

Effects of Moderate Alcohol Intake on Fasting Insulin and Glucose Concentrations and Insulin Sensitivity in Postmenopausal Women

A Randomized Controlled Trial

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MODERATE ALCOHOL INTAKE has been shown to be cardioprotective. Hyperinsulinemia and reduced insulin sensitivity are risk factors for cardiovascular disease and type 2 diabetes mellitus¹⁻⁴ and appear to be influenced by alcohol intake. Alcohol intake (1-2 drinks per day) is associated with reduced risk for type 2 diabetes, reduced fasting insulin concentration, and/or improved insulin sensitivity.⁵⁻⁹ Furthermore, menopause is associated with increased risk for cardiovascular disease,^{10,11} increased prevalence of hyperinsulinemia, and reduced insulin sensitivity.^{12,13} Therefore, we evaluated whether daily consumption of low to moderate amounts of alcohol influences insulin and glucose concentration and insulin sensitivity in postmenopausal women who consumed controlled diets.

METHODS

Postmenopausal women participated in a study conducted at the Beltsville Human Nutrition Research Center (Beltsville, Md) from 1998 through 1999 with primary objectives of evaluating the effect of daily moderate alcohol consumption on risk for cancer and cardiovascular disease.^{14,15} Eligibility criteria

Context Epidemiologic data demonstrate that moderate alcohol intake is associated with improved insulin sensitivity in nondiabetic individuals. No controlled-diet studies have addressed the effects of daily moderate alcohol consumption on fasting insulin and glucose concentrations and insulin sensitivity.

Objective To determine whether daily consumption of low to moderate amounts of alcohol influences fasting insulin and glucose concentrations and insulin sensitivity in nondiabetic postmenopausal women.

Design, Setting, and Participants Randomized controlled crossover trial of 63 healthy postmenopausal women, conducted at a clinical research center in Maryland between 1998 and 1999.

Interventions Participants were randomly assigned to consume 0, 15, or 30 g/d of alcohol for 8 weeks each as part of a controlled diet. All foods and beverages were provided during the intervention. An isocaloric beverage was provided in the 0-g/d arm. Energy intake was adjusted to maintain constant body weight.

Main Outcome Measures Fasting insulin, triglyceride, and glucose concentrations, measured at the end of each dietary period; insulin sensitivity, estimated with a published index of glucose disposal rate corrected for fat-free mass based on fasting insulin and fasting triglyceride concentrations, compared among treatments with a mixed-model analysis of variance.

Results A complete set of plasma samples was collected and analyzed for 51 women who completed all diet treatments. Consumption of 30 g/d of alcohol compared with 0 g/d reduced fasting insulin concentration by 19.2% ($P=.004$) and triglyceride concentration by 10.3% ($P=.001$), and increased insulin sensitivity by 7.2% ($P=.002$). Normal-weight, overweight, and obese individuals responded similarly. Only fasting triglyceride concentration was significantly reduced when comparing 0 and 15 g/d of alcohol (7.8%; $P=.03$), and no difference was found between consumption of 15 and 30 g/d of alcohol; however, there was a significant linear trend ($P=.001$). Fasting glucose concentrations were not different across treatments.

Conclusions Consumption of 30 g/d of alcohol (2 drinks per day) has beneficial effects on insulin and triglyceride concentrations and insulin sensitivity in nondiabetic postmenopausal women.

