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Weight and metabolic effects of dietary weight loss and exercise interventions in postmenopausal antidepressant medication users and non-users: A randomized controlled trial ☆

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ABSTRACT

Objective. Antidepressants may attenuate the effects of diet and exercise programs. We compared adherence and changes in body measures and biomarkers of glucose metabolism and inflammation between antidepressant users and non-users in a 12-month randomized controlled trial.

Methods. Overweight or obese, postmenopausal women were assigned to: diet (10% weight loss goal, N = 118); moderate-to-vigorous aerobic exercise (225 min/week, N = 117); diet + exercise (N = 117); and control (N = 87) in Seattle, WA 2005–2009. Women using antidepressants at baseline were classified as users (N = 109). ANCOVA and generalized estimating equation approaches, respectively, were used to compare adherence (exercise amount, diet session attendance, and changes in percent calorie intake from fat, cardiopulmonary fitness, and pedometer steps) and changes in body measures (weight, waist and percent body fat) and serum biomarkers (glucose, insulin, homeostasis assessment-insulin resistance, and high-sensitivity C-reactive protein) between users and non-users. An interaction term (intervention × antidepressant use) tested effect modification.

Results. There were no differences in adherence except that diet session attendance was lower among users in the diet + exercise group ($P < 0.05$ vs. non-users). Changes in body measures and serum biomarkers did not differ by antidepressant use ($P_{interaction} > 0.05$).

Conclusion. Dietary weight loss and exercise improved body measures and biomarkers of glucose metabolism and inflammation independent of antidepressant use.

Introduction

Antidepressant medications are frequently prescribed in the United States; prevalence of use in adults has increased more than threefold (Paulose-Ram et al., 2007). Several studies show that individuals taking antidepressants have increased risk for obesity or weight gain (Kivimaki et al., 2010; Patten et al., 2011; Rubin et al., 2010a; Serretti and Mandelli, 2010), diabetes (Kivimaki et al., 2010; Pan et al., 2012; Rubin et al., 2008, 2010b), and cardiovascular disease (Cohen et al., 2000; Hamer et al., 2011b; Smoller et al., 2009).

It is not clear if antidepressant use has a physiological effect on weight loss efficacy and risk factors associated with chronic disease, or if the impact of antidepressants is tied to behavioral factors. *In vitro* studies show that fluoxetine (Garcia-Colunga et al., 1997), paroxetine (Fryer and Lukas, 1999), nefazodone (Fryer and Lukas, 1999), and venlafaxine (Fryer and Lukas, 1999), commonly prescribed antidepressants, non-competitively inhibit muscle nicotinic acetylcholine receptors, which may reduce energy expenditure. Paroxetine and sertraline inhibit insulin signaling in rat hepatoma cells (Levkovitz et al., 2007), suggesting potential direct effects of antidepressants on energy balance and insulin resistance. Among adults

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with type 2 diabetes, antidepressant users were more likely to have clinical and behavioral cardiovascular disease risk factors including high blood pressure or antihypertensive use, high cholesterol or lipid lowering drug use, high triglyceride or lipid lowering drug use, current smoking, and BMI >30 kg/m^2 (Rubin et al., 2010a).

Dietary weight loss and exercise interventions can reduce weight in patients with depression (Ludman et al., 2010; Pagoto et al., 2007; Richardson et al., 2005). Whether antidepressant use modifies intervention effects on weight is not well established, however. In a 24-month exercise and dietary weight loss intervention in 1632 overweight adult women, antidepressant users lost less weight vs. non-users (Linde et al., 2004). In 131 obese adults, participants with major depressive disorder lost less weight compared to those without the disorder (Pagoto et al., 2007), using the Diabetes Prevention Program (DPP) (Knowler et al., 2002). In 190 obese women with or without major depressive disorder attending a 12-month group-based caloric reduction and exercise weight loss intervention, there were no significant differences in weight loss between the two groups; those who attended ≥12 sessions reduced weight independent of depression status (Ludman et al., 2010).

Several dietary weight loss and exercise intervention studies have shown that individuals with depression have low adherence (Flegal et al., 2007; Somerset et al., 2011) and high dropout rates (Pagoto et al., 2007). Lower intervention adherence among antidepressant users may account for differences in weight loss between antidepressant users and non-users.

The primary aim of this analysis was to compare the effects of 12-month dietary weight loss and/or exercise interventions on body composition (weight, waist circumference, and percent body fat); and biomarkers of glucose metabolism (fasting glucose, insulin, and homeostasis assessment-insulin resistance [HOMA-IR]) and inflammation (high-sensitivity c-reactive protein [hs-CRP]) between overweight or obese postmenopausal women taking or not taking antidepressants. To our knowledge, no studies have tested whether antidepressant use modifies changes in biomarkers of glucose metabolism and hs-CRP, an inflammatory biomarker used to assess risk of coronary heart disease (Buckley et al., 2009). The secondary aim of this analysis was to compare adherence to the diet and exercise programs between those using and not using antidepressants.

