

Effects of Postmenopausal Hormone Replacement Therapy on HbA_{1c} Levels

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OBJECTIVE — Estrogen seems to contribute to glucose homeostasis in women. The objective of this study was to examine the effects of hormone replacement therapy (HRT) on HbA_{1c} levels in Japanese postmenopausal women and to determine whether the effects varied with age.

RESEARCH DESIGN AND METHODS — We studied 99 postmenopausal women taking HRT (mean \pm SD age 56.5 \pm 6.9 years, BMI 21.5 \pm 2.3 kg/m²) and 101 postmenopausal women not on HRT (51.4 \pm 6.1 years, 21.3 \pm 2.4 kg/m²). HRT consisted of continuous conjugated equine estrogen (CEE; 0.625 mg/day) and medroxyprogesterone acetate (MPA; 2.5 mg/day) for >2 years.

RESULTS — HbA_{1c} levels are positively associated with age and BMI in women who use HRT as well as in those who do not use HRT. After adjusting for age and BMI, HRT showed no effects on HbA_{1c} levels. However, HbA_{1c} levels were significantly lower in postmenopausal women aged 40–49 years who were taking HRT than in women of similar age who were not taking HRT (mean \pm SE 4.776 \pm 0.092 vs. 5.096 \pm 0.078%, $P < 0.05$). No differences in HbA_{1c} levels between women who did and did not use HRT were observed in those older than 50 years.

CONCLUSIONS — Oral HRT involving CEE combined with MPA may decrease HbA_{1c} levels in women aged 40–49 years and is likely to have no adverse effects on HbA_{1c} levels in women older than 50 years.

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Menopause seems to be associated with increased risk of glucose intolerance and type 2 diabetes (1,2). The most likely reason for this deterioration in health in postmenopausal women is loss of estrogen. Therefore, use of estrogen in postmenopausal women is believed to have beneficial effects on glucose homeostasis and to reduce the incidence of type 2 diabetes, although this remains controversial. Some studies have suggested that estrogen replacement therapy (ERT) or estrogen plus progesterone replacement therapy (hormone replacement

therapy [HRT]) increases insulin sensitivity and glucose tolerance (3,4), whereas others have shown little benefit or adverse effects (5,6). The results of epidemiologic or long-term follow-up studies are similar, reporting conflicting data in the incidence of diabetes in women on ERT/HRT (7–10). To address the effects of estrogen, detailed information is required. This information includes the type of estrogen used (conjugated equine estrogen [CEE] or 17 β -estradiol), whether estrogen is taken alone or in combination with progesterone, the route of estrogen

administration (oral or transdermal), and the duration of hormone therapy. Furthermore, the age of subjects should be considered, because responsiveness to estrogen may depend on age, possibly due to age-related changes in estrogen receptor isoforms (11,12).

Differences in methods used to assess glycemic control may also account for the conflicting results. Glycohemoglobin reflects glucose homeostasis over the preceding months and is commonly used as an index of mean blood glucose levels. HbA_{1c}, a chief component of glycohemoglobins, can be measured conveniently at any time of day, unlike fasting 2-h plasma glucose levels or the oral glucose tolerance test (OGTT). These characteristics prompted us to consider HbA_{1c} in the assessment of the effects of estrogen on glucose homeostasis.

The aim of this study was to evaluate the long-term effects of HRT on HbA_{1c} levels in healthy postmenopausal women. We focused on subjects taking continuous oral CEE plus medroxyprogesterone acetate (MPA), which is the most common and widely recommended HRT preparation for women with an intact uterus, to exclude factors concerning hormone prescriptions that may affect the results. Based on previous results indicating that age and BMI cause an elevation in HbA_{1c} levels in the normal population (13,14), we examined the age- and BMI-associated changes in HbA_{1c} levels in women taking HRT.