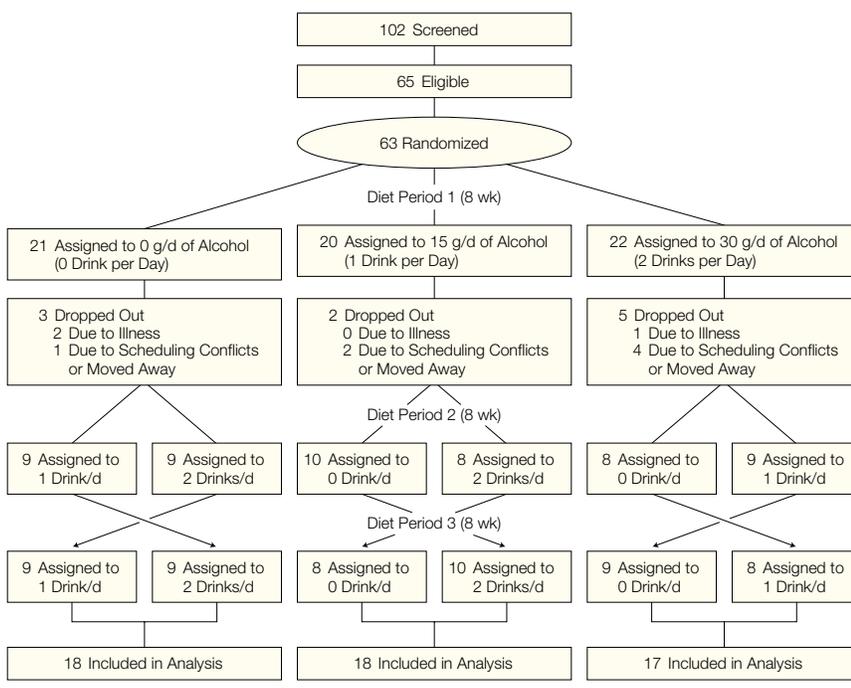
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were no history of alcoholism by the woman or her parents, at least 50 years old, postmenopausal (last menses at least 1 year earlier and follicle-stimulating hormone concentration >0.04 IU/L), not using hormone replacement therapy, 90% to 140% of ideal weight, no signs of major health problems, and not tak-

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Figure. Crossover Flow of Diet-Controlled Study

ing medications that could interfere with carbohydrate or lipid metabolism. The study was approved by the institutional review boards of the National Cancer Institute and Johns Hopkins University School of Hygiene and Public Health. All volunteers provided informed consent and received base compensation of \$3000.

A total of 63 women were randomized and initiated the study, and 53 completed the study (FIGURE). The sample size was based on the anticipated need to detect the effect of alcohol on estradiol and dehydroepiandrosterone. Women consumed either 15 g/d of alcohol (1 drink), 30 g/d of alcohol (2 drinks), or an isocaloric beverage (0 g/d alcohol) as part of a controlled diet in a randomized crossover design for 8 weeks per diet treatment. Each period was preceded by a 2- to 5-week washout period. Random allocation to treatment sequence and washout periods were used to eliminate carryover from previous treatment. All foods and beverages were prepared and supplied by the Center's Human Studies Facility. Menus were prepared to provide 54% of calories from

carbohydrates or carbohydrates and alcohol, 32% from fat, and 14% from protein. Alcohol was supplied as ethanol (Everclear, Daniel Sherman Corp, St Louis, Mo) in orange juice (340 mL). Energy from alcohol was replaced with energy from carbohydrates (Polydose, Ross Products Division, Columbus, Ohio) and soft drinks. Vitamin and mineral supplementation was not permitted. Energy intake was adjusted to maintain constant weight. Volunteers were not informed of the alcohol content of the beverages and were instructed to consume study beverages at home, at least 1 to 2 hours before bedtime, after completing tasks requiring substantial dexterity.

Blood was collected after an overnight fast on 3 separate days at the end of each dietary period. An equal volume of serum from each day was pooled for analyses. Glucose concentration was measured enzymatically (Sigma, St Louis, Mo) and insulin concentration was measured by an enzyme-linked immunosorbent assay (Diagnostic Systems Laboratories Inc, Webster, Tex). Fasting triglyceride concentration was determined enzymatically.¹⁵ Insulin

sensitivity was estimated with a recently published index (MFFM) that was developed using regression analysis to determine predictors of glucose disposal rates (M) corrected for fat-free mass (FFM) from hyperinsulinemic-euglycemic clamp test.¹⁶ This index was developed as a surrogate for the labor-intensive and time-intensive methods for assessing insulin sensitivity, the hyperinsulinemic-euglycemic clamp, and frequently sampled intravenous glucose tolerance tests. With this index, a weighted combination of log-transformed fasting insulin and triglyceride concentration is shown to predict insulin sensitivity in normoglycemic men and women.¹⁶

Statistical analyses were performed using SAS version 8.02 (SAS Institute, Cary, NC). Individuals were stratified by body mass index (BMI) according to clinically relevant cutpoints: normal weight ($n=17$, BMI <25 kg/m²), overweight ($n=21$, BMI ≥ 25 kg/m² and BMI ≤ 30 kg/m²), and obese ($n=13$, BMI >30 kg/m²). Insulin, glucose, triglyceride concentration, and MFFM were compared between treatments with a mixed analysis of variance model that included fixed terms for diet, BMI stratum, period, patient (repeated term), and a diet by BMI stratum interaction.

