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Effects of diet composition on weight loss, metabolic factors and biomarkers in a 1-year weight loss intervention in obese women examined by baseline insulin resistance status☆

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ABSTRACT

Background. Obesity is a risk factor for postmenopausal breast cancer incidence and premenopausal and postmenopausal breast cancer mortality, which may be explained by several metabolic and hormonal factors (sex hormones, insulin resistance, and inflammation) that are biologically related. Differential effects of dietary composition on weight loss and these metabolic factors may occur in insulin-sensitive vs. insulin-resistant obese women.

Objective. To examine the effect of diet composition on weight loss and metabolic, hormonal and inflammatory factors in overweight/obese women stratified by insulin resistance status in a 1-year weight loss intervention.

Methods and Results. Nondiabetic women who were overweight/obese (n = 245) were randomly assigned to a lower fat (20% energy), higher carbohydrate (65% energy) diet; a lower carbohydrate (45% energy), higher fat (35% energy) diet; or a walnut-rich (18% energy), higher fat (35% energy), lower carbohydrate (45% energy) diet. All groups lost weight at follow-up ($P < 0.0001$), with mean (SEM) percent loss of 9.2 (1.1)% in lower fat, 6.5 (0.9)% in lower carbohydrate, and 8.2 (1.0)% in walnut-rich groups at 12 months. The diet × time × insulin resistance status interaction was not statistically significant in the model for overall weight loss, although insulin sensitive women at 12 months lost more weight in the lower fat vs. lower carbohydrate group (7.5 kg vs. 4.3 kg, $P = 0.06$), and in the walnut-rich vs. lower carbohydrate group (8.1 kg vs. 4.3 kg, $P = 0.04$). Sex hormone binding globulin increased within each group except in the lower carbohydrate group at 12 months ($P < 0.01$). C-reactive protein and interleukin-6 decreased at follow-up in all groups ($P < 0.01$).

Conclusions. Findings provide some support for differential effects of diet composition on weight loss depending on insulin resistance status. Prescribing walnuts is associated with weight loss comparable to a standard lower fat diet in a behavioral weight loss intervention.

Abbreviations: BMI, body mass index; CRP, C-reactive protein; CV, coefficient of variation; FSH, follicle stimulating hormone; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment-insulin resistance index; IL-6, interleukin-6; LDL-C, low-density lipoprotein cholesterol; n, number; RBC, red blood cell; SHBG, sex hormone binding globulin.

☆ *Clinical Trial Registration:* NCT01424007 on http://www.clinicaltrials.gov.

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Weight loss itself may be the most critical factor for reducing the chronic inflammation associated with increased breast cancer risk and progression.

1. Introduction

Obesity is a risk factor for postmenopausal breast cancer incidence and premenopausal and postmenopausal breast cancer mortality [1–3]. Several mechanisms have been proposed to explain the adverse effect of obesity on the risk and progression of breast cancer. One possible mechanism relates to the effect of excess adiposity on circulating reproductive steroid hormones, because adipose tissue is an important extragonadal source of estrogens from precursor adrenal androgens. Endogenous circulating estrogen levels are higher in obese postmenopausal women than in women who are not overweight, and higher circulating estrogen levels are also a risk factor for breast cancer incidence and recurrence [4,5]. Further, obesity is associated with lower levels of sex hormone binding globulin (SHBG), which increases the bioavailable estrogen fraction [6].

Another possible mechanism relates to insulin and interactions between insulin and other metabolic factors associated with adiposity and weight gain [7]. Insulin and insulin-like growth factor-1 stimulate mammary cell proliferation and promote tumor development by inhibiting apoptosis in cell culture [8]. Obesity also is associated with chronic inflammation and increased cytokine production, a key causative factor in insulin resistance and hyperinsulinemia [9]. Further, insulin stimulates the synthesis of sex steroids and inhibits SHBG synthesis, so the effects of these various metabolic and hormonal factors (sex hormones, insulin resistance, and inflammation) are biologically related [10].

Optimal macronutrient distribution of weight loss diets has not been established, and successful weight loss has been shown to be achieved with either a low fat or low carbohydrate diet in the context of energy restriction [11,12]. Recent review panels and dietary guidelines recommend a range of energy intake from dietary carbohydrate and fat [13,14], with the only specific limitation targeting saturated fat (<10% of energy intake) [15]. Cancer control guidelines have historically recommended a low fat diet, but data from observational studies and clinical trials support the current conclusions that evidence linking higher fat intake with risk for breast cancer is not strongly supportive [1,2,16]. A dietary pattern that is higher in carbohydrate, especially if provided mainly from highly refined food choices, is associated with increased cardiometabolic risk factors, including hyperinsulinemia [17]. In previous short-term studies, it was observed that insulin sensitive individuals lost more weight in response to lower fat vs. lower carbohydrate intake, and individuals who were insulin resistant or secreting higher levels of insulin lost more weight in response to a lower carbohydrate vs. lower fat intake [18,19].

The source and type of dietary fatty acids also may affect metabolic and hormonal factors associated with obesity. Regular consumption of walnuts, which are rich in polyunsaturated fatty acids and bioactive food components, has been associated with a reduction in inflammatory markers in addition to improved lipid profile in observational and feeding studies [20,21]. Numerous clinical studies of nut consumption, primarily focused on the effects on cardiovascular disease risk factors and inflammatory markers, have observed minimal or no effect on body weight despite the potential additional energy intake contributed by the addition of nuts (including walnuts) to the diet [22,23]. The specific effects of nut consumption in the context of a weight loss intervention have been examined in a few previously published studies [24–28], which have tested the effects of almonds, pistachios and peanuts and have had mixed results. Also, a Mediterranean diet (which includes walnuts as one component of this dietary pattern) has been shown to promote weight loss in addition to favorable effects on lipids, fasting glucose and insulin levels [29,30].

This study was designed to examine the effect of three dietary approaches on weight loss, metabolic factors, and hormonal and inflammatory markers in overweight and obese women stratified by insulin resistance status, within a 1-year behavioral weight loss intervention. The diets compared were a lower fat, higher carbohydrate diet; a lower carbohydrate, higher fat diet; and a walnut-rich, higher fat, lower carbohydrate diet. Differential weight loss and metabolic response to variable macronutrient content of the diet is highly relevant to breast cancer given that these metabolic and hormonal factors may indeed explain the link between obesity and breast cancer risk and progression.

2. Methods

2.1. *Study Population*

The overall rationale and context of this randomized controlled trial has been published previously [10], and the plasma lipid responses at the 6-month interim follow-up time point have been previously reported [31]. As previously described [31], study participants were nondiabetic overweight and obese women. The UCSD institutional review board approved the study protocol, and all participants provided written informed consent.

Participants were randomly assigned to one of three study arms: lower fat (20% energy), higher carbohydrate (65% energy) diet; lower carbohydrate (45% energy), higher fat (35% energy) diet; or walnut-rich (18% energy), higher fat (35% energy), lower carbohydrate (45% energy) diet. The randomization used a sequence generated by the study statistician, stratified by menopausal status (older/younger than 55 years as a proxy) and insulin resistance status, which was calculated from the homeostasis model assessment — insulin resistance (HOMA-IR) index ([fasting glucose, mmol/L] × [insulin, mIU/L]/22.5) with HOMA-IR >3.0 considered indicative of insulin resistance [32]. Anthropometric measurements