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The association of elective hormone therapy with changes in lipids among glucose intolerant postmenopausal women in the diabetes prevention program

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ABSTRACT

Objective. It is unclear how lipids change in response to lifestyle modification or metformin among postmenopausal glucose intolerant women using and not using hormone therapy (HT). We examined the one-year changes in lipids among postmenopausal, prediabetic women in the Diabetes Prevention Program (DPP), and whether changes were mediated by sex hormones.

Materials/Methods. We performed a secondary analysis of a randomized controlled trial of 342 women who used HT at baseline and year 1 and 382 women who did not use HT at either time point. Interventions included intensive lifestyle (ILS) with goals of weight reduction of at least 7% of initial weight and 150 minutes per week of moderate intensity exercise, or metformin or placebo administered 850 mg up to twice a day. Women were not randomized to HT. Main outcome measures were changes between baseline and study year 1 in low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides.

Results. Compared to placebo, both ILS and metformin significantly reduced LDL-C and raised HDL-C among HT users, changes partially explained by change in estradiol and testosterone but independent of changes in waist circumference and 1/fasting insulin. In contrast, DPP interventions had no effect on LDL-C and HDL-C among non-HT users. ILS significantly lowered triglycerides among non-users but did not significantly change triglycerides among HT users. Metformin did not significantly change triglycerides among non-users but increased triglycerides among HT users.

Conclusions. The beneficial effects of ILS and metformin on lowering LDL-C and raising HDL-C differ depending upon concurrent HT use.

Abbreviations: AMPK, 5′ adenosine monophosphate-activated protein kinase; apoB, apolipoprotein B; BMI, body mass index; DPP, Diabetes Prevention Program; DHEA, dehydroepiandrosterone; E2, estradiol; FPG, fasting plasma glucose; FHS, follicle stimulating hormone; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment of insulin resistance; HT, hormone therapy; ILS, intensive lifestyle therapy; LDL-C, low-density lipoprotein cholesterol; OGTT, oral glucose tolerance test; SD, standard deviation; SHBG, sex hormone binding globulin; T, testosterone; VLDL, very low-density lipoprotein.

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1. Introduction

Clinical trials of hormone therapy (HT) in postmenopausal women using oral estrogen with and without progesterone have shown that HT has both favorable and adverse effects on the lipid profile. While HT reduces LDL-cholesterol (LDL-C) and increases HDL-cholesterol (HDL-C) [1–10], HT also increases triglycerides [1–6] and does not prevent cardiovascular disease events [2,4,5,11]. HT has potentially complex effects on the lipid profile through modulation of serum sex hormone levels and effects on key enzymes in the lipid/lipoprotein metabolic pathway. Oral HT raises sex hormone binding globulin (SHBG), which may increase endogenous estradiol (E2) and decrease endogenous free testosterone (T) levels [12]. E2 may also impact lipoprotein levels via its binding to estrogen receptors in visceral and subcutaneous adipocytes [13,14] and via its effects on lipoprotein lipase. Lipoprotein lipase activity is inversely correlated with E2 levels in obese women [15] and HT inhibits lipoprotein lipase activity, which can increase triglyceride levels [16]. E2 also inhibits hepatic lipase activity, thereby decreasing hydrolysis of cholesterol ester in HDL-C and increasing HDL-C levels [17]. These data suggest that interventions to manipulate serum sex hormones levels, beyond HT, may alter the lipid profile in post-menopausal women.

