

Influence of Moderate Chronic Wine Consumption on Insulin Sensitivity and Other Correlates of Syndrome X in Moderately Obese Women

Loren Cordain, Christopher L. Melby, Amy E. Hamamoto, D. Sean O'Neill, Marc-Andre Cornier, Hisham A. Barakat, Richard G. Israel, and James O. Hill

Epidemiologic studies indicate that alcohol consumption is associated with improved insulin sensitivity; however, scant experimental evidence confirms this observation. To determine the effects of regular moderate wine consumption on insulin sensitivity, 20 overweight women (body mass index [BMI], 29.8 ± 2.2 kg/m²) participated in a 20-week free-living randomized crossover trial. The subjects, serving as their own controls, consumed wine (190 mL red wine, 13% vol/vol ethanol, 5 days per week) for 10 weeks and abstained for 10 weeks or vice versa. The dependent variables (body weight, BMI, percent body fat, blood pressure, fasting blood glucose and insulin, blood lipids, dietary intake, and insulin sensitivity by intravenous glucose tolerance test [IVGTT]) were measured at the pretest, at the 10-week crossover, and at the 20-week completion of the study. Data were analyzed at the pretest and at completion of the wine drinking and abstinence periods of the study using ANOVA by order of treatment. Fasting glucose remained unchanged (mean \pm SD; $P > .05$) throughout the experiment (pretest, drinking, and abstinence, 91.1 ± 9.2 , 91.6 ± 9.1 , and 88.5 ± 11.2 mg/dL), as did the measures of insulin sensitivity, fasting insulin (pretest, drinking, and abstinence, 8.6 ± 3.3 , 8.6 ± 4.1 , and 9.1 ± 4.7 μ U/mg) and the insulin sensitivity index (3.60 ± 2.96 , 3.25 ± 2.17 , and 3.30 ± 1.84). Body composition and blood lipids also remained unchanged ($P > .05$) during treatment. Moderate wine consumption at this dose in overweight women did not improve or impair insulin sensitivity, nor did it change any of the known correlates of insulin sensitivity, including body weight and composition, blood lipids, and blood pressure.

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THE FAILURE OF SPECIFIC tissues in the body to respond appropriately to insulin (ie, insulin resistance) is at the root of several of the most common and deadly chronic diseases in the United States. Hypertension, type 2 diabetes, dyslipidemia, coronary artery disease (CAD), and obesity are all linked to insulin resistance and have collectively been termed syndrome X.^{1,2} Because insulin resistance is such a common phenomenon (affecting at least 25% of the population), it has been suggested that the various facets of syndrome X are involved to a substantial degree in the cause and clinical course of the major diseases of Western civilization.²

Regular moderate wine and alcohol consumption has been increasingly shown to favorably influence several health factors associated with syndrome X. The link between moderate wine and alcohol consumption and reduced mortality from CAD is well established³⁻⁶ and has been shown to be causal in nature.⁷ Moderate wine and alcohol consumption has been demonstrated to increase serum high-density lipoprotein (HDL) concentrations and thereby improve some aspects of the blood lipid profile.⁸ Although excessive alcohol consumption increases blood pressure, moderate wine and alcohol consumption appears either to have no effect or to reduce blood pressure.⁹ Recent data from our laboratory,¹⁰ as well as numerous epidemiologic studies reviewed previously,^{11,12} have shown that moderate wine and alcohol consumption does not increase metabolic risk factors for obesity, but may in fact be inversely related to the development of obesity. Consequently, moderate alcohol consumption may positively influence not only obesity but also most other disease factors associated with syndrome X. To date, this connection between moderate alcohol consumption and syndrome X has not been linked in the scientific literature, nor have attempts been made to determine an underlying mechanism. It is possible that moderate alcohol consumption modulates disease factors associated with syndrome X via its influence on insulin metabolism, which in turn influences all facets of syndrome X.

A number of recent observational reports have shown that moderate alcohol consumption is associated with enhanced

insulin sensitivity¹³⁻¹⁷ and that moderate drinkers (5 to 10 drinks per week) have a lower risk for type 2 diabetes than either abstainers or heavy drinkers.¹⁸ To date, no experimental studies have examined the effect of chronic moderate alcohol intake (specifically wine) on insulin sensitivity. Consequently, the aim of the present study was to determine prospectively whether moderate red wine consumption influences insulin sensitivity in moderately obese women over a 10-week treatment period.

