The Effect of Estrogen Use on Levels of Glucose and Insulin and the Risk of Type 2 Diabetes in American Indian Postmenopausal Women

The Strong Heart Study

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OBJECTIVE — To examine the associations between estrogen use and levels of insulin and glucose as well as the effect of estrogen use on the risk of type 2 diabetes.

RESEARCH DESIGN AND METHODS — This report is based on 857 women who were both nondiabetic and postmenopausal at the baseline examination (1989–1992) and who completed a second examination (1993–1995) an average of 4 years later. The participants were divided into three groups: never, past, and current users based on their baseline estrogen use status. ANCOVA was used to compare the insulin and glucose levels among estrogen use groups. Logistic regression was used to evaluate the association between estrogen use and the incidence of type 2 diabetes.

RESULTS — Postmenopausal estrogen use was associated with lower fasting glucose (0.2 mmol/l lower) but higher 2-h glucose levels (0.4 mmol/l higher) compared with never users. It was not significantly associated with the risk of type 2 diabetes compared with past and never users, based on American Diabetes Association or World Health Organization definitions of diabetes or on only a 2-h glucose level ≥11.1 mmol/l. However, the risk of type 2 diabetes increased with increasing duration of estrogen use among current users, with an odds ratio of 1.10 per year of use (95% CI: 1.01–1.19).

CONCLUSIONS — The data suggest that estrogen use in American Indian postmenopausal women may relate to deterioration of glucose tolerance. Longer duration of estrogen use among current users may relate to an increased risk of type 2 diabetes.

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Estrogen is prescribed for women who undergo surgical or natural menopause. It alleviates menopausal symptoms (1), and it is approved for osteoporosis prevention in postmenopausal women (2). Estrogen is associated with lower risk of cardiovascular disease (CVD) in observational studies (3–6). Randomized trial results from the Women's Health Initiative should help to better define this issue. Use of unopposed estrogen is known to increase the risk of endometrial cancer and is associated with a greater risk for breast cancer in some studies (1,6,7). There are also reports that estrogen may have favorable effects on rheumatoid arthritis and schizophrenia (7). It is not clear how postmenopausal estrogen use influences carbohydrate metabolism. Data from population studies showed that estrogen was associated with lower fasting glucose and insulin levels (3,8–10), but its use was related to a rise in 2-h insulin and glucose levels (8,11).

The association between risk of type 2 diabetes and postmenopausal estrogen use is not clear. Three longitudinal studies have shown no increase in the incidence of type 2 diabetes with postmenopausal estrogen use (9,12,13), although one study (9) reported a nonsignificant trend, with never users having the lowest risk of type 2 diabetes and continuous users having the highest risk. Most of the participants in these studies were Caucasians with low average annual incidence rates of type 2 diabetes (~1%). Data from other populations with higher incidence rates of type 2 diabetes are needed to further explore this issue. American Indians have a high prevalence and incidence of type 2 diabetes. In the Strong Heart Study (SHS) population, which represents 13 tribes in three geographic areas, the prevalence rates of type 2 diabetes range from 40 to 70% in women aged 45–74 years (14). This high prevalence of diabetes provides a unique opportunity to help clarify the role of estrogen use.

RESEARCH DESIGN AND METHODS

The SHS is a longitudinal study of morbidity and mortality from CVD in American Indians. The participants were

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Abbreviations: CVD, cardiovascular disease; OR, odds ratio; SHS, Strong Heart Study; WHR, waist-to-hip ratio.

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A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

volunteers from 13 Indian tribes/communities living in three geographic areas: Arizona, North and South Dakota, and Oklahoma. The design, survey methods, and laboratory techniques of this study have been presented in previous reports (15–17). At the baseline examination (1989–1992), there were 4,549 participants aged 45–74, of whom 2,703 were women. Of the women participating, 2,109 were postmenopausal. The surviving participants were re-examined between 1993 and 1995. Postmenopausal women who did not have a history of diabetes, did not take diabetic medication, and had a fasting plasma glucose level <7.0 mmol/l (126 mg/dl) and a 2-h postchallenge glucose level <11.1 mmol/l (200 mg/dl) at the baseline examination were eligible for the present analysis (n = 895). Of the 895 women, 890 (99.4%) women had complete information on estrogen use at the baseline examination and had completed both the baseline and second examinations. Another 33 women were excluded because of inconsistent information on estrogen use at the baseline and the second examination. The final sample size for this analysis was 857. The average follow-up time was ~4 years.

Postmenopausal women included those who had undergone either natural or surgical menopause. Natural menopause was defined as at least 12 months since the last menstrual period. If menopause was surgical, the participants were asked if only their uterus had been removed. Women who reported hysterectomy but no oophorectomy or who did not know whether their ovaries had been removed were included if they were ≥53 years old. The decision to include these subjects was based on the fact that 90% of the menopausal women in the SHS had attained natural menopause by age 53 years (4).