RESULTS

Of the 53 women who completed the study, we report data for 51 (1 woman was an outlier based on plasma triglyceride concentration and 1 woman had incomplete data). Baseline characteristics are presented in TABLE 1. Weight remained constant across treatments (overall mean [SEM], 73.6 [1.3] kg). No adverse events associated with alcohol consumption were reported.

Diet composition and intake were previously published.¹⁵ Daily caloric intake was similar with 0, 15, and 30 g/d of alcohol included in the diet (mean [SEM], 2378 [35], 2381 [38], and 2361 [38] kcal/d, respectively). Daily alcohol intake was 4.5% (range, 3.5%-5.3%) of caloric intake for 15 g/d of alcohol and 9.0% (range, 6.9%-10.6%) for 30 g/d of

alcohol. By design, total carbohydrate intake (315.1 [4.6], 281.6 [4.5], and 249.1 [4.0] g/d) was reduced with increasing alcohol intake. Energy from carbohydrates decreased from 53% with 0 g/d of alcohol to 47.3% with 15 g/d of alcohol to 42.2% with 30 g/d of alcohol with fat (energy, 32%-34%) and protein (energy, 15%) fixed.

Fasting insulin concentration was reduced by 19.2% ($P=.004$) after consumption of 30 g/d of alcohol compared with 0 g/d (TABLE 2) with no change in glucose concentration. When women consumed 30 g/d of alcohol compared with 0 g/d, there was a significant improvement of 7.2% in insulin sensitivity ($P=.002$), as estimated by MFFM. Fasting triglyceride concentrations were previously reported to be significantly reduced with alcohol consumption (7.8% [$P=.03$] after consumption of 15 g/d of alcohol and 10.3% [$P=.001$] after consumption of 30 g/d of alcohol) (Table 2).¹⁵ Fasting insulin concentration and insulin sensitivity were not significantly changed with intake of 15 g/d of alcohol compared with 0 g/d or 30 g/d of alcohol diet (Table 2). Although BMI influences fasting insulin and glucose concentrations and insulin sensitivity, there was no significant interaction between BMI stratification and treatment. Thus, the effect of alcohol on fasting insulin and triglyceride concentration and insulin sensitivity was similar with respect to magnitude and direction for all BMI strata ($P=.001$).

COMMENT

This study is the first to our knowledge to demonstrate that fasting insulin

concentration is reduced with daily moderate alcohol intake (30 g/d of alcohol or 2 drinks per day) compared with a placebo drink in postmenopausal women. Given the source of alcohol (ethanol) used and the careful control of other dietary factors, the response can be attributed to the ethanol. It is unknown if alcohol derived from other sources (eg, beverages that contain sugar) may impart the same response. We also evaluated the association between alcohol intake and fasting insulin concentration for clinically relevant strata of BMI. We found that fasting insulin concentration remained lower when consuming 30 g/d of alcohol compared with 0 g/d within each BMI stratum. Although weight gain can influence fasting insulin,¹⁷ weight was constant across diet treatments.

Alcohol consumption influences insulin sensitivity (or insulin resistance), as assessed by different methods.^{5-7,9,18,19} The MFFM index includes fasting insulin and triglyceride concentration, both independent risk factors for type 2 diabetes and cardiovascular disease.¹ Fasting triglyceride concentration was reduced by approximately

10% when comparing 30 g/d of alcohol with 0 g/d.¹⁵ Insulin sensitivity was enhanced after consumption of 30 g/d of alcohol compared with 0 g/d, independent of BMI, which confirms the findings of recent cross-sectional studies.^{7,9,18,19} These results do not support those who report that the protective effect of alcohol intake on insulin sensitivity is diminished after adjusting for differences in body composition.²⁰

No changes in insulin concentration and insulin sensitivity were found when these women consumed 15 g/d of alcohol compared with a placebo beverage. These findings are consistent with the results of Cordain et al²¹ and with epidemiologic data.²²⁻²⁴ Moreover, the relative risk for developing type 2 diabetes is significantly reduced in women who consume more than 15 g/d of alcohol (≥ 1 alcoholic drinks per day) compared with nondrinkers.⁵ The significant linear effect indicates that this study population may have been too small to detect the small changes between 0 g/d and 15 g/d of alcohol relative to the SE. Although the effect of alcohol is linear within the range of BMI for volunteers in the study cohort, it is unknown if the response

Table 1. Characteristics of Postmenopausal Women (N = 51) Prior to Controlled Diets

