Hormone Replacement Therapy Is Associated With Better Glycemic Control in Women With Type 2 Diabetes

The Northern California Kaiser Permanente Diabetes Registry

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OBJECTIVE — In women with diabetes, the changes that accompany menopause may further diminish glycemic control. Little is known about how hormone replacement therapy (HRT) affects glucose metabolism in diabetes. The aim of this study was to examine whether HbA_{1c} levels varied by current HRT among women with type 2 diabetes.

RESEARCH DESIGN AND METHODS — In a cohort of 15,435 women with type 2 diabetes who were members of a health maintenance organization, HbA_{1c} and HRT were assessed by reviewing records in the health plan's computerized laboratory and pharmacy systems. Sociodemographic and clinical information were collected by survey.

RESULTS — The mean age was 64.7 years (SD ± 8.7). The study cohort comprised 55% non-Hispanic whites, 14% non-Hispanic blacks, 12% Hispanics, 11% Asians, 4% "other" ethnic groups, and 4% with missing ethnicity data. Current HRT was observed in 25% of women. HbA_{1c} levels were significantly lower in women currently using HRT than in women not using HRT (age-adjusted mean ± SE: 7.9 ± 0.03 vs. 8.5 ± 0.02, respectively, $P = 0.0001$). No differences in HbA_{1c} level were observed between women using unopposed estrogens and women using opposed estrogens. In a Generalized Estimating Equation model, which took into account patient clustering within physician and adjusted for age, ethnicity, education, obesity, hypoglycemic therapy, diabetes duration, self-monitoring of blood glucose, and exercise, HRT remained significantly and independently associated with decreased HbA_{1c} levels ($P = 0.0001$).

CONCLUSIONS — HRT was independently associated with decreased HbA_{1c} level. Clinical trials will be necessary to understand whether HRT may improve glycemic control in women with diabetes.

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In women with type 2 diabetes, the changes in sex-hormone levels, abdominal fat, and insulin metabolism that accompany menopause (1,2) may represent additional impediments in achieving good glycemic control. There is evidence that exogenous estrogens might reduce some of these adverse changes. Recent small randomized placebo-controlled trials (3,4) conducted among 40 diabetic women (or less) have shown that short-term hormone replacement therapy (HRT) with estrogen alone improves HbA_{1c} level and reduces hyperandrogenicity in postmenopausal women with type 2 diabetes. In women without diabetes, the Postmenopausal Estrogen/Progestin Intervention trial (5) has shown that either estrogen alone or in combination with progestins slightly decreases fasting glucose levels compared with placebo, whereas estrogen in combination with medroxyprogesterone acetate increases 2-h glucose levels. As a result, there is an increasing demand by women with diabetes for information on the usefulness of HRT (6).

An association among HRT, lower fasting glucose, and insulin level has also been found in several large observational studies (7–10). None of these studies included women with clinically diagnosed diabetes, and only one (7) included U.S. race-ethnicity minorities (African-Americans).

We report the HbA_{1c} levels by current HRT use among a multiethnic population of 15,435 women with type 2 diabetes aged ≥50 years, who were identified by the Northern California Kaiser Permanente Diabetes Registry, and consider the possible effects of age, hypoglycemic therapy, diabetes duration, self-monitoring of blood glucose (SMBG), BMI, and education on the observed differences between women using and not using HRT.

RESEARCH DESIGN AND METHODS

— The setting for this study was the Kaiser Permanente Medical Care Program (KPMCP) of Northern California, which is a group practice, prepaid health plan. The sociodemographic characteristics of KPMCP members are generally representative of the population living in the same area (11).

The population for this study was drawn from the Northern California Kaiser Permanente Diabetes Registry. The diabetes registry was started in 1993 by identifying probable diabetic individuals from automated health plan sources (including pharmacy prescriptions for diabetic medications), abnormal HbA_{1c} values (≥6.7%), and any inpatient or out-

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Abbreviations: GEE, Generalized Estimating Equation; HRT, hormone replacement therapy; KPMCP, Kaiser Permanente Medical Care Program; OHA, oral hypoglycemic agent; SMBG, self-monitoring of blood glucose.
A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

patient diagnosis of diabetes (12). As of January 1996, the diabetes registry included 91,018 people aged ≥19 years and current KPMCP members. At that time, the registry was estimated to have 96% sensitivity for diagnosed diabetes when matched against two large mailed surveys of random membership samples conducted in 1990 and 1993. The registry has also been found to contain ~3% false positives.