SUBJECTS AND METHODS

Subjects

Twenty sedentary and overweight middle-aged premenopausal women were recruited for this study, which was approved by the Human Research Committee at Colorado State University and the Colorado Multiple Institution Review Board. Potential subjects completed an initial health-screening questionnaire to determine eligibility for participation, with enrollment criteria as follows: age 30 to 50 years, body mass index ([BMI] weight/height²) within the overweight and moderately obese range of 27 to 33 kg/m², occasional alcoholic beverage consumption (between 2 standard drinks per month and 2 drinks per week), and willingness to consume 2 standard servings of red wine per day 5 days per week, for a total of 10 consecutive weeks.

From the Departments of Health and Exercise Science; and Food Science and Human Nutrition, Colorado State University, Fort Collins, CO; East Carolina University School of Medicine, Greenville, NC; and the Center for Nutrition, University of Colorado Health Sciences Center, Denver, CO.

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Address reprint requests to Loren Cordain, PhD, Department of Health and Exercise Science, Colorado State University, Fort Collins, CO 80523.

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Potential subjects were excluded if they exhibited any of the following: health problems that can influence normal food intake and normal physical activity; use of any medications (including oral contraceptives) that can influence metabolism, appetite, or plasma lipids, glucose, and insulin; history of alcohol abuse or misuse; current alcohol intake greater than 2 standard servings per week; total avoidance of alcoholic beverages; use of supplemental omega-3 fatty acids; and participation in formal exercise more than 2 times per week.

Experimental Design

The 20 subjects participated in a 20-week free-living study using a crossover design in which they either drank wine for the first 10 weeks and then abstained for the next 10 weeks or vice versa. During the treatment arm of the study, subjects consumed two 135-mL servings of red wine (13% vol/vol ethanol) 5 days per week (average daily intake over 10 weeks, 190 mL wine). On the control arm of the study, subjects were asked to refrain from any alcohol use.

Subjects underwent a battery of measurements at 3 different times: (1) prior to commencement of the first 10-week period of the study, (2) immediately following the first 10-week period prior to the crossover, and (3) at the end of 20 weeks. Measurements at each period included body weight, body composition via hydrostatic weighing and skinfold assessment, dietary assessment by 4-day records, physical activity assessment by recall, resting blood pressure, venous blood sampling for determination of fasting glucose, insulin, and blood lipids, and a frequently sampled intravenous glucose tolerance test (IVGTT) to determine insulin sensitivity.

Body Weight and Composition

Body weight was measured to the nearest 0.1 kg using a calibrated electronic scale, with the subjects wearing shorts and a lightweight shirt but no shoes for all 3 weight measurements over the 20-week period. Height without shoes was measured to the nearest 0.1 cm using a vertical stadiometer. The BMI was calculated as weight in kilograms divided by height in meters squared. The percent body fat was estimated using the Siri equation¹⁹ from body density by underwater weighing. Residual lung volume was determined by the oxygen dilution method.²⁰ Skinfold thickness at the following 8 sites was measured using skinfold calipers (Lange, Cambridge, MA): midhigh, abdomen, subscapular, suprailiac, pectoral, calf, biceps, and triceps. From the skinfold measures, body density was determined using procedures described by Jackson et al²¹ and percent body fat was calculated as recommended by Lohman.²²

Dietary Assessment

At each of the 3 measurement points, dietary data were collected for each subject using 4-day records including 2 weekdays and 2 weekend days. Subjects were asked to keep meticulous records of everything eaten or consumed, with special attention devoted to accurate recording of the serving size of the foods ingested. For mixed dishes such as salads and casseroles, the subjects were asked to identify each of the ingredients along with the amount consumed. The food records were analyzed for total daily energy and macronutrient composition using the software program from Nutritionist IV (N² Computing, Salem, OR) that uses the nutrient data bases established by the US Department of Agriculture.

Blood Pressure

Three seated blood pressure measurements were taken for each subject using a standard mercury sphygmomanometer (PyMah, Flemington, NJ). The subjects sat quietly in a comfortable chair for 10 minutes, at which time 3 blood pressure measurements were taken separated by a 2-minute interval between readings. Special care was taken to use the appropriate cuff size so that the bladder width was at least 40% of the

arm circumference and the length of the bladder was at least 80% of the arm circumference. Air was bled from the bladder at a rate of 2 to 3 mm Hg per second, except in circumstances of bradycardia, where the rate of cuff deflation was 3 mm Hg per heart beat. The first and fifth Korotkoff sounds were used to determine systolic and diastolic pressure, respectively.

