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ASSOCIATION BETWEEN HORMONE REPLACEMENT THERAPY AND GLYCEMIC CONTROL IN POSTMENOPAUSAL WOMEN WITH TYPE 2 DIABETES

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Abstract

Introduction. 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 HbA1C levels are influenced by current HRT among postmenopausal women with type 2 diabetes.

Methods. A total of 40 postmenopausal women with type 2 diabetes were enrolled. All of them fulfilled the criteria of natural menopause, with intact uterus, low estrogen levels (E2) and high follicle-stimulating hormone (FSH) levels. Half of them (20 women) were assigned to take HRT (DM-HRT group). The other half (20 women) were assigned to the control group, those who did not take HRT (DM-non HRT group). HRT consisted of 17 β-estradiol (E2) 1 mg and drospirenone (DRSP) 2 mg. Fasting plasma glycemia, insulinemia and HbA1C were followed in both groups throughout 12 months.

Results. The mean age was 49 years (SD±3,3) and 48,5 (SD±3.1), respectively. HRT was associated with statistically significant decrease in serum fasting glucose, HbA1C and insulinemia levels in the DM-HRT group. There was no significant reduction in glucose levels and HbA1C together with no significant increase in insulinemia levels in the DM non-HRT group throughout 12 months.

Conclusion. HRT was associated with statistically significant decrease of plasma glucose levels and HbA1C level. Larger clinical trials are necessary to understand whether HRT may improve glycemic control in women with diabetes, especially when it is given shortly after entering menopause.

Key words: menopause, diabetes, HbA1C, hormone replacement therapy (HRT)

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Introduction

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 have shown that short-term hormone replacement therapy (HRT) with estrogen alone improves HbA1C 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 decrease fasting glucose levels compared to 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].

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 [6,7], whereas others have shown little benefit or adverse effects [8,9]. 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 [10-14]. To address the effects of estrogen, detailed information is required. This information includes the type of estrogen used (conjugated equine estrogen [CEE] or 17β-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 [15,16].

An association among HRT, lower fasting glucose, and insulin level has also been found in several large observational studies [17-20]. A large meta-analysis found that

women with diabetes taking HRT had significantly reduced insulin resistance, reduced fasting glucose and reduced fasting insulin, compared to those taking placebo or no treatment. However, observational studies are limited by the issue of temporality [21].

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 the day, unlike fasting 2-h plasma glucose levels or the oral glucose tolerance test (OGTT). These characteristics have prompted us to consider HbA1C in the assessment of the effects of HRT on glucose homeostasis.

Materials and methods

We prospectively studied 40 postmenopausal women with type 2 diabetes, Diabetes was diagnosed using the criteria of the World Health Organization, at least 2 years before entering the study. In order to maintain their glucose levels in an acceptable range, women with type 2 diabetes were on dietary management alone (two patients) or taking oral anti-diabetic drugs that consisted of metformin and sulfonylureas (38 patients). Each diabetic patient received a diabetic diet of 1300 ckal/day. The women were instructted not to change their diet. None of them were taking insulin. None of the women were taking anti-lipidemic, corticosteroid or anti-convulsant therapy. The anti-diabetic medications were left unchanged during the study.

Menopause was confirmed by the absence of menstruation for at least 12 months and by high serum levels of FSH (>30 mIU/ml) and low serum levels of estradiol (E_2) (<20pg/ml). They all had intact uterus. The subjects had not received HRT previously. Gynecological examination and mammogram were normal in all subjects.

Half of the subjects (20 women) were assigned to take HRT (DM-HRT) group. The other half (20 women) were assigned to the control group, those who did not take HRT (DM-non HRT group). The randomization of the subjects was done based on the willingness and motivation to cooperate. Subjects in the DM-HRT group had been taking oral HRT consisting of 17β-estradiol (E2) 1 mg and DRSP (drospirenone) 2 mg-Angeliq®, Schering AG, Germany, l tablet daily for 12 months. Subjects in DM-non HRT group were followed in the same way as the examined group. Exclusion criteria in both groups were: 1) hypertension (systolic blood pressure ≥140 or diastolic blood pressure ≥90 mmHg); 2) anemia; 3) various degrees of renal insufficiency; 4) evidence of significant liver disease; and 5) hysterectomy or a history of recent surgery or significant chronic alcohol intake. All patients in this study gave written informed consent.

This study was approved by the local medical ethics committee.

All of the participants enrolled in our study were contacted by telephone in a three-month interval in order to discover any adverse effects of HRT. All metabolic and physical examinations were performed at the beginning of the study and then again after 12 months of receiving HRT. Blood samples were taken after a 12 h fast. HbA1C was determined on a Cobas c 111 analyzer using commercial kits supplied from Roche Diagnostic Gmbh (Switzerland), and glucose levels were determined in a Beckman Analyzer 2 automated analyzer by using commercial kits supplied from Analox Instruments Ltd, London (UK). Insulinemia was determined in an Elecsys 2010 analyzer using commercial kits from Roche Diagnostics Gmbh (Switzerland).

Statistical analysis

Statistical analysis was carried out with descriptive statistics, t-test for related samples and t test for independent samples. The data are expressed as means ±SEM. Statistical significance was set at $P<0.05$. Data were analyzed using the statistical package Statistica, version 10.0 (StatSoft).