All of the diabetes registry members aged ≥19 years identified before 1996 received a survey questionnaire either by mail or computer-assisted telephone interview between January 1995 and March 1997. The response rate among diabetic women aged ≥50 years was 89% using this combined approach. The survey included questions on ethnicity, education, weight, height, age at diabetes diagnosis, current hypoglycemic therapy and date of starting insulin, diet and exercise as part of their treatment for diabetes, smoking history, and practice and frequency of SMBG. BMI was calculated as weight (kilograms) divided by height (meters) squared and used as a measure of overall obesity.

Type 2 diabetes was defined on the basis of reported treatment according to the following criteria: *1*) reported diet and/or exercise and no hypoglycemic medication use, or oral hypoglycemic agents used alone or in combination with insulin; *2*) insulin use only and diabetes diagnosis at age ≥30 years; and *3*) insulin use only and diabetes diagnosis at age 20–29 years and initiation of insulin therapy >2 years after diabetes diagnosis.

HbA_{1c} values measured between 1 January 1995 and 31 December 1996 were obtained from the computerized laboratory database, which captures all laboratory tests and results performed at the KPMCP regional laboratory. All HbA_{1c} measurements were analyzed at the regional laboratory by a high-performance liquid chromatography analyzer from 1 January 1995 to 4 November 1995 and turbidimetric immunoinhibition assay from 5 November 1995 to 31 December 1996. The two methods were highly correlated ($r = 0.986$) (13). The majority (88%) of HbA_{1c} levels reported in this study were measured by the turbidimetric immunoinhibition assay.

Use of HRT was assessed by reviewing records in the health plan's computerized pharmacy system. This database is used for all pharmacy operations; the name and type of the pharmaceutical is entered directly by the pharmacy personnel as the prescription is filled. Computerized health plan benefit records were also reviewed to identify women who had or did not have prepaid medication benefits. Women were defined as current HRT users if they filled a prescription for estrogens and/or progestins, which are indicated for menopausal symptoms between 1–6 months before the date of the HbA_{1c} laboratory test. This time interval was chosen because HbA_{1c} reflects the glycemic control during the 2- to 3-month period before the blood sample was obtained, and most HRT prescriptions (96%) contained a 100-pill supply. All remaining women were classified as not current HRT users.

The assessment of HRT using a computerized pharmacy system database was validated among 295 diabetic women, aged ≥50 years, who also responded to a large mailed survey of random KPMCP membership that was sampled in 1996. In this survey, women were asked if during the past 12 months they had regularly used HRT. There was an agreement of 90% between the two sources. The sensitivity and specificity of the computerized pharmacy system database for assessing HRT used during the same 12-month period versus the self-reported HRT were 86 and 93%, respectively.

Study population

As of 1 January 1995, there were 28,837 women aged ≥50 years who were members of the diabetes registry. There were 22,105 women who were continuously enrolled in the health plan from 1 January 1995 through 31 December 1996. Women continuously enrolled in the health plan compared with women who were not continuously enrolled in the health plan were more likely to have HbA_{1c} measured (84 and 33%, respectively) and to have filled an HRT prescription (30 and 14%, respectively). To ensure complete ascertainment of HRT use, only women who were continuously enrolled in the health plan (no gap allowed) were considered eligible for this study. Of these, 19,979 responded to the survey, and 579 (2.9%) stated on the survey that they did not have diabetes and were therefore excluded. Among the 19,400 women who confirmed that they had diabetes, 94.5% had type 2 diabetes, 1.9% had type 1 diabetes, and 4.5% could not be classified for type of diabetes because of missing data. Among women with type 2 diabetes, the 15,435 (85%) women who had HbA_{1c} measured at least once became the final cohort for all analyses in this study.

Statistical analyses

The comparison of characteristics between women currently using HRT and women not currently using HRT was performed using two sample *t* tests for continuous variables and χ^2 tests for categorical variables. Age-adjusted mean levels of HbA_{1c} and BMI by HRT were computed and compared using analysis of covariance. A generalized estimating equation (GEE) model was constructed to assess the association between HRT and HbA_{1c} level after taking into account the clustering of patients' characteristics treated by the same physician and adjusting for age, ethnicity, education, BMI, hypoglycemic therapy, diabetes duration, SMBG, and exercise. Tests for interaction in the GEE models were performed to assess whether the association between HRT and HbA_{1c} differed by ethnicity and age. Only the interaction term between HRT and age was statistically significant ($P < 0.0001$). However, in analyses stratified by age, the association between HRT and HbA_{1c} had the same direction and was statistically significant in all age strata, although the association became less pronounced with age (Fig. 1). Confounders were included in the GEE models if their inclusion resulted in appreciable changes in the HRT coefficient or if the variable was shown by previous scientific publications to be associated with both the outcome and the exposure.