RESEARCH DESIGN AND METHODS

ALL subjects were healthy postmenopausal Japanese women, 40–70 years of age, recruited at the Department of Obstetrics and Gynecology, Nagoya University Hospital, Nagoya, Japan. Menopause was defined as a minimum of 12 consecutive months of amenorrhea. The study population consisted of 101 postmenopausal women who were not receiving HRT (control group) and 99 postmenopausal women who were receiving HRT (HRT group). Subjects of the control group were admitted for gynecological examination; results of routine blood chemistry analysis as

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Abbreviations: CAD, coronary artery disease; CEE, conjugated equine estrogen; ERT, estrogen replacement therapy; HRT, hormone replacement therapy; MPA, medroxyprogesterone acetate; WHI, Women's Health Initiative.

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

well as Papanicolaou smear were considered normal. Subjects in the HRT group had been taking oral HRT consisting of 0.625 mg CEE plus 2.5 mg MPA daily for >2 years (range 2.3–7.2). Exclusion criteria in both groups included 1) hypertension (systolic blood pressure \geq 140 or diastolic blood pressure \geq 90 mmHg); 2) diabetes (previous history of diabetes or fasting plasma glucose levels >110 mg/dl); 3) anemia; 4) various degrees of renal insufficiency; 5) evidence of significant liver disease; and 6) hysterectomy or a history of recent surgery. Subjects who had taken any medication within 48 h of the test, who had ever smoked or were currently smoking >20 cigarettes per day for 3 months, or who demonstrated significant chronic alcohol intake, were also excluded. All patients in this study gave written informed consent.

Blood samples were collected in the morning after a 12-h overnight fast. Serum lipid and glucose levels were determined by standard methods. HbA_{1c} was measured using an automatic high-performance liquid chromatography device (BML, Tokyo, Japan). The intra-assay and interassay coefficients of variation were 3.4 and 3.0%, respectively.

Height and weight were measured in the standing position without shoes. BMI was calculated as the weight in kilograms divided by the square of the height in meters.

Study characteristics were compared between two groups using Student's *t* test. Simple regression analysis was performed to assess the linear relationship between study parameters. Pearson's correlation coefficients were calculated. ANCOVA was performed to examine differences in adjusted means of HbA_{1c} between two groups. Results were considered significant at $P < 0.05$. Data analyses were performed using Statview 4.5 software (Abacus Concepts, Berkeley, CA).

RESULTS — Clinical characteristics of both groups are shown in Table 1. Women in the HRT group were significantly older and had significantly lower total plasma and LDL cholesterol levels. Similarly, the durations of menopause were significantly longer in this group, although the ranges were broadly overlapping. No differences in the height, weight, and BMI were observed between the two groups. Crude mean HbA_{1c} values did not

Table 1—Characteristics of postmenopausal women by HRT status

	Women on HRT (n = 99)	Women not on HRT (n = 101)
Age (years)	56.5 (6.9)*	53.8 (6.4)
Height (m)	1.54 (0.05)	1.55 (0.05)
Weight (kg)	50.9 (5.3)	51.4 (6.1)
BMI (kg/m ²)	21.5 (2.3)	21.3 (2.4)
Age at menopause (years)	48.2 (2.4)	48.5 (2.4)
Number of postmenopausal years	8.1 (5.8)*	6.1 (4.8)
Duration of HRT (years)	4.8 (2.7)	—
Total cholesterol (mg/dl)	204.5 (39.7)*	216.8 (37.6)
LDL cholesterol (mg/dl)	120.4 (30.0)*	129.3 (31.7)
HDL cholesterol (mg/dl)	74.6 (17.7)	71.5 (20.2)
Triglycerides (mg/dl)	103.4 (46.8)	108.5 (53.3)
Fasting glucose (mg/dl)	88.1 (9.6)	89.5 (10.6)
HbA _{1c}		
Crude means (%)	5.16 (0.04)	5.12 (0.04)
Age-adjusted means (%)	5.13 (0.04)	5.16 (0.04)

Data are means (SD). * $P < 0.05$.

differ between the HRT and control groups. The respective proportions of women who had never smoked at all were 92.6 and 93.7% in the HRT and control groups.

