obesity, or differential hormone use by women with known glucose intolerance. There were no significant differences in glucose and insulin levels in those taking conjugated equine estrogen (Premarin) alone compared to those taking it with medroxyprogesterone acetate (Provera). (Arteriosclerosis 10:531–534, July/August 1990)

A large body of epidemiological data supports the hypothesis that postmenopausal estrogen therapy reduces the risk of subsequent ischemic heart disease (IHD). The mechanism is unknown, but the more favorable lipoprotein levels associated with exogenous estrogens are strong explanatory candidates for this apparent protection. Altered endogenous insulin levels could also play a role, either directly as a risk factor for IHD or indirectly as a determinant of lipoproteins, but little work has been done on insulin or carbohydrate tolerance in women using replacement estrogens.

In this article, we report the fasting and post-challenge glucose and insulin levels in 469 nondiabetic women ages 55 years and older, 194 of whom were taking noncontraceptive estrogen at the time of glucose tolerance testing. We also describe the relationship of hormone replacement to glucose and insulin levels in women using estrogen alone versus estrogen plus progestin.

Methods

Between January 1984 and June 1987, 1239 postmenopausal women ages 55 to 92 years from a defined population, Rancho Bernardo, California, participated in a study of diabetes and other chronic diseases. A medical history including all current medication use was obtained by a clinic nurse, who examined the medicines and prescriptions brought to the clinic for confirmation. Behaviors (cigarette smoking, alcohol intake, and leisure-time physical activity) were determined by a standardized questionnaire. Height and weight were measured with participants in light clothing without shoes. A standard 75 g oral glucose tolerance test was performed between 7:00 A.M. and 11:00 A.M. after a requested 12-hour fast. Venous blood was obtained after fasting and 2 hours after the glucose load; plasma was analyzed for glucose by an oxidase method, and insulin, by a double radioimmunoassay method in a diabetes research laboratory.

Standardized plasma insulin levels were not available until November 1984; 535 postmenopausal women were seen after that date. Sixty-six women with diabetes defined by history and World Health Organization criteria were excluded, leaving 469 women for these analyses.

Age, body mass index, and behavioral covariates (alcohol, cigarettes, and exercise) were determined according to use or nonuse of noncontraceptive estrogen. Crude, age-adjusted, and age- and body mass index-adjusted levels of plasma glucose and insulin were determined by hormone use status by using analysis of covariance. Comparison of unadjusted means between two groups was done with analysis of variance. Logarithmic transformation was used in all statistical analyses for fasting and 2-hour insulin; untransformed values are shown. Data are presented for women taking any postmenopausal estrogen, almost all of which was an oral preparation, and for those using the most common regimens, Premarin alone and Premarin plus Provera.

Use of Premarin was defined as 20 or more days per month; of Provera, at least 7 days per month. (Trade names are used because of possible problems with generic equivalency of sex hormones.) No other brand or type of estrogen or progestin preparation was used with sufficient frequency for separate analysis.

Results

Table 1 shows that the 194 women taking any estrogen were significantly younger than the 275 women not taking
Over 80% of all estrogen used was conjugated equine estrogen identified as Premarin, and over 80% of all progestin used was medroxyprogesterone identified as Provera. As shown in Table 3, women taking unopposed Premarin had significantly lower fasting glucose and fasting insulin levels than nonusers. Women using Premarin plus Provera also had lower fasting and insulin levels than nonusers, although the differences did not achieve statistical significance, owing to the smaller sample size. Post-challenge glucose and insulin levels tended to be lower in the Premarin plus Provera than in the unopposed Premarin group, but none of the differences were statistically different from levels in untreated women. There was no statistically significant difference in any age-adjusted glucose or insulin level between Premarin only versus Premarin plus Provera users. The results were not materially changed by adjusting for body mass index, glucose, exercise, smoking, and alcohol use (Table 3).