Statistical Analysis System version 6.11 was used for all analyses (16). All *P* values are for two-tailed tests with statistical significance defined as $P \leq 0.05$.

RESULTS — Among 15,435 women aged 50–98 years (mean 64.7, SD ± 8.7) who had type 2 diabetes and HbA_{1c} measured during the 2-year study period, 3,852 (25%) were currently using HRT before the HbA_{1c} test. Among women currently using HRT, 62% were using unopposed estrogens, 36% were using opposed estrogen, and 2% were using progestins alone. The study cohort comprised 55% non-Hispanic whites, 14% non-Hispanic blacks, 12% Hispanics, 11% Asian/Pacific Islanders, 4% belong-

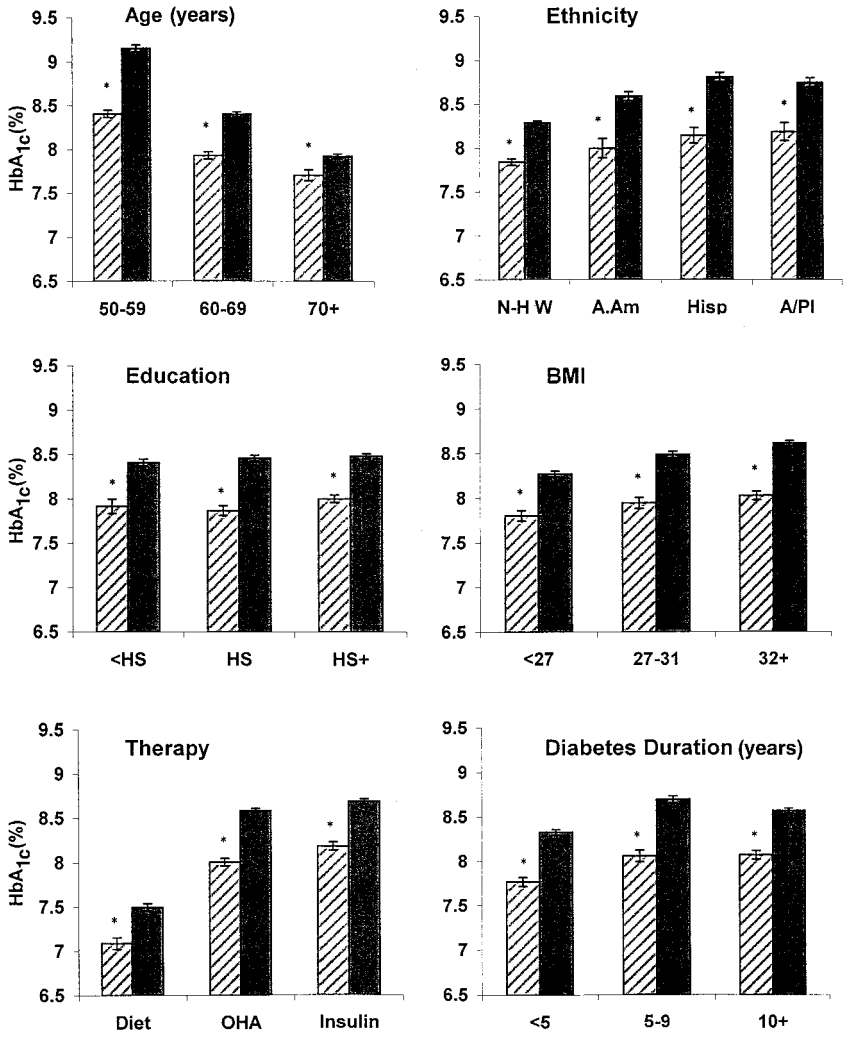

Figure 1—*Age-specific and age-adjusted HbA_{1c} means and SE by current HRT, the Northern California Kaiser Permanente Diabetes Registry 1995–1996. N-H W, non-Hispanic White; A.Am, African-American; Hisp, Hispanic; A/PI, Asian/Pacific Islanders; HS, high school; OHA, oral hypoglycemic agents.* ▨, *women using HRT;* ■, *women not using HRT.* *P ≤ *0.001 for women using HRT vs. women not using HRT for each strata.*

ing to "other" race-ethnicity groups, and 4% women having missing data on race ethnicity.