Results

All of the women who were enrolled into the investtigation completed the study. The mean age of the subjects was 49±3.34 and 48.5±3.1 years, and their mean body mass index (BMI) was 27.27±3.32 and 28.3±2.4 kg/m^2 in the DM-HRT and DM non-HRT groups, respectively. High school educationhad completed 58.3% and 54.2%, respectively. The baseline characteristics of the subjects are given in Table 1. Two subjects in the DM-HRT group and one subject in the DM non-HRT group complained on abnormal vaginal bleeding such as metrorrhagia and four patients reported breast tenderness in the DM-HRT group. Other adverse effects were not seen.

Table 1. Baseline characteristics of postmenopausal women by HRT status

	Women on HRT (*n*=20)	Women not on HRT (*n*=20)	p
Age (years)	49 ±3.34	48.5±3.1	NS
BMI (kg/m^2)	27±3.32	28.3±2.4	NS
Fasting plasma glucose (mmol/l)	7.8±0.86	8.0±0.9	NS
HbA1C (%)	7.6±0.54	7.9±0.5	NS
Insulinemia (μU/ml)	12.2±3.41	12.3±3.2	NS

HRT was associated with a statistically significant decrease in serum fasting glucose, HbA1C and insulinemia levels in the DM-HRT group. There was no significant reduction in glucose levels and HbA1C together with no significant increase in insulinemia levels in the DM non-HRT group throughout 12 months. There was no significant difference observed between the two groups at baseline and after 12 months. The changes in serum fasting glucose, HbA1c levels and fasting insulin levels are given in Table 2.

Table 2. Effects of HRT on Fasting Plasma Glucose (FPG), HbA1C & Insulinemia

	Women on HRT (*n*=20)	P value	Women not on HRT (*n*=20)	P value	P* value
FPG (mmol/l)					
Baseline	7.8±0.86	p<0.001	8.0±0.9	P=0.66	
12 months	6.9±0.6		7.8±1.1		P*<0.0001
HbA1C %					
Baseline	7.6±0.54	p<0.001	7.9±0.5	p=0.477	
12 months	7.2±0.43		7,7±0.4		P*<0.0001
Insulinemia (μU/ml)					
Baseline	12.2±3.41	p<0.001	12.3±3.2	p=0.08	
12 months	10.4±2.92		13.1±3.7		P*<0.0001

P<0.05 statistically significant for all postmenopausal women included in adequate group at baseline and after 12 months; P*<0.05 statistically significant for group comparison at 12 months

Discusion

Estrogen replacement is well-documented to reduce the risk of coronary artery disease (CAD) via several mechanisms [22,23]. One of the most established mechanisms is through alterations in lipids and lipoproteins [24], which is belived to explain ~30% of the benefit. Therefore, estrogen is likely to affect other CAD risk factors. Impaired glucose tolerance, decrease in insulin sensitivity, and hyperinsulinemia [25] 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 estrogen therapy and glucose homeostasis in women who do not have diabetes. However, the results of the studies are conflicting. Most studies [26,27] have evaluated fasting or 2-h insulin and glucose levels. Some studies have shown that estrogen use decreases fasting insulin levels [27], whereas others have revealed little or no association between HRT and fasting insulin levels [27]. This is also the case for fasting glucose levels [26,28].

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 [29]. In addition, measuring glycohemoglobin is reportedly more sensitive than measuring fasting plasma glucose as a screening test for diabetes [30-32], although some reports have suggested the converse [33,34]. 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. HbA1C increases with age and BMI affects the age-dependent increase in HbA1C [19,20]. Therefore, in our study, we only observed the HbA1C-lowering effect of HRT in postmenopausal women at the beginning of their menopausal life span. The cellular mechanisms regulating the age-dependent response of HbA1C to estrogen have yet to be elucidated.

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 can not exclude the possibility that these biases explain the lower HbA1C levels in HRT users in early menopausal period, and as such, these factors should be evaluated in a future study.

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 [11,28]. In contrast, the Postmenopausal Estrogen/Progestin Interventions (PEPI) trial demonstrated no obvious effects by three progestin regimens [27]. 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 Drospirenon (2 mg/day) plus 17β-estradiol (1 mg/day). Duration of HRT may also affect the relationship between HRT and glucose homeostasis [35,36]. A cohort study using a large number of subjects with type 2 diabetes also indicated that HRT was independently associated with a decrease in HbA1C levels [37]. To evaluate the relative long-term effects of HRT, we confined our subjects to women receiving HRT for 2 years. But that might be a subject for another study.

Conclusion

In conclusion, our study has indicated that continuous oral HRT results in a significant HbA1C -lowering effect in postmenopausal women given shortly after entering menopause. In our opinion, HRT, given in the first 2-3 years after entering menopause, might be the key point in improving glucose homeostasis in diabetic postmenopausal women.

Larger randomized, placebo-controlled trials and studies elucidating the cellular mechanisms to explain the age-related effects of HRT on HbA1C levels are necessary, where we could expect to see the beneficial effects of HRT on glycemic control in younger postmenopausal women.

Conflict of interest statement. None declared

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