Blood Lipids and Lipoprotein Profiling

Fasting venous blood samples (5 mL) were obtained from an antecubital vein of the forearm between 6 and 8 AM with the subjects having refrained from any consumption of food and caffeine-containing beverages for 12 hours. Because of the possible influence of the menstrual cycle phase on insulin metabolism, all blood samples were drawn during the follicular phase of the menstrual cycle. Blood was obtained in vacutainer tubes and centrifuged (3,000 rpm) for 15 minutes, and the plasma was transferred to capped vials and stored at -80°C . The plasma was then analyzed in duplicate for total cholesterol, total triglycerides, and HDL-C by colorimetric assays. Subclasses of HDL-C, low-density lipoprotein cholesterol (LDL-C), and very-low-density lipoprotein-triglyceride (VLDL-TG), average lipoprotein particle size, and lipoprotein particle number were determined by nuclear magnetic resonance spectroscopy.²³

Insulin Sensitivity

Insulin sensitivity was estimated using the frequently sampled, insulin-augmented IVGTT. IVGTTs were performed at the General Clinical Research Center at the University of Colorado Health Sciences Center following an overnight fast in each subject. Each test was performed during the follicular phase of the subject's menstrual cycle. The procedure involves an initial placement of catheters in each arm. From the blood collection catheter, 4 baseline samples (time -10 , -5 , -2 , and -1 minutes) were obtained for determination of fasting glucose and insulin, followed by a single bolus of glucose infused at time 0 minutes (0.3 g/kg body weight) over a 90-second interval. Blood samples were obtained at 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, and 19 minutes following the glucose infusion. Insulin was then infused at 20 minutes (0.03 U/kg body weight) with blood sampling for measurement of glucose and insulin at 22, 23, 24, 25, 27, 30, 40, 50, 60, 70, 90, 100, 120, 140, 160, and 180 minutes after the glucose infusion. Glucose was analyzed with a YSI glucose analyzer (Yellow Springs Instruments, Yellow Springs, OH) and insulin was measured by radioimmunoassay.²⁴ Insulin sensitivity was estimated using Bergman's minimal model.²⁵

Statistical Analysis

The data were analyzed using the Statistical Analysis System (SAS Institute, Cary, NC). Descriptive statistics were initially computed. The endpoints of body weight, body composition, energy and macronutrient intake, blood pressure, blood lipids, insulin, glucose, and insulin sensitivity were analyzed by repeated-measures ANOVA with Tukey's post hoc tests to determine treatment differences. A *P* level less than .05 indicated statistical significance.

RESULTS

Table 1 shows the physical characteristics of the subjects. The study sample was composed of overweight and obese middle-aged women with normal blood pressure. The results of the repeated-measures ANOVA showed no significant time \times treatment interaction for any of these subject characteristics, indicating that the addition of 190 mL red wine per day over a 10-week period had no effect on blood pressure, body weight, or body composition as determined by both hydrostatic weighing and multisite skinfold measurements.

The estimated mean dietary intake of specific macronutrients

Table 1. Physical Characteristics of Study Subjects (N = 20) at Baseline, Following 10 Weeks of Wine Consumption, and Following Abstinence (mean \pm SD)

Variable	Baseline	Wine	Abstinence
Body weight (kg)	78.6 \pm 7.0	77.7 \pm 6.6	78.3 \pm 6.2
BMI (kg/m ²)	29.8 \pm 2.2	29.8 \pm 2.2	29.8 \pm 2.1
Systolic blood pressure (mm Hg)	115 \pm 7	116 \pm 5	116 \pm 3
Diastolic blood pressure (mm Hg)	80 \pm 5	77 \pm 5	79 \pm 5
Sum of skinfold thickness (mm)	280 \pm 34	276 \pm 30	281 \pm 30
Body fat (%)			
Skinfold measurements	39.9 \pm 4.1	37.4 \pm 4.5	38.5 \pm 3.8
Hydrostatic weighing	34.7 \pm 6.7	35.7 \pm 5.0	35.1 \pm 4.2

NOTE. None of the values were significantly different at $P < .05$.