Table 1 shows the characteristics of the study population by current HRT. Women currently using HRT were younger, leaner, better educated, and more likely to be non-Hispanic whites than women not using HRT. These differences were statistically and clinically significant. As shown in Table 1, women currently using HRT were also more likely to self-monitor their blood glucose levels, have a shorter diabetes duration, report exercise as part of their diabetes treatment, and be a past or current smoker versus women who were not using HRT. Hypoglycemic treatment varied very little by current HRT. Although all these differences were statistically significant, given the large sample size, they were not clinically meaningful.

Mean HbA_{1c} levels were significantly lower in women currently using HRT than in women not using HRT, and these differences increased after adjusting for age. The difference in age-adjusted HbA_{1c} mean levels between HRT users and nonusers was ~0.5 points (Table 1). No differences in HbA_{1c} level were observed between women using opposed estrogens and women using unopposed estrogens ($P = 0.48$). Both women using estrogens alone or estrogens in combination with progestins had significantly lower HbA_{1c} mean levels than women not using HRT (age-adjusted mean [SE] 8.0 [0.03] and 8.0 [0.04], respectively, vs. 8.5 [0.02]; $P = 0.0001$).

Because women who were currently using HRT were more likely to have medication benefits for the entire 2-year study period than diabetic women not currently using HRT (Table 1), analyses were repeated after excluding the 2,232 women without continuous medication benefits, and similar differences in HbA_{1c} levels were observed between current HRT users and nonusers ($P = 0.0001$).

To evaluate whether the observed association between HRT and decreased HbA_{1c} levels varied by age, women were stratified in three age groups (50–59, 60–69, and ≥70 years), and age-specific mean HbA_{1c} levels by HRT were calculated (Fig. 1). Although the association between current HRT and decreased HbA_{1c} levels remained statistically significant in all of the age strata, it was most significant in women aged 50–59 years, intermediate in women aged 60–69 years, and smallest in women aged ≥70 years. To evaluate whether the association between HRT and decreased HbA_{1c} levels varied by levels of covariates of HRT, age-adjusted HbA_{1c} levels by HRT were calculated after stratifying women by type of hypoglycemic therapy, ethnicity, level of education, BMI, and diabetes duration (Fig. 1). The association between HRT and decreased HbA_{1c} levels remained statistically significant and approximately the same magnitude in all of the strata. Similar associations between HRT and decreased HbA_{1c} levels were found when women were stratified by exercise and SMBG practice (data not shown).

A GEE model was constructed to assess the association between HRT and HbA_{1c} level after taking into account the clustering of patients' characteristics treated by the same physician and adjusting for age, ethnicity, education, BMI, hypoglycemic therapy, diabetes duration, SMBG, and exercise (Table 2). As shown in Table 2, current HRT remained significantly and independently associated with decreased HbA_{1c} levels in these multiple-adjusted models. Current HRT use was associated with 0.47-point lower HbA_{1c} levels. Other significant independent predictors of decreased HbA_{1c} levels were older age and treatment with diet alone. Insulin treatment compared with oral hypoglycemic agent (OHA) treatment was associated with significantly in-

creased HbA_{1c} levels. Other significant predictors of increased HbA_{1c} levels were U.S. minority ethnic groups, obesity, and longer diabetes duration. There was a significant direct association between SMBG practice less than once a week and HbA_{1c}, suggesting that women who were practicing SMBG had somewhat more severe diabetes. Education was not associated with HbA_{1c} level.

CONCLUSIONS — Among the study cohort of 15,435 women with type 2 diabetes, 25% were currently using HRT before their HbA_{1c} test, and HRT was significantly associated with decreased HbA_{1c} levels. The association between HRT and decreased HbA_{1c} levels was independent of age, ethnicity, education, BMI, type of hypoglycemic therapy, diabetes duration, SMBG practice, and exercise.