Three definitions of diabetes have been used in the analysis to define incident cases. One is based on a fasting plasma glucose ≥7.0 mmol/l (American Diabetes Association). One is based on fasting glucose ≥7.0 mmol/l or 2-h glucose level ≥11.1 mmol/l (World Health Organization). The third one is based only on elevated 2-h postchallenge glucose level (≥11.1 mmol/l; 75-g oral glucose tolerance test).

The cohort for analysis was divided into three groups: never users (n = 604), past users (n = 119), and current users (n = 134) of estrogen, based on their use at the baseline examination. Never users had never used estrogen. Past users had used estrogen before the baseline examination but were not taking estrogen at baseline. Current users were using estrogen at the time of the baseline examination. Estrogen use was ascertained by interview and was confirmed by examination of pills and prescriptions brought to the visit. Of the participants, 34% had had a hysterectomy. Whether women using estrogen were also taking a progestogen agent was not ascertained at the baseline visit. Indian Health Service practice guidelines recommend estrogen replacement therapy to women without a uterus and progestogen-estrogen replacement therapy for those with a uterus.

Baseline comparisons of risk factors among the three estrogen use groups were made by ANOVA for continuous variables and χ^2 test for categorical variables. If continuous variables were not suitable for ANOVA, the rank sum test was used. Because of the skewed distribution of fasting insulin level, it was log-transformed in all analyses. Covariates were grouped as *1*) obesity indexes: BMI and waist-to-hip ratio (WHR); *2*) sociodemographic variables: age, American Indian heritage, SHS center, and years of education; *3*) family history of diabetes; *4*) lifestyle variables: smoking (yes or no) and physical activity (hours of physical activity per week); and *5*) reproductive variables: parity and hysterectomy status (yes or no). ANCOVA was used to compare the fasting and 2-h glucose levels and the fasting insulin levels among the different estrogen use groups, adjusted for covariates. Each covariate that may be related to fasting insulin and fasting or 2-h glucose was considered. The adjusted means were only adjusted for those covariates that were significantly related to insulin or glucose levels. Logistic regression was used to assess the independent contributions of estrogen use and duration of estrogen use to the incidence of type 2 diabetes, adjusted for covariates. At first, the covariates that could possibly be associated with diabetes risk were entered into the full model. Then, the model was reduced by stepwise selection. The final odds ratios (ORs) were adjusted for those covariates that remained in the final selected logistic model, with $P \leq 0.05$. The ORs and their 95% CIs were used to express the relative risk of certain factors.

RESULTS

Baseline characteristics

Compared with never users, past and current users were more educated; had a higher hysterectomy rate; had lower American Indian heritage, gravidity, and parity; were more active; and had a lower WHR. Compared with past users and never users, current users were younger, with a lower BMI. During the 4-year follow-up period, there were a total of 97, 157, and 117 new cases of type 2 diabetes based on the three definitions of diabetes (fasting glucose level, fasting glucose or 2-h glucose levels, or only 2-h glucose level). Based on those three definitions, the average annual incidence rates were 2.8, 5.6, and 4.4%, and the cumulative incidence rates were 11, 22.4, and 17.7, respectively.

Cross-sectional associations between estrogen use and baseline levels of glucose and insulin

Current estrogen users had lower fasting insulin and fasting glucose levels than past users and never users, when other risk factors (age, obesity, etc.) were not considered (Table 1). After adjustment for obesity variables, sociodemographic variables, lifestyle factors, family history of diabetes, and reproductive variables, current users had lower fasting glucose than never users (0.2 mmol/l lower) but higher 2-h glucose levels than never users (0. 4 mmol/l higher). There was no difference in fasting insulin levels between current users and never users after adjustment for covariates. Insulin and glucose levels in past users were not different from never users. Results did not change when we conducted the same analyses by strata of BMI, family history, or baseline age (data not shown).