As previously reported,³ levels of fasting, but not post-challenge, glucose were significantly (p<0.05) lower in women taking unopposed Premarin at 0.625 mg/day or more compared to women taking less Premarin or no estrogen. A similar trend was observed for insulin. The numbers did not permit an analysis of the dose response for combination therapy.

Discussion

Houssay¹² first drew attention to the relation of sex hormones to glucose tolerance; in his 1951 review he noted that estrogen given to partially pancreatectomized castrated rats reduced the 6-month incidence of diabetes. Later Costrini and Kalkhoff¹³ reported that estradiol (with or without progestrone) significantly lowered post-challenge plasma glucose levels in female rats, and Bailey and Ahmed-Sorour¹⁴ found that the ovarectomy-induced increase in plasma glucose concentrations in mice was reversible with daily estradiol, progesterone, or both. In rhesus monkeys, estradiol and estriol had no effect on peripheral Insulin response to glucose, but progesterone produced a marked increase in plasma insulin response to (intravenous) glucose and a mild, but significant, peripheral insulin resistance.¹⁵

Most of the work in humans on sex hormones and carbohydrate tolerance has been with oral contraceptives, which generally show a diabetogenic effect with basal and post-challenge hyperinsulinemia.¹⁶ In 1975 Kalkhoff¹⁶ reviewed the literature in an attempt to distinguish the isolated effects of estrogens versus progestins on glucose metabolism and noted the variable results, lack of details about the selection of subjects, and the multiple regimens: deterioration of glucose tolerance was seen in one-third of 11 studies of 227 women who received one of four oral estrogens for periods ranging from 10 days to 36 months. In 11 studies of 117 subjects treated with parenteral estrogens, improved carbohydrate tolerance was found in two-thirds. Among the progestin studies reviewed by Kalkhoff, only depot medroxyprogesterone acetate was associated with deterioration of glucose tolerance in a significant proportion of patients. In the Rancho Bernardo cohort, plasma glucose levels did not differ significantly in estrogen alone versus estrogen plus progestin users.⁹

Overall, estrogen replacement therapy was not associated with impaired glucose tolerance, and treated
### Table 3. Mean Glucose and Insulin Levels in Postmenopausal Women according to Type of Estrogen Replacement Therapy, Rancho Bernardo, 1984-1987

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No estrogen (n=275)</th>
<th>Unopposed Premarin (n=81)</th>
<th>Premarin + Provera (n=45)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>70.8±7.8</td>
<td>65.8±5.9‡</td>
<td>64.8±5.8‡</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>24.3±3.6</td>
<td>23.9±3.9</td>
<td>23.8±3.2</td>
</tr>
<tr>
<td>Fasting glucose (mmol/l)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted (±SD)</td>
<td>5.33±0.61</td>
<td>5.16±0.49*</td>
<td>5.21±0.52</td>
</tr>
<tr>
<td>Adjusted for age</td>
<td>5.34</td>
<td>5.15*</td>
<td>5.18</td>
</tr>
<tr>
<td>Adjusted for age, BMI</td>
<td>5.34</td>
<td>5.17*</td>
<td>5.21</td>
</tr>
<tr>
<td>2-hour glucose (mmol/l)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted (±SD)</td>
<td>7.08±1.70</td>
<td>7.34±1.88</td>
<td>6.79±2.03</td>
</tr>
<tr>
<td>Adjusted for age</td>
<td>6.96</td>
<td>7.53*</td>
<td>7.04</td>
</tr>
<tr>
<td>Adjusted for age, BMI</td>
<td>6.97</td>
<td>7.55*</td>
<td>7.14</td>
</tr>
<tr>
<td>Fasting Insulin (pmol/l)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted (±SD)</td>
<td>99.0±127.0</td>
<td>73.2±37.3†</td>
<td>78.2±48.1</td>
</tr>
<tr>
<td>Adjusted for age</td>
<td>101.2</td>
<td>70.3†</td>
<td>75.3</td>
</tr>
<tr>
<td>Adjusted for age, BMI</td>
<td>99.7</td>
<td>72.5*</td>
<td>78.9</td>
</tr>
<tr>
<td>Adjusted for age, fasting glucose</td>
<td>98.9</td>
<td>74.0*</td>
<td>77.7</td>
</tr>
<tr>
<td>Adjusted for age, BMI, fasting glucose</td>
<td>97.7</td>
<td>76.3*</td>
<td>81.3</td>
</tr>
<tr>
<td>2-hour insulin (pmol/l)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted (±SD)</td>
<td>713.9±477.1</td>
<td>638.6±378.8</td>
<td>590.5±378.8</td>
</tr>
<tr>
<td>Adjusted for age</td>
<td>699.6</td>
<td>651.5</td>
<td>607.7</td>
</tr>
<tr>
<td>Adjusted for age, BMI</td>
<td>693.8</td>
<td>661.5</td>
<td>635.7</td>
</tr>
<tr>
<td>Adjusted for age, 2-hour glucose</td>
<td>720.4</td>
<td>606.9</td>
<td>612.3</td>
</tr>
<tr>
<td>Adjusted for age, BMI, 2-hour glucose</td>
<td>714.8</td>
<td>620.4</td>
<td>633.5</td>
</tr>
</tbody>
</table>