Women with type 2 diabetes from U.S. minorities were less likely to use HRT than diabetic women who identified themselves as non-Hispanic white. This race-ethnicity difference in HRT has been reported previously (17,18). In this setting, differences in age, ethnicity, and education were the most clinically significant differences between HRT users and nonusers. These results are consistent with recent national surveys (18,19) that found demographic and socioeconomic characteristics to be among the major predictors of HRT use.

The difference in HbA_{1c} levels between women currently using HRT and women not using HRT was ~0.5 points. Based on published findings from the U.K. Prospective Diabetes Study (20), the observed difference in HbA_{1c} of 0.5 points between women currently using HRT and women not currently using HRT would translate roughly into a 10% reduction for any diabetes complications, an 18% reduction for microvascular complications, and a 7% reduction for myocardial infarction. Therefore, the observed difference in HbA_{1c} between HRT users and nonusers is of clinical relevance not only in relation to glycemic control but also in relation to possible reduction in diabetes complications.

Our findings are consistent with the results of two small randomized placebo-controlled trials of estrogens and HbA_{1c} in postmenopausal women with type 2 diabetes (3,4). Brussard et al. (3) found that the mean change in HbA_{1c} in the 20 women who were assigned to estradiol was significantly greater than the mean change observed in the placebo group (−0.66 vs. −0.34%). Anderson et al. (4) studied 24 postmenopausal women with type 2 diabetes in a randomized double-blind crossover design. Mean HbA_{1c} significantly decreased from 8.7% before estrogen therapy to 7.5% after estrogen therapy.

In nondiabetic postmenopausal women, exogenous estrogens have been found to improve whole-body insulin sensitivity (measured by an insulin tolerance test) (21–23) and to increase hepatic insulin clearance (24). A study of women with type 2 diabetes (3) found that improved insulin sensitivity (measured by an euglycemic-hyperinsulinemic clamp) after estrogen therapy was mainly because of increased insulin sensitivity of the liver, resulting in increased insulin-mediated suppression of hepatic glucose production. In animal models, estrogens have also been found to suppress hepatic gluconeogenesis (25). Furthermore, it has been suggested that reduced hepatic glucose production observed after estrogen therapy might also be mediated by the reduced abdominal fat mass observed in HRT users (26,27). Finally, Anderson et al. (4) suggested that estrogen may im-

Table 1—*Characteristics of 15,435 women with type 2 diabetes by HRT: the Northern California Kaiser Permanente Diabetes Registry, 1995–1996*

	Women using HRT (n = 3,406)	Women not using HRT (n = 11,583)	P
Age (years)			
Means (SD)	61.2 (7.6)	65.9 (8.8)	0.0001
BMI (kg/m^2)			
Crude means (SD)	30.7 (6.5)	30.4 (6.8)	0.01
Age-adjusted means (SE)	30.0 (0.1)	30.6 (0.1)	0.0001
HbA_{1c} (%)			
Crude means (SD)	8.1 (1.7)	8.4 (2.0)	0.001
Age-adjusted means (SE)	7.9 (0.03)	8.5 (0.02)	0.0001
Ethnicity (%)			0.001
Non-Hispanic Whites	60.9	53.2	
African-Americans	9.4	15.0	
Hispanics	12.9	12.3	
Asian/Pacific Islanders	9.4	11.5	
Other/unknown	7.4	8.0	
Education (%)			0.001
High school or less	48.2	57.2	
Some college	32.5	27.7	
College	19.3	15.1	
Therapy (%)			0.01
Diet	13.9	12.2	
OHA	51.5	53.4	
Insulin	34.6	34.4	
Diabetes duration (%)			0.001
<5 years	38.0	36.2	
5–9 years	23.9	21.6	
≥10 years	38.1	42.2	
SMBG practice (%)			0.001
Never	19.9	26.4	
<1/week	18.2	17.1	
≥1/week	61.8	56.5	
Smoking (%)			0.001
Current	9.7	8.9	
Former	36.0	31.6	
Never	54.3	59.5	
Exercise (%)	52.4	46.9	0.001
Medication benefit (%)	87.9	83.9	0.001

Table 2—*Regression coefficients for variables predicting HbA_{1c} from GEE models with variance estimates that take into account patient clustering by physician: the Northern California Kaiser Permanente Diabetes Registry, 1995–1996*