and micronutrients (alcohol excluded) at baseline during 10 weeks of wine consumption, and during 10 weeks of alcohol abstinence are provided in Table 2. The women ingested approximately 55% of energy from carbohydrate, 15% from protein, and 30% from fat. There were no treatment differences in energy intake or any of the macronutrients and micronutrients. The addition of 190 mL/d red wine during the 10 weeks of

Table 2. Mean Daily Nutrient Intake Determined From Four-Day Dietary Records at Baseline and During Wine Consumption and Abstinence (mean \pm SD)

Variable	Baseline	Wine	Abstinence
Energy (kcal)	1,760 \pm 308	1,743 \pm 303	1,746 \pm 474
Carbohydrate			
g	241.2 \pm 59.6	226.4 \pm 50.1	232.4 \pm 63.5
% energy	55.0 \pm 6.9	52.1 \pm 7.7	53.3 \pm 4.4
Protein			
g	68.4 \pm 15.9	66.0 \pm 18.5	66.2 \pm 16.8
% energy	15.5 \pm 2.1	15.2 \pm 3.5	15.2 \pm 1.8
Fat			
g	59.3 \pm 12.6	58.8 \pm 15.6	63.3 \pm 18.4
% energy	30.4 \pm 6.4	30.1 \pm 5.9	32.6 \pm 2.9
Saturated fat			
g	20.6 \pm 5.8	20.3 \pm 7.5	20.5 \pm 8.4
% energy	10.2 \pm 2.0	10.3 \pm 3.4	10.4 \pm 1.4
Polyunsaturated fat			
g	9.8 \pm 3.8	9.4 \pm 3.7	11.1 \pm 3.7
% energy	5.2 \pm 2.2	4.8 \pm 1.3	5.7 \pm 1.5
Monounsaturated fat			
g	18.4 \pm 4.3	17.2 \pm 4.8	20.3 \pm 6.3
% energy	9.5 \pm 2.2	8.9 \pm 1.8	10.5 \pm 1.6
Cholesterol (mg)	207 \pm 107	225 \pm 132	221 \pm 159
Fiber (g)	13.4 \pm 5.2	11.3 \pm 3.4	10.2 \pm 3.9
Chromium (mg)	0.045 \pm 0.030	0.031 \pm 0.020	0.035 \pm 0.035

NOTE. None of the values were significantly different at $P < .05$. During the wine period of the trial, the mean daily wine intake was 190 mL (158 kcal).

wine consumption contributed approximately 130 additional kcal/d as alcohol, which corresponds to 6% to 7% of the subject's total energy intake during this period.

Fasting plasma glucose and insulin, and insulin sensitivity values at baseline and following both 10 weeks of wine consumption and 10 weeks of abstinence are shown in Table 3. Glucose and insulin concentrations were in the normal range for all subjects and did not change from baseline on either the wine consumption or alcohol abstinence periods of the study. There were also no changes from baseline on either arm of the experiment for insulin sensitivity and the acute insulin response to glucose, indicating no effect of chronic wine consumption on either insulin sensitivity or the magnitude of insulin release in response to infused glucose.

The mean plasma lipid concentrations including subpopulations of LDL-C, HDL-C, and VLDL-TG (Table 4) were well within the normal range for these women and did not change significantly from baseline on either the wine or abstinence period of the study. Also, there were no changes from baseline for either the wine or abstinence treatments for LDL, HDL, and VLDL particle number or mean particle size. These data indicate that regular, moderate wine consumption over the 10-week treatment period did not significantly affect the blood lipid profile in any way in these overweight women.

DISCUSSION

The primary finding of the present study is that chronic, moderate red wine consumption with the evening meal neither improved nor worsened insulin sensitivity. This evidence is in contrast to the acute effects of moderate alcohol consumption. In healthy people, there is abundant experimental information showing that acute alcohol consumption augments insulin release, leading to a transient hyperinsulinemia²⁶⁻²⁹ that in turn may cause an accelerated clearance of glucose from the bloodstream.^{26,30-33} However, epidemiologic evidence suggests that this series of metabolic events does not necessarily lead to chronic hyperinsulinemia and insulin resistance, but rather the opposite, particularly with moderate alcohol consumption. Recent observational studies show that alcohol consumption is associated with better insulin sensitivity¹³⁻¹⁷ and a reduced risk of type 2 diabetes.^{18,34-36} Hence, it seems likely that the acute