In Fig. 1, individuals in the HRT group are plotted according to HbA_{1c} and age. Age and HbA_{1c} were linearly related, and the linear regression line had a correlation coefficient of 0.149 ($P < 0.05$). Similar positive correlation was obtained in the control group (data not shown). We also examined the relationship between HbA_{1c} and BMI in the HRT group (Fig. 1), which demonstrated positive correlation ($r^2 = 0.110$, $P < 0.05$). Similar results were seen in the control group (data not shown). Because age- and BMI-related changes in HbA_{1c} levels were observed in both groups, we adjusted for age and BMI to evaluate the effects of HRT on HbA_{1c} levels. Even after adjustment for age and BMI, no significant difference was observed between the two groups (mean \pm SE; 5.134 \pm 0.039 in the HRT group vs. 5.159 \pm 0.039 in the control group) (Table 1).

To assess whether responsiveness of HbA_{1c} to HRT is dependent on age, we divided subjects into three age-groups (40–49, 50–59, and 60–69 years) (Fig. 2). In women aged 40–49 years, a small but significant decrease in HbA_{1c} levels was observed in HRT users ($n = 22$) compared with nonusers ($n = 24$) (4.776 \pm 0.092 vs. 5.096 \pm 0.078, $P < 0.05$), whereas significant differences between

the HRT and control groups were not seen in the other two age-groups: 50–59 years, 5.218 \pm 0.057 ($n = 49$) vs. 5.140 \pm 0.051 ($n = 55$), NS; 60–69 years, 5.270 \pm 0.061 ($n = 28$) vs. 5.173 \pm 0.090 ($n = 22$), NS.

CONCLUSIONS — The present study initially demonstrated no significant changes in HbA_{1c} levels between women who used HRT and those who did not use HRT, after adjusting for age and BMI. However, evaluation of HRT effects on HbA_{1c} by age indicated that HRT users aged 40–49 years had significantly lower HbA_{1c} levels than nonusers of the same age, whereas HRT users aged 50–59 and 60–69 years showed no significant difference in HbA_{1c} levels.

Estrogen replacement is well documented to reduce the risk of coronary artery disease (CAD) via several mechanisms (15,16). One of the most established mechanisms is through alterations in lipids and lipoproteins (17), which is believed to explain \sim 30% of the benefit. Therefore, estrogen is likely to affect other CAD risk factors. Impaired glucose tolerance, decreases in insulin sensitivity, and hyperinsulinemia (18) are all known to lead to elevated blood glucose levels and to increase the risk of CAD. Estrogen may reduce the risk of CAD through modifying these elements of glucose metabolism and improving glucose homeostasis. Therefore, several studies have attempted to elucidate the association between es-

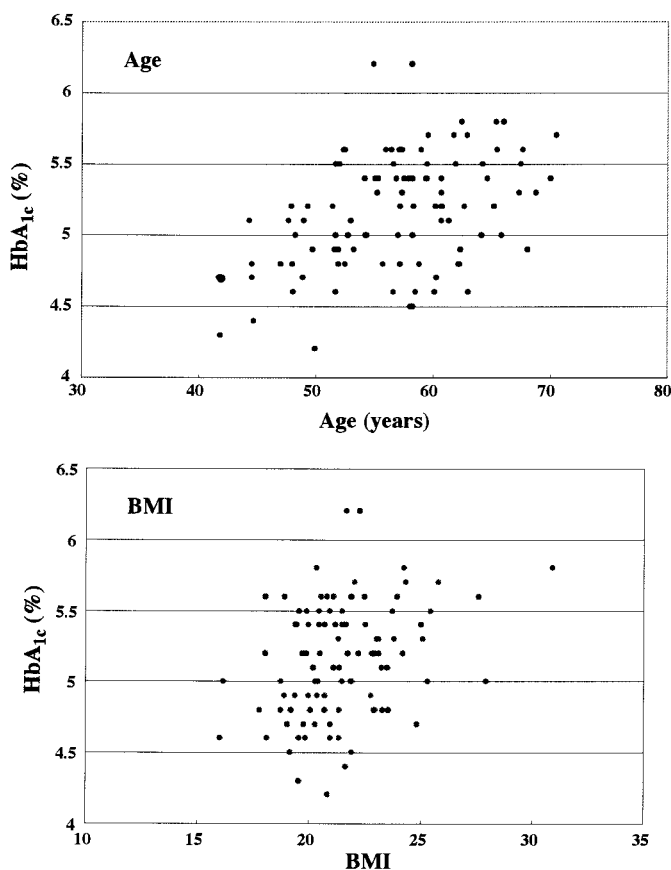


Figure 1—Effect of age and BMI on HbA_{1c} levels in postmenopausal women taking HRT. Correlation coefficients for age and BMI versus HbA_{1c} levels were both statistically significant ($P < 0.05$).