	β coefficient	SE	*P*
Age	–0.047	0.002	0.0001
HRT			
No (reference)	—	—	
Yes	–0.475	0.04	0.0001
BMI			
<27 (reference)	—	—	
27–31	0.110	0.05	0.01
≥31	0.099	0.04	0.02
Ethnicity (%)			
Non-Hispanic Whites (reference)	—	—	
African-Americans	0.200	0.06	0.0005
Hispanics	0.290	0.06	0.0001
Asian/Pacific Islanders	0.322	0.06	0.0001
Other	0.171	0.08	0.04
Unknown	0.644	0.10	0.0001
Education (%)			
High school graduate (reference)	—	—	
High school or less	0.020	0.05	0.68
Some college	–0.012	0.04	0.75
Therapy			
OHA (reference)	—	—	
Diet	−0.946	0.05	0.0001
Insulin	0.030	0.04	0.047
Diabetes duration			
<5 years (reference)	—	—	
5–9 years	0.271	0.04	0.0001
≥10 years	0.264	0.04	0.0001
SMBG practice			
Never (reference)	—	—	
<1/week	0.166	0.06	0.004
≥1/week	0.014	0.05	0.77
Exercise			
No (reference)	—	—	
Yes	0.002	0.003	0.95

prove glycemic control in postmenopausal women with type 2 diabetes by reducing their hyperandrogenicity. Reduced androgenecity may improve insulin sensitivity on skeletal muscle (28), which is the major tissue responsible for insulin-dependent glucose disposal during the fed state. However, estrogens have also been found to hamper glucose metabolism in the fed state by delaying the insulin secretion in response to a glucose load (29).

Some studies (21,30–33) suggest that the addition of progesterone to estrogens may reduce the beneficial effect of estrogens on glucose metabolism. Clinical trials (5,34) have shown that although fasting glucose and insulin levels decrease after estrogen therapy (with or without progestins), the addition of progestins worsens postchallenge glucose levels. In our study, 62% of women currently using HRT were using unopposed estrogens. The most common estrogen and progestin used was conjugated equine estrogen (90% of women used estrogen alone or in combination with progesterone) and medroxyprogesterone acetate (98% of women used progestins alone or in combination with estrogens), respectively. No differences in HbA_{1c} levels were observed between women using unopposed estrogen and women using opposed estrogen. These findings suggest that in women with type 2 diabetes, the possible adverse impact of estrogens on glucose homeostasis during the fed state (e.g., higher postchallenge glucose levels) observed in women without diabetes (5) might be offset by improved glucose metabolism during the fasting state, possibly by reducing hepatic glucose production (3,25).

Previous studies (35) have shown that women who were currently using HRT were more likely to have health behaviors that are associated with improved glucose metabolism than women who were not currently using HRT. Similarly, among women with type 2 diabetes in this study, those who were currently using HRT reported exercising and self-monitoring their blood glucose more frequently than women who were not currently using HRT. However, the association between HRT and decreased HbA_{1c} persisted after controlling for exercise and SMBG.

Premenopausal plasma insulin levels have been found to be lower among women who subsequently used HRT than women who subsequently did not use HRT (36). It is possible that HRT is more frequently prescribed to diabetic women with better glycemic control or less severe diabetes. However, no clinically relevant differences were found in the use of insulin (a disease severity indicator) between women using HRT and women not using HRT. Moreover, similar associations between HRT and decreased HbA_{1c} levels were found in women who were treated with diet only, OHAs, or insulin, although these three groups of women have very different degrees of hyperglycemia. Therefore, it seems unlikely that selective prescribing patterns explain our findings.

The association between HRT and decreased HbA_{1c} level was similar in all ethnic groups, as well as in all strata (except age) of education, BMI, hypoglycemic therapy, diabetes duration, and SMBG practice. The association was less pronounced in women aged ≥70 years. This was partially a result of a reduced variability in the outcome variable because HbA_{1c} levels decreased with age.

In observational studies in which treatment is not randomly assigned, differences in the covariates between the treated and untreated group might be so large that they lead to biased estimates of the treatment effect, even after conventional adjustment. The propensity score methods have been proposed as an approach that reduces such potential biases (37). We performed the propensity score analyses (results not shown) in order to balance the covariates (e.g., age, education, hypoglycemic therapy, BMI, diabe-

tes duration, exercise, and SMBG) among HRT users and nonusers. We first calculated the propensity score (defined as the conditional probability of being treated given the covariates) using logistic regression and then adjusted for the propensity score in the GEE models. In the propensity score–adjusted models, the direction and the magnitude of the association between HRT and HbA_{1c} did not vary substantially from the standard GEE models and remained statistically significant ($P < 0.0001$).