Table 3. Fasting Plasma Glucose and Insulin and Insulin Sensitivity Values at Baseline and Following 10 Weeks of Wine Consumption and 10 Weeks of Abstinence (mean \pm SD)

Variable	Baseline	Wine	Abstinence
Fasting glucose (mg/dL)	91.1 \pm 9.2	91.6 \pm 9.1	88.5 \pm 11.2
Fasting insulin (μ U/mL)	8.6 \pm 3.3	8.6 \pm 4.1	9.1 \pm 4.7
Insulin sensitivity index ($\times 10^4$ μ U/mL \cdot min)	3.60 \pm 2.96	3.25 \pm 2.17	3.30 \pm 1.84
Acute insulin response to glucose (pmol/mL \cdot min)	549 \pm 273	506 \pm 374	507 \pm 293

NOTE. None of the values were significantly different at $P < .05$.

Table 4. Blood Lipid and Lipoprotein Data at Baseline and Following 10 Weeks of Wine Consumption and 10 Weeks of Abstinence (mean \pm SD, n = 17)

Variable	Baseline	Wine	Abstinence
Total cholesterol (mg/dL)	179.3 \pm 39.2	177.1 \pm 48.1	170.3 \pm 33.9
Total triglycerides (mg/dL)	110.5 \pm 57.7	106.1 \pm 37.4	101.2 \pm 36.6
VLDL-TG (mg/dL)	75.2 \pm 56.4	71.4 \pm 35.7	68.1 \pm 36.9
VLDL ₆	7.3 \pm 14.5	5.0 \pm 3.7	2.7 \pm 2.6
VLDL ₅	18.6 \pm 25.6	18.0 \pm 14.4	14.4 \pm 15.1
VLDL ₄	22.3 \pm 14.7	21.6 \pm 12.4	24.9 \pm 14.7
VLDL ₃	12.2 \pm 9.4	14.0 \pm 10.6	11.6 \pm 11.9
VLDL ₂	12.3 \pm 8.6	10.8 \pm 7.0	13.1 \pm 8.4
VLDL ₁	2.5 \pm 2.6	2.1 \pm 1.8	1.5 \pm 1.6
VLDL size	49.2 \pm 7.6	51.0 \pm 5.0	46.6 \pm 5.4
LDL-C (mg/dL)	122.1 \pm 35.7	119.6 \pm 46.8	115.0 \pm 35.9
LDL ₃	62.0 \pm 25.0	57.6 \pm 23.7	56.5 \pm 25.2
LDL ₂	30.0 \pm 18.4	32.6 \pm 35.3	29.4 \pm 24.4
LDL ₁	26.8 \pm 21.3	26.8 \pm 20.7	25.8 \pm 18.6
LDL size	20.8 \pm 0.5	20.7 \pm 0.4	20.8 \pm 0.5
LDL (nmol/L)	1,351 \pm 433	1,335 \pm 568	1,280 \pm 432
IDL-C (mg/dL)	3.3 \pm 5.6	2.5 \pm 2.7	3.4 \pm 3.5
HDL-C (mg/dL)	44.3 \pm 12.6	45.2 \pm 11.9	43.4 \pm 8.8
HDL ₅	6.9 \pm 4.0	7.4 \pm 4.3	7.2 \pm 4.3
HDL ₄	11.8 \pm 11.3	10.2 \pm 10.7	10.0 \pm 9.1
HDL ₃	9.9 \pm 4.6	11.2 \pm 4.7	10.3 \pm 3.6
HDL ₂	6.5 \pm 6.3	7.4 \pm 5.9	7.6 \pm 5.2
HDL ₁	9.3 \pm 7.1	9.0 \pm 8.4	8.4 \pm 6.7
HDL size	9.0 \pm 0.4	9.0 \pm 0.5	9.0 \pm 0.4
Chylomicrons (mg/dL)	0.7 \pm 0.9	0.7 \pm 0.8	0.3 \pm 0.5

NOTE. None of the values were significantly different at $P < .05$.

and chronic consequences of moderate alcohol consumption have a dissimilar influence on insulin metabolism. The transient insulin resistance caused by acute alcohol consumption may ultimately lead either to no change in long-term insulin sensitivity, as our results indicate, or to an enhanced long-term insulin sensitivity as the epidemiologic evidence suggests.