Longitudinal analyses of the association between estrogen use and the risk of type 2 diabetes

Because past users and never users had similar insulin and glucose levels at the baseline survey, they were combined for analyses of the risk of type 2 diabetes. After adjustment for other risk factors, estrogen was not associated with increased risk of type 2 diabetes, using any of the three criteria for diabetes (Table 2). However, there was an increasing trend of ORs based on the inclusion of 2-h glucose. Before adjustment, the ORs for diabetes risk

Table 1—*Comparison of fasting insulin, fasting glucose, and 2-h glucose levels in estrogen use groups at baseline visit*

Model Groups	Adjusted mean		
	Fasting insulin* (pmol/1)	Fasting glucose (mmol/l)	2-h glucose (mmol/l)
Unadjusted			
Current users (n = 134)	4.1†	5.4†	7.1
Past users (n = 119)	4.3	5.7	7.0
Never users (n = 604)	4.4	5.7	7.1
Adjusted			
Current users	4.3	5.5†	7.5‡
Past users	4.3	5.7	7.2
Never users	4.4	5.7	7.1
Covariates remaining in the adjusted models§	BMI, WHR, American Indian heritage, physical activity, smoking	BMI, WHR, baseline age, family history of diabetes	BMI, WHR, education (years), SHS center, smoking

*Because of the skewed distribution of fasting insulin level, it was log-transformed in all analyses. †$P < 0.05$ (current users vs. past users and never users); ‡$P < 0.05$ (current users vs. never users). §The adjusted mean is only adjusted for those covariates that were significantly related to fasting insulin, fasting glucose, or 2-h glucose as described in RESEARCH DESIGN AND METHODS.

by criteria of only fasting glucose, fasting or 2-h glucose, or only 2-h glucose were 0.33, 0.66, and 0.82, respectively. After adjustment, the ORs for diabetes risk were 0.48, 1.11, and 1.58, respectively.

Analysis of the association between duration of estrogen use and risk of type 2 diabetes was conducted only among current users (Table 3)

The definition of diabetes based only on fasting glucose identified only six new diabetes cases. Increasing duration of estrogen use was associated with a significant increase in the risk of type 2 diabetes in current users when using the criteria of fasting and 2-h glucose (OR 1.10, CI 1.01–1.18) or only 2-h glucose (1.10, 1.01–1.19). Thus, the risk of type 2 diabetes increased by 10% for each year of current estrogen use. The possible interactions among estrogen use and other independent variables were tested, and none of them were statistically significant.

CONCLUSIONS— In the cross-sectional analyses of baseline data, compared with never users, current users of estrogen had lower fasting glucose (0.2 mmol/l lower) but higher 2-h glucose levels (0.4 mmol/l higher). During a 4-year follow-up period, postmenopausal estrogen use was not significantly associated with increased incidence of type 2 diabetes, but ORs increased as 2-h glucose was added to the definitions of diabetes. With increasing duration of postmenopausal

Table 2—*Estrogen use and the risk of type 2 diabetes*

Definition of diabetes	Models Groups	OR*	95% CI	Covariates remaining in the final model†
Fasting glucose ≥7.0 mmol/l (126 mg/dl)	Unadjusted			
	Current users	0.33	0.14–0.78	
	Past and never users	1.0		
	Adjusted			
	Current users	0.48	0.20–1.14	BMI, WHR, American Indian heritage
	Past and never users	1.0		
Fasting glucose ≥ 7.0 mmol/l or 2-h glucose ≥11.1 mmol/l	Unadjusted			
	Current users	0.66	0.39–1.12	
	Past and never users	1.0		
	Adjusted			
	Current users	1.11	0.62–1.97	BMI, American Indian heritage, SHS center
	Past and never users	1.0		
2-h glucose ≥11.1 mmol/l (200 mg/dl)	Unadjusted			
	Current users	0.82	0.47–1.43	
	Past and never users	1.0		
	Adjusted			
	Current users	1.58	0.81–3.1	BMI, education (years), family history, hysterectomy status
	Past and never users	1.0		

*The comparisons are current users vs. never users and past users. †Covariates remaining in the final selected logistic model were selected among obesity indices, sociodemographic variables, family history of diabetes, lifestyle variables, and reproductive variables (as described in the RESEARCH DESIGN AND METHODS section) by stepwise selection method with $P \leq 0.05$.

Table 3—*Duration of estrogen use and the risk of type 2 diabetes in current users*

Definition of diabetes Models (n = 134)	Variables	OR	95% CI	Covariates remaining in the final model†
Fasting glucose ≥7.0 mmol/l (new diabetes = 6)				
Unadjusted	Duration*	1.01	0.9–1.12	
Adjusted	Duration	1.01	0.9–1.12	None
Fasting glucose ≥7.0 mmol/l or 2-h glucose ≥11.1 mmol/l (new diabetes = 16)				
Unadjusted	Duration	1.02	0.96–1.10	
Adjusted	Duration	1.10	1.01–1.18	BMI, hysterectomy status (yes or no)
2-h glucose ≥11.1 mmol/l (new diabetes = 14)				
Unadjusted	Duration	1.02	0.95–1.10	
Adjusted	Duration	1.10	1.01–1.19	BMI, hysterectomy status (yes or not)

*Duration of estrogen use (years). †Covariates remaining in the final selected logistic model were selected as described in Table 2 and in RESEARCH DESIGN AND METHODS.

estrogen use, the risk of type 2 diabetes showed a significant increase among current users.

