Do Estrogens Reduce Glycemic Levels?

There is increasing evidence that hyperglycemia is associated with a greater risk of cardiovascular disease (1–3), and interventions that might improve glucose levels in middle-aged and older adults are of special interest. The article by Espeland et al. (4) appearing in this issue is exemplary in that it effectively demonstrates reductions in fasting glucose and insulin among women receiving estrogen replacement therapy (ERT) who participated in the Postmenopausal Estrogen/Progestin Interventions trial (4).

Observational studies have suggested that ERT was beneficial for glucose homostasis (5–8), but the current investigation was prospective and took place in a clinical trial format. The investigators standardized the estrogen dose and considered the potential impact of regimens that included progestins. Although previous studies suggested that favorable glycemic effects of postmenopausal estrogens were mitigated or eliminated by progestins (9,10), the current report convincingly demonstrates no diminution in improved fasting glucose and insulin levels in hormonal replacement regimens that included progestins. The data even hint that a favorable impact on fasting insulin is more likely with continuous progestins than with cyclic preparations, but timing of the oral glucose tolerance test with the menstrual cycle was not standardized.

Clinicians who care for postmenopausal women must balance the divergent effects of ERT. Among the favorable effects are increased HDL cholesterol, decreased LDL cholesterol, decreased fibrinogen, less coronary heart disease, less osteoporosis, and reduced incidence of hip fracture (8,11–15). It appears that we may now add improved fasting glucose and insulin to this list.

On the other hand, ERT may affect some metabolic factors unfavorably. For instance, postprandial glucose and insulin levels did not improve in the current study. Women on ERT may develop hypertriglyceridemia, venous thromboembolism, or breast cancer, and carcinogenicity may be a problem in studies that span ≥5 years (16,17).

Experimental research in rats supports the view that reduced estrogen levels foster insulin resistance. For instance, ovariectomy in rats was followed by an increase in insulin resistance, which was determined using euglycemic-hyperinsulinemic clamp techniques. Estrogen replacement, with or without progesterone, restored insulin sensitivity (18). Similarly, estrogen withdrawal augmented fasting and glucose-stimulated insulin levels in juvenile rats that were made insulin resistant and hypertensive with a sucrose diet (19). Hormonal replacement in postmenopausal cynomolgus monkeys has yielded different results: progestins, alone or with estrogens, were associated with greater insulin resistance, which was assessed using the minimal model after a frequently sampled intravenous glucose tolerance test (20).

The theme that hyperglycemia is atherogenic and partly androgenic is gaining acceptance, but the metabolic issues are complex. ERT has been associated with lower androgen levels and less insulin resistance in postmenopausal women with type 2 diabetes (21,22). Conversely, total estrogen levels were reported to be increased in postmenopausal women with insulin-treated diabetes, and high levels of sex hormone–binding globulin were thought to keep the free fraction of the sex hormone levels within normal limits (23). The polycystic ovary syndrome, typified by high levels of androgens, hyperglycemia, oligomenorrhea, and infertility, represents a condition in which glycemia and androgens foster a milieu that increases the risk for cardiovascular disease (24,25). The estrogen/androgen balance and menstrual irregularity may also be tipped unfavorably by obesity, diabetes, and cigarette smoking before menopause (26–28). It has been suggested that diabetic women taking insulin before menopause may experience shorter periods of fertility and a higher incidence of menstrual disturbances compared with nondiabetic women.

The current investigation has limitations. It was a pilot study of <1,000 postmenopausal women, and most of the participants were Caucasian (4,13). The analyses focused on the reported use of ERT and not on the intention to treat. Such methods may overstate the favorable glycemic effects of ERT.

Long-term ERT with conjugated equine estrogens (CEEs) and estradiol has been shown to be cardioprotective in observational studies, and clinical trials are underway (16). Effects on lipoprotein cholesterol fractions, particularly HDL cholesterol, are thought to account for ~50% of the protective effect. The use of selective estrogen receptor modulators holds promise for postmenopausal women. These agents may reduce the risk of osteoporosis without increasing the risk of breast cancer. Selective estrogen receptor modulators also appear to have fewer favorable effects on LDL cholesterol and minimal changes in HDL cholesterol lipid profiles compared with traditional CEE therapy. The long-term cardioprotective potential of the newer estrogen agents is unknown (29).

The current study bolsters the evidence that modern ERT regimens are particularly beneficial for glycemia and lipids—are important metabolic features that underlie cardioprotection. Short-term ERT has been shown to reduce glycosylated hemoglobin in patients with type 2 diabetes, but long-term effects are not known (7). A trend toward reduced incidence of type 2 diabetes was present in women who received ERT in the Rancho Bernardo Study, but the association was not statistically significant after adjustment for age and obesity (6). The present study demonstrated improved mean levels of fasting glucose and insulin, but preventing or delaying the onset of impaired glucose function or diabetes was beyond the scope of investigation. A favorable metabolic effect of oral CEEs under fasting conditions has been demonstrated, but more data on the metabolic effects of the newer estrogen products are needed, because the risks of hyperglycemia and cardiovascular disease increase inexorably with age (30).

Peter WF Wilson, MD
From the National Heart, Lung, and Blood Institute, Framingham, Massachusetts.
Address correspondence to Peter WF Wilson, MD, Framingham Heart Study, 5 Thurber St., Framingham, MA 01701. E-mail: peters@fram.nhlbi.nih.gov.

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