Although the explanation for the higher insulin sensitivity in moderate drinkers in a number of cross-sectional studies¹³⁻¹⁷ is unknown, it is possible that regular low doses of alcohol act in a manner similar to the hypoglycemic sulfonylurea medications used in the treatment of type 2 diabetes. These agents function by stimulating insulin secretion leading to hypoglycemia and by augmenting the effect of insulin.³⁷ Alcohol is known to act in a comparable fashion.³⁸ In support of this view are epidemiologic reports showing that moderate alcohol consumption reduces the risk of type 2 diabetes.^{18,34-36}

In the present study, moderate red wine drinking (190 mL) with the evening meal did not improve insulin sensitivity or any of the other physiologic indices (BMI, percent body fat, blood pressure, and blood lipids) associated with syndrome X. It is possible that a threshold dose exists for moderate alcohol consumption below which the therapeutic effects may not be apparent. The daily alcohol dose in the present study (approximately 19 g) amounted to 6% to 7% of the total energy intake during the wine arm of the trial. Although no other experimental

human studies exist with which we may directly compare our results, in animal studies chronic alcohol consumption has been shown to beneficially influence insulin sensitivity at higher doses than were used in the present study.^{39,40}

It is possible that there was an interaction between the alcohol dose we used and the body composition of our subjects that could have masked the potential beneficial changes in insulin sensitivity. In contrast to normal-weight individuals, obese subjects exhibit a lesser tendency for hypoglycemia following acute alcohol ingestion,⁴¹⁻⁴³ and moderate alcohol intake does not augment insulin sensitivity or produce a transient hyperinsulinemia in type 2 diabetics.^{42,43} These data suggest the possibility that metabolic responses to alcohol differ between obese and lean subjects. Our subjects not only were obese (BMI, 29.8 kg/m²; body fat, 35%) but also had low insulin sensitivity values, and consequently, the moderate alcohol dose (19 g) they ingested may not have caused either transient hyperinsulinemia or hypoglycemia, which may serve as the acute metabolic events required to enhance chronic insulin sensitivity in a manner similar to sulfonylureas.

Interestingly, regular wine consumption over a 10-week period had no effect on the plasma lipid profile of our subjects. Given the well-known positive relationship between alcohol intake and plasma HDL-C concentrations, one might question the compliance of our subjects during the wine consumption phase of the study. However, each subject was queried every 2 weeks when she received her new supply of wine, and all subjects indicated compliance with the wine consumption protocol. Given that compliance by the subjects appeared to be high, why would wine consumption not favorably affect HDL-C concentrations? In a fashion similar to that described for insulin sensitivity, some data suggest that excess body fat may negate the beneficial effect of alcohol consumption on HDL-C concentrations. Fricker et al,⁴⁴ in a study of over 600 women, noted alcohol intake to be positively associated with HDL-C in normal-weight women, but not in obese women. Support for this phenomenon can be found in men as well. Hagiage et al⁴⁵ found that consumption of 30 g alcohol (wine) daily over 14 days increased HDL₂, apoproteins AI and AII, and cholesterol ester transfer activity in normal-weight men (BMI, 22 kg/m²) but had no effect on these variables in obese men (BMI, 30 kg/m²). How the level of adiposity interacts with alcohol consumption to modify its effect on HDL-C is presently unclear. While wine consumption had no obvious favorable influence on the lipid profile, note that the subjects did not exhibit an alcohol-induced increase in plasma triglyceride concentrations, a clinically relevant issue. The interaction of body composition with alcohol intake on lipoprotein metabolism and on glucose/insulin metabolism reflects the obvious complexity of this issue.

Although we did not measure the phenolic content of the red wine used in this study or the LDL oxidizability, numerous reports have demonstrated that certain flavonoid components of red wine are powerful antioxidants that reduce LDL susceptibility to oxidation and also improve endothelium-dependent vasodilation, thereby reducing the risk for CAD.⁴⁶⁻⁴⁸ A recent report has suggested that nonalcoholic compounds in wine such as tannic acid may lead to slight decreases in blood glucose.⁴³ It

is therefore possible that certain phenolic compounds in red wine may influence glucose and insulin metabolism independently of an ethanol effect.

In conclusion, our data support the notion that moderate alcohol consumption with the evening meal has no beneficial

effect on insulin sensitivity or any of its known correlates including body composition, plasma lipids, and blood pressure in obese women. On the other hand, this study also indicates the lack of any deleterious effects on long-term insulin metabolism and glycemic control in this population.

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