Characteristic	Mean (SEM)	Range
Age, y	59.5 (1.1)	49-79
Height, m	1.64 (0.09)	1.52-1.80
Weight, kg	73.4 (2.3)	41.3-116.1
Body mass index, kg/m ²	27.4 (0.8)	17.2-41.0
Fasting insulin, μ U/mL [pmol/L]	6.5 (0.8) [45.1 (5.3)]	1.9-28.7 [13.0-199.0]
Fasting triglycerides, mg/dL [mmol/L]	127.4 (8.0) [1.44 (0.09)]	54.9-314.2 [0.62-3.55]
Fasting glucose, mg/dL [mmol/L]	101.3 (1.8) [5.62 (0.10)]	78.6-138.7 [4.36-7.70]

Table 2. Fasting Serum Insulin, Triglyceride, and Glucose Concentrations and Insulin Sensitivity Index (MFFM) in 51 Postmenopausal Women*

Characteristic	Alcohol, g/d (Drink Equivalent/d)				Probability of Main Effects and Interaction			P for Trend for Alcohol
	0 (0)	15 (1)	30 (2)	SEM†	Alcohol	BMI	Alcohol \times BMI Interaction	
Insulin, μ U/mL (pmol/L)	8.3 (59.8)‡	7.1 (51.2)‡	6.7 (48.3)‡	0.8 (5.6)	.004	<.001	.22	.001
MFFM	7.63‡	7.90‡	8.18‡	0.27	.002	<.001	.33	<.001
Triglyceride, mg/dL (mmol/L)	128.4 (1.45)‡	118.7 (1.34)‡	115.1 (1.30)‡	6.2 (0.07)	.001	.11	.53	.001
Glucose, mg/dL (mmol/L)	103.1 (5.72)	102.9 (5.71)	101.6 (5.64)	1.8 (0.10)	>.99	.03	.93	.97

*MFFM indicates glucose disposal rates (M) corrected for fat-free mass (FFM); BMI, body mass index. BMI was coded as a discrete variable based on outpoints for normal weight (<25 kg/m²), overweight (≥ 25 kg/m² and ≤ 30 kg/m²), and obese (>30 kg/m²).

†SEM is the same for each of the 3 means within a row.

‡Treatment means within a row are significantly different from each other ($P<.05$).

to alcohol remains linear for women with a BMI greater than those in the study cohort.

In the present study, energy from alcohol was replaced with energy from carbohydrates (Polycose and soft drinks). Although low-fat, high-carbohydrate diets influence plasma triglyceride concentration,²⁵ there are conflicting reports on the effects of increasing dietary carbohydrates on fasting insulin concentration and insulin sensitivity.²⁶ Moreover, most study designs involving changes in dietary carbohydrates include concomitant changes in dietary fat, which also influence fasting insulin concentration and insulin sensitivity.²⁷⁻³² These studies demonstrate the complex nature of interpreting results from studies involving macronutrient manipulation. Most studies alter energy from carbohydrate by nearly 20% for comparisons between diets. In the present study, energy from carbohydrates increased from 42.2% to 53.0% when comparing the 30 g/d of alcohol diet with the 0 g/d alcohol diet. Since the difference in carbohydrate energy between treatments was well below those reported by others,³⁰⁻³² the observed insulin changes were likely related to alcohol intake and not alterations in dietary carbohydrates.

In conclusion, consumption of 30 g/d of alcohol reduced insulin concentration and improved insulin sensitivity in nondiabetic, postmenopausal women independent of BMI. The observed effects are attributed to ethanol, though other components in red wine may impart additional cardioprotective effects.³³ Elevated fasting insulin concentration is associated with increased insulin resistance,⁴ which is a shared pathology in the degenerative diseases, type 2 diabetes and cardiovascular disease.³⁴ The observed changes with alcohol intake may reduce the risk of developing type 2 diabetes and cardiovascular disease in this population of women. In addition to these potentially beneficial changes in insulin sensitivity, an improved lipid profile is reported in this cohort of women while consuming 2 drinks per day compared with the placebo treatment. How-

ever, in contrast to these potentially beneficial findings, alcohol intake (1-2 drinks per day) in this cohort significantly increased serum levels of dehydroepiandrosterone sulfate and estrone sulfate compared with the placebo.¹⁴ These steroid hormones are risk factors for breast cancer.³⁵ While the magnitude of the effect of alcohol on risk for cardiovascular disease in this group of women can be estimated,¹⁵ it is more difficult to assess the relative effect on risk for breast cancer or diabetes. These data might prove helpful when counseling women on alcohol consumption.

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