Although such a robust finding in an observational study of the association between HRT and decreased HbA_{1c} does not establish causality, it is consistent with the results of small randomized placebo-controlled trials of women with type 2 diabetes. There is a growing body of literature that points in the direction of a beneficial effect of HRT on glycemic control among women with diabetes. Long-term clinical trials, larger than those conducted thus far among women with diabetes, will be necessary to understand whether and to what extent HRT may improve glycemic control.

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References

1. Matthews KA, Meilahn E, Kuller LH, Kelsey SF, Caggiula AW, Wing RR: Menopause and risk factors for coronary heart disease. *N Engl J Med* 321:641–646, 1989
2. Poehlman ET, Toth MJ, Gardner AW: Changes in energy balance and body composition at menopause: a controlled longitudinal study. *Ann Intern Med* 123:673–675, 1995
3. Brussaard HE, Gevers Leuven JA, Frolich M, Kluft C, Krans HM: Short-term oestrogen replacement therapy improves insulin resistance, lipids and fibrinolysis in postmenopausal women with NIDDM. *Diabetologia* 40:843–849, 1997
4. Andersson B, Mattsson LA, Hahn L, Marin P, Lapidus L, Holm G, Bengtsson BA, Bjorntorp P: Estrogen replacement therapy decreases hyperandrogenicity and improves glucose homeostasis and plasma lipids in postmenopausal women with noninsulin-dependent diabetes mellitus. *J Clin Endocrinol Metab* 82:638–643, 1997
5. The Writing Group for the PEPI Trial: Effects of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women: the Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. *JAMA* 273:199–208, 1995
6. Sattar N, Jaap AJ, MacCuish AC: Hormone replacement therapy and cardiovascular risk in post-menopausal women with NIDDM. *Diabet Med* 13:782–788, 1996
7. Nabulsi AA, Folsom AR, White A, Patsch W, Heiss G, Wu KK, Szklo M: Association of hormone-replacement therapy with various cardiovascular risk factors in postmenopausal women: the Atherosclerosis Risk in Communities Study Investigators. *N Engl J Med* 328: 1069–1075, 1993
8. Barrett-Connor E, Laakso M: Ischemic heart disease risk in postmenopausal women: effects of estrogen use on glucose and insulin levels. *Arteriosclerosis* 10:531–534, 1990
9. Ferrara A, Barrett-Connor E, Wingard DL, Edelstein SL: Sex differences in insulin levels in older adults and the effect of body size, estrogen replacement therapy, and glucose tolerance status: the Rancho Bernardo Study, 1984–1987. *Diabetes Care* 18:220–225, 1995
10. Salomaa V, Rasi V, Pekkanen J, Vahtera E, Jauhiainen M, Vartiainen E, Ehnholm C, Tuomilehto J, Myllyla G: Association of hormone replacement therapy with hemostatic and other cardiovascular risk factors: the FINRISK Hemostasis Study. *Arterioscler Thromb Vasc Biol* 15:1549–1555, 1995
11. Krieger N: Overcoming the absence of socioeconomic data in medical records: validation and application of a census-based methodology. *Am J Public Health* 82:703–710, 1992
12. Selby JV, Ray GT, Zhang D, Colby CJ: Excess costs of medical care for patients with diabetes in a managed care population. *Diabetes Care* 20:1396–1402, 1997
13. Chang J, Hoke C, Ettinger B, Penerian G: Evaluation and interference study of hemoglobin A1c measured by turbidimetric inhibition immunoassay. *Am J Clin Pathol* 109:274–278, 1998
14. Zeger SL, Liang KY: Longitudinal data analysis for discrete and continuous outcomes. *Biometrics* 42:121–130, 1986
15. Liang KYZSL: Longitudinal data analysis using generalized linear models. *Biometrika* 73:13–22, 1986
16. SAS Institute, Inc. SAS/STAT Software: *Changes and Enhancements Through Release 6.11*. SAS Institute, Inc., Cary, NC, 1998
17. Marsh JV, Brett KM, Miller LC: Racial differences in hormone replacement therapy prescriptions. *Obstet Gynecol* 93:999–1003, 1999
18. Brett KM, Madans JH: Use of postmenopausal hormone replacement therapy: estimates from a nationally representative cohort study. *Am J Epidemiol* 145:536–545, 1997
19. Keating NL, Cleary PD, Rossi AS, Zaslavsky AM, Ayanian JZ: Use of hormone replacement therapy by postmenopausal women in the United States. *Ann Intern Med* 130:545–553, 1999
20. Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, Hadden D, Turner RC, Holman RR: Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ* 321:405–412, 2000
21. Lindheim SR, Presser SC, Ditkoff EC, Vijod MA, Stanczyk FZ, Lobo RA: A possible bimodal effect of estrogen on insulin sensitivity in postmenopausal women and the attenuating effect of added progestin. *Fertil Steril* 60:664–667, 1993
22. Lindheim SR, Duffy DM, Kojima T, Vijod MA, Stanczyk FZ, Lobo RA: The route of administration influences the effect of estrogen on insulin sensitivity in postmenopausal women. *Fertil Steril* 62:1176–1180, 1994
23. Wilcox JG, Hwang J, Hodis HN, Sevanian A, Stanczyk FZ, Lobo RA: Cardioprotective effects of individual conjugated equine estrogens through their possible modulation of insulin resistance and oxidation of low-density lipoprotein. *Fertil Steril* 67:57–62, 1997
24. Cagnacci A, Soldani R, Carriero PL, Paoletti AM, Fioretti P, Melis GB: Effects of low doses of transdermal 17 beta-estradiol on carbohydrate metabolism in postmenopausal women. *J Clin Endocrinol Metab* 74:1396–1400, 1992
25. Matute ML, Kalkhoff RK: Sex steroid influence on hepatic gluconeogenesis and glucogen formation. *Endocrinology* 92: 762–768, 1973
26. Samaras K, Hayward CS, Sullivan D, Kelly RP, Campbell LV: Effects of postmenopausal hormone replacement therapy on central abdominal fat, glycemic control, lipid metabolism, and vascular factors in type 2 diabetes: a prospective study. *Diabetes Care* 22:1401–1407, 1999
27. Haarbo J, Marslew U, Gotfredsen A, Christiansen C: Postmenopausal hormone replacement therapy prevents central distribution of body fat after menopause. *Metabolism* 40:1323–1326, 1991
28. Marin P, Andersson B, Krotkiewski M, Bjorntorp P: Muscle fiber composition and capillary density in women and men with NIDDM. *Diabetes Care* 17:382–386, 1994
29. Larsson-Cohn U, Wallentin L: Metabolic and hormonal effects of post-menopausal oestrogen replacement treatment. I. Glucose, insulin and human growth hormone levels during oral glucose tolerance tests.