*P<0.05, †P<0.01, ‡P<0.001: Premarin, or Premarin and Provera vs. no estrogen.

Women had lower levels of insulin. This difference was unexplained by age and obesity (as defined by body mass index), or by smoking, alcohol, or exercise. Women in this cohort who were taking estrogen did not differ from women who were not taking estrogen with regard to pre-prescription health status. The difference in insulin levels by estrogen use is also unlikely to be due to differential prescription of estrogen for women with known diabetes, who were excluded from this analysis; their rate of use was similar (39% in diabetic vs. 41% in nondiabetic women), and, among those with diabetes, there was a lower fasting plasma glucose (5.8 mmol/l in the 26 estrogen-using women compared to 6.8 mmol/l in the 40 nonestrogen-using women, P<0.05). The 12% prevalence of diabetes (excluded from this study) in this sample is similar to that reported in a national sample of older women based on the same criteria.

Obese adults often have hyperinsulinemia with or without hyperglycemia. Estrogen may have a weight-limiting effect in postmenopausal women. This could reduce obesity-associated insulin resistance and result in lower plasma insulin levels. However, the animal work cited above and this study also suggest that the long-term effect of sex hormones on glucoregulation may be independent of body weight. Some studies suggest that estrogens and progestins play a different role in the maintenance of β-cell function in the female; in an isolated islet cell model, glucose-stimulated insulin release was reduced by ovariectomy and restored by estrogen, progesterone, or the combination; in addition, the number of β-cells was reduced by ovariectomy, and medication with hormone reversed this effect. These results demonstrating that estrogen use is associated with significantly lower basal insulin levels independently of glucose levels and other confounding factors suggest that estrogen therapy can reduce insulin resistance in women. The observation here that the largest observed differences were for fasting insulin is compatible with this hypothesis, since fasting insulin levels correlate well with insulin resistance determined by insulin clamp techniques.

Clinical trials will be needed to confirm these results and determine which estrogen replacement regimen has the most desirable effect on glucose tolerance and insulin resistance. Given the increasing frequency of long-term postmenopausal estrogen use, the issue is of considerable potential clinical significance. The relationship to...

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*Estrogen and Insulin* by Barrett-Connor and Laakso, 533.
cardiovascular disease will be of particular interest: we have previously reported that fasting insulin is significantly (p<0.001) and positively associated with high total triglycerides and conversely associated with low high density lipoprotein cholesterol in the cohort.23

References

Index Terms: estrogen • glucose • insulin • menopause
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