trogen therapy and glucose homeostasis in women who do not have diabetes. However, the results of the studies are conflicting. Most studies (3–6,19,20) have evaluated fasting or 2-h insulin and glucose levels. Some studies have shown that estrogen use decreases fasting insulin levels (3,19), whereas others have revealed little or no association between HRT and fasting insulin levels (5,20).

This is also the case for fasting glucose levels (3–6,19,21).

To assess the association between estrogen and glycemic control, we measured HbA_{1c} in postmenopausal women. Subjects with HbA_{1c} levels closer to the cutoff value have an increased likelihood of experiencing deterioration of glucose metabolism than those with the lower HbA_{1c} levels (22). In addition, measuring

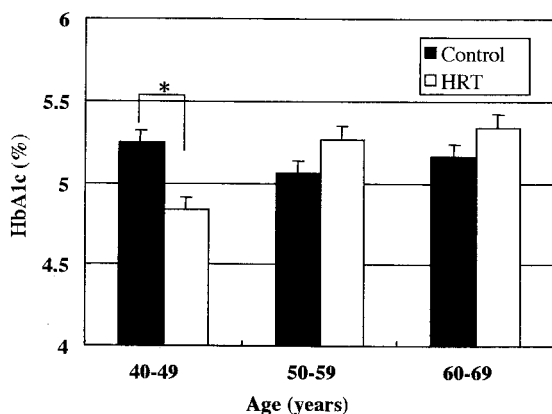


Figure 2—Effects of HRT on HbA_{1c} levels with age. * $P < 0.05$ for postmenopausal women taking HRT versus postmenopausal women not taking HRT.

glycohemoglobin is reportedly more sensitive than measuring fasting plasma glucose as a screening test for diabetes (23–25), although some reports have suggested the converse (26,27). HbA_{1c}, the time-integrated index of plasma glucose level, may therefore be the most accurate indicator of average plasma glucose, particularly in the assessment for the long-term effects of treatments such as HRT. Because HbA_{1c} increases with age and BMI affects the age-dependent increase in HbA_{1c} (13,14), we adjusted for age and BMI to evaluate the effects of HRT on HbA_{1c}. In our study, we did not observe any influence of HRT on HbA_{1c} values after adjusting for age and BMI, and we only observed the HbA_{1c}-lowering effect of HRT in women aged 40–49 years. Although the cellular mechanisms regulating the age-dependent response of HbA_{1c} to estrogen have yet to be elucidated, this is also the case for endometrium (28) and bone (29).

Our results are unlikely to have resulted from chance, but several possible biases should be considered. One would be the possibility that the lack of reduction in HbA_{1c} in HRT users might be due to the longer duration of menopause. This is unlikely, because we failed to obtain significant changes in HbA_{1c} after adjustment for duration of menopause. The beneficial effects of HRT on HbA_{1c} in women aged 40–49 years may be attributed to fewer smokers being selected among HRT users, because an association between higher HbA_{1c} and smoking has been reported (30,31). We excluded former and current smokers from this study, but the proportion of nonsmokers was similar in HRT users and nonusers in all age-groups. Another possible selection bias exists: HRT users may have tendency toward a healthy lifestyle, possibly taking more nutritional supplements, eating more vegetables, or getting more exercise. Furthermore, HRT users may be more educated or in a higher socioeconomic stratum. We cannot exclude the possibility that these biases explain the lower HbA_{1c} levels in HRT users aged 40–49 years, and as such, these factors should be evaluated in a future study.