Methods and subjects

Study design and participants

The Nutrition and Exercise for Women (NEW) study was a 12-month, randomized controlled trial conducted from 2005 to 2009 at the Fred Hutchinson Cancer Research Center (FHCRC), Seattle, WA. The study examined the individual and combined effects of 12 months of reduced calorie diet and/or exercise interventions on breast cancer biomarkers. The primary outcome was serum estrone (Campbell et al., 2012). Secondary outcomes were additional sex hormones (Campbell et al., 2012), glucose metabolism (Mason et al., 2011), body composition (Foster-Schubert et al., 2012), quality of life (Imayama et al., 2011), and complete blood count (Imayama et al., 2012). In an ancillary study we assessed the interventions' effects on inflammatory biomarkers (Imayama et al., 2012). The trial was designed to have at least 80% power for a 0.05/3 level test to detect a difference of 10% in 12-month estrone changes for 3 primary comparisons. Because of funding limitation and expected adherence and retention after half of the women completed the trial, power calculations were repeated and the recruitment goal was changed from 503 to 439. The study procedures were reviewed and approved by the FHCRC Institutional Review Board. All participants provided signed Informed Consent.

The study design, recruitment, and intervention methods have been reported elsewhere (Foster-Schubert et al., 2012). Participants were recruited from the greater Seattle area (Fig. 1). Eligibility criteria included: 50–75 years of age; BMI ≥25.0 kg/m^2 (if Asian-American ≥23.0 kg/m^2); <100 min/week of moderate activity; postmenopausal; not taking postmenopausal hormone therapy for the past 3 months; no history of breast cancer, heart disease, diabetes mellitus, or other serious medical conditions; fasting glucose <126 mg/dL; non-smoking; ≤2 alcohol drinks/day; able to attend diet/exercise sessions at the intervention site; and a normal exercise tolerance test.

Randomization and interventions

A total of 439 women were randomized to dietary weight loss with a goal of 10% weight reduction (N = 118); moderate-to-vigorous intensity aerobic exercise for 45 min/day, 5 days/week (N = 117); combined exercise and diet (N = 117); or control (N = 87). Computerized randomization was stratified by BMI (<30.0, ≥30.0 kg/m^2) and race/ethnicity (non-Hispanic white, black, other). Permuted blocks allocated a smaller number of women to the control group. The sequence was concealed until the allocation was determined. Study staff enrolled and informed participants of group assignment. Other than statisticians, all study staff involved in assessments and investigators were blinded to randomization.

The dietary weight loss intervention was based on the DPP (Knowler et al., 2002) and the Action for Health in Diabetes trial lifestyle interventions (Ryan et al., 2003) with the following goals: caloric intake of 1200–2000 kcal/day based on weight, ≤30% calories from fat, and 10% weight loss by week 24, with weight maintenance thereafter. Dietitians with training in behavior modification conducted the diet intervention. Participants had 2–4 individual sessions with a study dietitian, attended weekly group sessions (5–10 women) until week 24, and completed daily food logs for at least 6 months or until they reached their weight loss goal. Afterwards they attended monthly group sessions and had e-mail/phone contact. The diet + exercise group attended separate diet sessions from the diet-only group.

The exercise goal was 45 min/day, 5 days/week of moderate-to-vigorous intensity exercise for 12 months. Participants attended 3 supervised sessions/week at the facility and exercised 2 days/week at home. They gradually increased exercise training to 70–85% of maximal heart rate (based on baseline VO_2max treadmill test) for 45 min/session by week 7 and maintained thereafter. At each session participants wore Polar heart rate monitors (Polar Electro, New Hyde Park, NY, USA) and recorded exercise mode, duration, peak heart rate, and perceived exertion in facility and home activity logs. Activities with ≥4 METs were counted toward the prescribed exercise target (Ainsworth et al., 2000).

Exercise-only and diet-only participants were asked not to change their respective diet and exercise habits. Controls were asked not to change their diet or exercise habits. At the end of 12 months, controls were offered 4 group diet sessions and 8 weeks of supervised exercise sessions.

Measurements

Demographics, medication use, depressive symptoms, exercise and diet behaviors, cardiopulmonary fitness, pedometer counts, weight, waist circumference, and percent body fat were assessed at baseline and at 12 months. We used standardized questionnaires to collect demographic information. Participants brought current prescription and over-the-counter medication bottles to clinic visits. Participants regularly taking prescription antidepressant medications (selective serotonin reuptake inhibitors, serotonin–norepinephrine reuptake inhibitors, tricyclics, and atypical antidepressants) at baseline were classified as antidepressant users. Because of concerns about a subgroup analysis using post-randomization factors, we defined user status according to baseline data (Yusuf et al., 1991).

Depression was measured using the validated Brief Symptom Inventory-18 (Derogatis, 2001; Derogatis and Melisaratos, 1983). Type, intensity and duration of exercise over the previous 3 months were assessed (Taylor et al., 1978). We used the 120-item food frequency questionnaire (FFQ) to assess usual dietary intake, and calculated percent of caloric intake from fat (Patterson et al., 1999). Cardiopulmonary fitness was assessed using a modified branching treadmill protocol (Foster-Schubert et al., 2012; Pate et al., 1991; Schauer and Hanson, 1987). Participants wore pedometers (Accusplit, Silicon Valley, CA, USA) for 7 consecutive days from which the mean steps/day was determined. Height, weight and waist circumference were measured and BMI was calculated as kg/m^2 (Foster-Schubert et al., 2012). Body fat was measured by a dual-energy x-ray absorptiometry whole-body scanner (GE Lunar, Madison, WI, USA).

Twelve-hour fasting blood samples were collected at baseline and 12 months, with no exercise for 24 h. The intra- and inter-assay coefficients of variations (CVs) for glucose were 1.1% and 3.5%, respectively. The intra-assay CV was 4.5% for insulin. We calculated HOMA-IR =fasting insulin(mU/L) × fasting glucose(mmol/L)/22.5 (Matthews et al., 1985). The