There are two potential ways to manipulate serum sex hormone levels–use of HT and lifestyle interventions including physical activity and dietary changes. Results of prior studies using lifestyle interventions have been mixed [18–20]. The Diabetes Prevention Program (DPP) was a randomized trial of intensive lifestyle change (ILS) and metformin in overweight, glucose-intolerant adults at high risk of diabetes. Both interventions had favorable effects on the lipid profiles including decreased triglycerides, increased HDL-C, and decreased small, dense LDL-C [21]. This analysis was not stratified by sex, menopausal status or HT use in women, although we have previously demonstrated that changes in serum sex hormones differ by HT use [22]. Due to the potential effects of exogenous estrogen on enzymes that affect lipid metabolism, the favorable effects of the DPP interventions on lipids could vary by HT use as both the interventions and HT use can alter serum sex hormone levels. We therefore sought to determine (1) the one year association of the DPP interventions on the lipid profile in glucose intolerant, obese post-menopausal women, (2) whether intervention-induced changes in lipid parameters were associated with changes in serum sex hormones, and (3) whether these changes differed by HT use status (Fig. 1).

2. Materials and methods

2.1. Study population

Characteristics of DPP participants have been published [23]. Briefly, DPP inclusion criteria included age ≥ 25 years, fasting plasma glucose (FPG) 95–125 mg/dL and 2-hour plasma glucose of 140–199 mg/dL following a 75-gram oral glucose load, and body mass index (BMI) ≥ 24 kg/m^2 (≥22 kg/m^2 for Asian-Americans). Participants were recruited from 26 clinical centers located throughout the United States (Baton Rouge, LA; Chicago, IL; Philadelphia, PA; Miami, FL; San Antonio, TX; Denver, CO; Boston, MA; Seattle, WA; Memphis, TN; Boston, MA; La Jolla, CA; New York, NY; Indianapolis, IN; Hyattsville, MD; Alhambra, CA; St. Louis, MO; Baltimore, MD; Albuquerque, NM; New York City, NY; Pittsburgh, PA; Honolulu, HI; and Phoenix, AZ). The Phoenix center is the site for 4 Indian Health Service areas and Chicago is the location for centers at the University of Chicago and Northwestern University. Written informed consent was obtained from all participants before screening, consistent with the guidelines of each participating center's institutional review board.

Eligible participants recruited between 1996 and 1999 were randomly assigned to one of three interventions: 850 mg metformin twice daily, placebo twice daily, or ILS designed to achieve and maintain a weight reduction of at least 7% of initial body weight through consumption of a low-calorie, low-fat diet, and moderate physical activity for at least

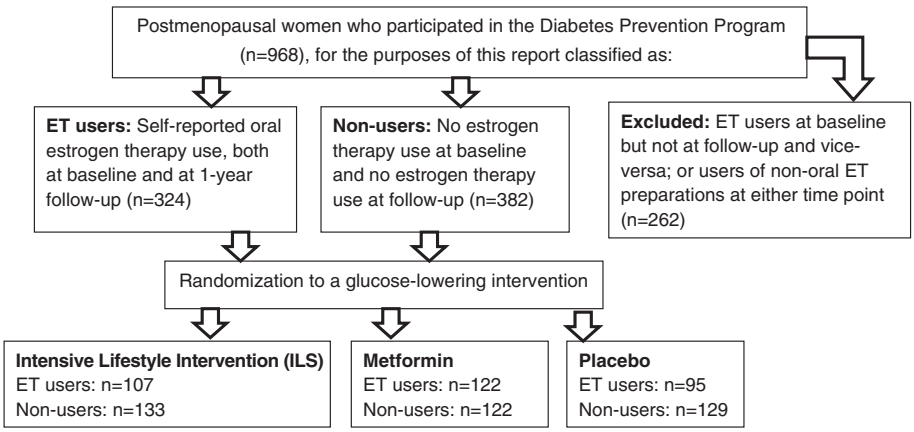

Fig. 1 – Secondary analysis design. We conducted an analysis of the effectiveness of interventions in a randomized trial (the Diabetes Prevention Program), among postmenopausal women who were either 1) oral estrogen users at baseline and at 1-year follow-up or 2) non-estrogen users at baseline and at 1-year follow-up. Adapted from: Kim C et al. Reduction in Glucose Among Postmenopausal Women Who Use and Do Not Use Estrogen Therapy. *Menopause*, 2013;20:393–400.