Little evidence exists suggesting the effects of ERT/HRT on HbA_{1c} levels (20,32,33). Our results indicating no association between HRT and HbA_{1c} after adjustment for age and BMI are consistent with those of a previous report that used

oral 17 β -estradiol with norethindrone acetate over a 6-month period (20), although our study used CEE, the only form of oral estrogen therapy in clinical use, and examined the effects over 2 years. In contrast to our results, Troisi et al. (33) found a small but significant decrease in HbA_{1c} levels in current users of HRT compared with never or past users after adjustment for age and BMI. However, they did not evaluate or focus on the type of HRT preparation.

Differences in ERT/HRT prescriptions could account for some of the controversy. Addition of progestogen, generally in a continuous manner after menopause, is essential to reducing the risk of endometrial cancer related to unopposed estrogen use in women with a uterus. Most studies investigating the impact of progestogens have indicated that progestogens are likely to attenuate glucose homeostasis and insulin sensitivity (6,20). In contrast, the Postmenopausal Estrogen/Progestin Interventions (PEPI) trial demonstrated no obvious effects by three progestin regimens (19). Furthermore, because transdermal therapy and oral therapy may have distinct effects on insulin and glucose concentrations, data from subjects taking transdermal 17 β -estradiol should be carefully considered (34,35). Because the purpose of this study was to clarify the influences of prevalent HRT methods on glucose homeostasis, we limited our study to women taking continuous oral CEE (0.625 mg/day) plus MPA (2.5 mg/day). Duration of HRT may also affect the relationship between HRT and glucose homeostasis (36,37). Because HRT is so widely accepted, the duration of hormone use is increasing. To evaluate the relative long-term effects of HRT, we confined our subjects to women receiving HRT for >2 years (mean 4.8).

Several studies have reported findings in women with type 2 diabetes similar to those obtained from normal subjects in this study. CEE alone and oral 17 β -estradiol alone were found to decrease HbA_{1c} levels in women with type 2 diabetes, although only short-term effects were observed (38,39). A cohort study using a large number of subjects with type 2 diabetes also indicated that HRT was independently associated with a decrease in HbA_{1c} levels (40).

The surprising results of the Women's Health Initiative (WHI) were recently reported (41). This first randomized pri-

mary prevention trial of postmenopausal HRT was prematurely terminated because the risks, such as cardiovascular events and breast cancer, had surpassed the potential benefits. Because we did not observe adverse effects of HRT on glycemic levels, the increased rate of CAD in HRT users in the WHI study may have been independent of deterioration of glycemic control. Several recent studies have demonstrated that HRT is associated with an increased risk of venous thrombosis (42,43) and higher concentrations of C-reactive protein, a risk factor for future cardiovascular events (44,45). Through these mechanisms related to accelerated atherosclerosis, plaque destabilization, or thrombosis, HRT might increase the incidence of CAD. Furthermore, it should be noted that there were several differences in the background data of subjects between the WHI study and the present study. First, the WHI study did not exclude smokers and had a relatively high prevalence of smoking among study subjects. Second, women in the WHI study were older and had higher BMI.

Another point of interest in this study is the effect of unopposed estrogen on HbA_{1c}, particularly because the WHI is continuing with the other portion of the trial, comparing estrogen alone with placebo in women with hysterectomies. Our preliminary examination demonstrated no obvious effects of ERT on HbA_{1c}, although the limited number and younger age of the subjects made it difficult to match background data with the control or combined HRT groups.

In conclusion, our study indicates that long-term continuous oral CEE plus MPA results in a small but significant HbA_{1c}-lowering effect in postmenopausal women aged 40–49 years and shows no adverse effects of HRT on HbA_{1c} levels in those older than 50 years. Because the mean age of menopause is ~49 years, our results suggest that HRT does not deteriorate average plasma glucose, even in women experiencing menopause at a younger age. Larger randomized, placebo-controlled trials and studies elucidating the cellular mechanisms to explain the age-related effects of HRT on HbA_{1c} levels are necessary, if we could expect the beneficial effects of HRT on glycemic control in younger postmenopausal women.

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