Acta Endocrinol (Copenh) 86:583–596, 1977
30. Lindheim SR, Presser SC, Ditkoff EC, Vijod MA, Stanczyk FZ, Lobo RA: A possible bimodal effect of estrogen on insulin sensitivity in postmenopausal women and the attenuating effect of added progestin. *Fertil Steril* 60:664–667, 1993
31. Godsland IF, Gangar K, Walton C, Cust MP, Whitehead MI, Wynn V, Stevenson JC: Insulin resistance, secretion, and elimination in postmenopausal women receiving oral or transdermal hormone replacement therapy. *Metabolism* 42:846–853, 1993
32. Stevenson JC, Proudler AJ, Walton C, Godsland IF: HRT mechanisms of action: carbohydrates. *Int J Fertil Menopausal Stud* 39 (Suppl. 1):50–55, 1994
33. Cefalu WT, Wagner JD, Bell-Farrow AD, Wang ZQ, Adams MR, Toffolo G, Cobelli C: The effects of hormonal replacement therapy on insulin sensitivity in surgically postmenopausal cynomolgus monkeys (*Macaca fascicularis*). *Am J Obstet Gynecol* 171:440–445, 1994
34. Lobo RA, Pickar JH, Wild RA, Walsh B, Hirvonen E: Metabolic impact of adding medroxyprogesterone acetate to conjugated estrogen therapy in postmenopausal women: the Menopause Study Group. *Obstet Gynecol* 84:987–995, 1994
35. Barrett-Connor E: Postmenopausal estrogen and prevention bias. *Ann Intern Med* 115:455–456, 1991
36. Matthews KA, Kuller LH, Wing RR, Meilahn EN, Plantinga P: Prior to use of estrogen replacement therapy, are users healthier than nonusers? *Am J Epidemiol* 143:971–978, 1996
37. D'Agostino RBJ: Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. *Stat Med* 17:2265–2281, 1998