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ORIGINAL ARTICLE

Combined estrogen replacement therapy on metabolic control in postmenopausal women with diabetes mellitus

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Abstract Previous studies have shown that the incidence of diabetes is higher when women come to menopause. This study was carried out to examine the effects of combined estrogen replacement therapy (ERT) on diabetes in postmenopausal women. PubMed/MEDLINE was searched for English-language articles published between January 1997 and June 2011. Studies that examined ERT on the incidence of diabetes and randomized clinical trials that evaluated combined ERT (estrogen plus progesterone) on diabetic indices in postmenopausal women were included. Pooled relative risks were calculated using a random- or a fixed-effects model. Sixteen studies comprising 17,971 cases were included. Based on the pooled data, ERT significantly reduced the incidence of diabetes [odds ratio (OR), 0.61; 95% confidence interval (CI), 0.55–0.68, ERT past/current/continuous use vs. never use; OR, 0.57; 95% CI, 0.51–0.65, ERT current/continuous use vs. past/never use]. Women with combined ERT have significantly lower levels of fasting plasma glucose (mean difference, −1.41 mM/L; 95% CI, −2.49 to −0.33 mM/L) and HbA1c (mean difference, −0.73%; 95% CI, from −1.28 to −0.18%) compared with placebo. Furthermore, combined ERT dramatically reduced plasma total cholesterol (mean difference, −0.34 mM/L; 95% CI, from −0.53 to −0.15 mM/L) and low-density lipoprotein (mean difference, −0.43 mM/L; 95% CI, from −0.71 to −0.14 mM/L) but slightly increased

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high-density lipoprotein (mean difference, 0.02 mM/L; 95% CI, from −0.07 to 0.12 mM/L) levels as compared with placebo control. This systemic review and meta-analysis provides evidence that postmenopausal women taking low-dose combined ERT have a decreased risk of developing diabetes and have better diabetic control.

Introduction

Diabetes, with long-term consequences including kidney failure, amputations, genitourinary, and cardiovascular symptoms, is one of the most common chronic diseases and a major public health problem [1]. It is estimated that the number of diabetic patients in the world will double from 171 million in 2000 to 366 million in 2030 [2]. It is therefore important to identify interventions that can decrease the risk of diabetes.

Several factors increase the risk of diabetes, including overweight, physical inactivity, advancing age, and family history of diabetes [3,4]. There is a growing consensus that the decline in ovarian hormone levels at the time of menopause may play a role [5]. Epidemiological studies found that the ratio of using estrogen in diabetic women was only about half of that in nondiabetic women [6—10], and the incidence of diabetes dramatically increased when women came to the postmenopausal period [2]. A study reported that the prevalence of diabetes among women aged 50 years and older was at least 15% in the United States [11]. It is postulated that the high incidence of diabetes in postmenopausal women is due to the imbalance of endogenous sex hormone levels in that the plasma estrogen is significantly reduced when women come to the menopausal period. The exact biological mechanism is not fully understood, but there are several factors that may help to explain the relationship, including increasing antioxidative stress and anti-inflammation ability, modulating cholesterol metabolism [12], or increasing insulin sensitivity [13] by estrogen. Insulin sensitivity is closely related with the plasma concentration of estrogen. It is reported previously that estrogen *per se* augmented insulin sensitivity at low concentrations but diminishes insulin sensitivity at high concentrations when examined on a pregnancy rat model [14]. There is a report indicating that insulin-stimulated glucose uptake was improved by estrogen replacement even in postmenopausal nondiabetic women [15]. Recently, Bonds and colleagues [16] conducted the Women's Health Initiative randomized trial and found that estrogen replacement therapy (ERT) with conjugated equine estrogen possessed protective effects against diabetes.

During the past 2 decades, several studies have evaluated the effect of ERT in postmenopausal women; however, most of these studies primarily concern women without diabetes. Moreover, there is discrepancy in the therapy effect because of the different trial designs used in these studies. To comprehensively assess the association between ERT and diabetes in postmenopausal women, we conducted a meta-analysis to summarize these studies. Previously, a randomized, double-blind prospective trial concerning 15,641 postmenopausal women also identified that combined administration with estrogen plus progestin had favorable effects on glucose homeostasis [17]. To this end, we also investigated whether combined ERT could ameliorate indices including carbohydrate and lipid metabolism in postmenopausal diabetic patients.

Methods

Search strategy and selection criteria

A literature search of PubMed/MEDLINE and EMBASE (January 1997—June 2011) using the keywords and Medical Subject Headings *diabetes* combined with *estrogen replacement therapy* was conducted. To be included, studies had to be written in English in peer-reviewed journals.

Specifically, to evaluate the influence of ERT on the incidence of diabetes, trials should meet the following criteria: (1) Involving diabetes (either type 1 or type 2 diabetes mellitus); (2) ERT (single ERT with estradiol only, or combined ERT with estradiol plus progesterone); (3) postmenopausal women; and (4) reported with means and standard deviation (SD; or sufficient data to calculate).

As single ERTs may increase the risk of estrogen-related disease, combined ERT administration was mostly applied. To evaluate the therapeutic effects of combined ERT on diabetic indices, we further sourced trials using the following criteria: (1) postmenopausal women being diagnosed with diabetes (either type 1 or type 2 diabetes mellitus) at baseline; (2) combined oral estrogen plus progesterone administration; (3) randomized and placebo-controlled prospective study; (4) there should be a washout period of at least 4 weeks between treatments for crossover studies; (5) reported diabetic indices including fasting plasma glucose, glycated hemoglobin (HbA1c), insulin, total cholesterol (TC), low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglyceride (TG); and (6) reported with means and SD (or sufficient data to calculate).

Diabetes is defined as a fasting blood glucose level of $\geq$6.9 mM/L (126 mg/dL); patients who are currently taking antihyperglycemic agents or have a medical history of diabetes were also included. Postmenopause was the condition if more than 12 months had elapsed since the patient's last natural menstruation or if she had experienced bilateral oophorectomy.

Data extraction

Two investigators (Y.X. and J.L.) independently reviewed the titles, abstracts, and full articles of the original references for