Insulin and glucose level

After adjusting for other variables, fasting insulin level was not related to estrogen use, a finding consistent with a number of previous studies (4,18,19). Some studies have shown that estrogen has a favorable effect on fasting insulin (3,8,10,20), whereas a few studies have reported that oral estrogen may increase insulin resistance (11). The populations in those studies varied, and different results may also be due to differences in estrogen prescriptions (21). Data from long-term randomized trials in diverse populations are needed to resolve this issue.

The SHS data are consistent with previous studies that reported lower fasting glucose levels in estrogen users (3,8–10,20). Other reports find that estrogen use is not associated with fasting glucose level (18,19).

The present study found that the mean 2-h glucose was ~0.4 mmol/l higher in current users compared with never users, after adjusting for obesity, sociodemographic, lifestyle, and reproductive variables. The magnitude of the difference in fasting glucose (0.2 mmol/l lower in current users than in never users) was less than the difference in 2-h glucose (0. 4 mmol/l higher in current users than in never users). A number of studies have shown that oral estrogens can cause deterioration in glucose tolerance (8,11). Only a few have reported that estrogen therapy did not influence the 2-h glucose level (3).

Our results from longitudinal analyses also suggest that estrogen use is more closely related to postprandial glucose level. When we add 2-h glucose to the diabetes definition or use only 2-h glucose to define diabetes, the ORs increased (before adjustment: 0.33, 0.66, and 0.82; after adjustment: 0.48, 1.11, and 1.58, respectively). These results are consistent with the results from the cross-sectional analyses for baseline data, which showed that estrogen has a significant effect on 2-h glucose.

The mechanism for the effect of estrogen on glucose metabolism has not been fully elucidated. It has been reported that estrogen-related decreases in fasting glucose may be caused by suppressed hepatic glucose production (8,20). The rise in 2-h glucose has been suggested to be related to decreased pancreatic response to rising glucose, thereby delaying the release of insulin. An increase in insulin clearance, with consequent decrease in glucose disposal by peripheral tissues, may also be involved (8,22,23). Others suggest that estrogen increases hepatic insulin elimination, with no compensatory increase in the original pancreatic insulin response, resulting in a relative reduction in the initial plasma insulin level. This would result in a reduction in the glucose elimination and an overall rise in glucose concentrations (21).

Different preparations of estrogen may influence the effect of estrogen on carbohydrate metabolism (11,21). Our baseline data did not include the type of estrogen preparation, so we cannot comment on possible differences between drugs. After a hysterectomy, estrogen is usually taken without added progestogen. In our study, 34% of the women participating had a hysterectomy.

Risk of type 2 diabetes

The SHS results indicate overall that current estrogen use is not significantly related to risk of type 2 diabetes when compared with never and past users. However, increasing duration of estrogen use was associated with a statistically significant increased risk of type 2 diabetes in current users.

Reports from observational studies have not shown a material increase in the incidence of type 2 diabetes with estrogen use (9,12,13,21). Some previous studies have shown that before adjusting for other covariates, estrogen users had a lower risk for type 2 diabetes than nonusers, but after adjusting for other covariates (such as BMI, age, and family history of diabetes), the apparent protective effects of estrogen on the risk for type 2 diabetes disappeared (9,12). One study showed that before adjusting for confounding variables, there was a nonsignificant, decreasing linear trend in risk with increasing duration of estrogen use (ORs for past users, current users, and continuous users were 1.02, 0.88, and 0.83, respectively). After adjustment for confounding variables, the relationship was reversed (1.11, 1.10, and 1.23, respectively) (9). Our study showed that women who have used estrogen are thinner, more educated, have fewer children, and are more active than women who have never used estrogen. Adjustment for covariates is

needed to properly examine the association between estrogen use and risk for type 2 diabetes.

The mechanism by which estrogen influences diabetes risk is not fully understood. It can directly influence glucose metabolism as described above (24). Other suggested biological mechanisms for a diabetogenic effect of exogenous estrogens include a direct intracellular antagonism of the effects of insulin, elevated levels of growth hormone and glucocorticoids, and changes in intestinal glucose absorption (25,26). Randomized trials are needed to define the effects of postmenopausal estrogen use on diabetes risk and to establish the mechanism of action in different populations.

In summary, in this population, postmenopausal estrogen therapy showed favorable associations with fasting glucose but was associated with a deterioration of glucose tolerance. Longer duration of current estrogen use may increase the risk of type 2 diabetes. American Indians have much higher rate of type 2 diabetes than other populations. A clinical trial is needed to clarify this issue in American Indian women.

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