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Metabolic effects of alcohol in the form of wine in persons with type 2 diabetes mellitus

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Abstract

Moderate alcohol consumption is associated with reduced cardiovascular disease rates in nondiabetic populations. However, the effects of alcohol in people with diabetes are not well defined. Accordingly, we tested the hypothesis that alcohol would raise plasma high-density lipoprotein (HDL) cholesterol or have other beneficial metabolic effects in persons with type 2 diabetes mellitus. To assess the acute effects of alcohol on plasma glucose and serum insulin, subjects were inpatients for 2 days during which they received, in random order, 240 mL wine or grape juice with their evening meal. To assess the chronic effects of alcohol on fasting plasma lipids, subjects consumed, in random order, 120 to 240 mL wine daily for 30 days and abstained from alcohol for 30 days. Participants were 18 non–insulin-treated volunteers with type 2 diabetes mellitus. Acutely, 240 mL wine containing 24 g alcohol had no effect on plasma glucose or serum insulin. Chronically, wine consumption for 30 days (mean consumption, 18 g alcohol per day) compared with abstinence for 30 days resulted, respectively, in mean ± SEM fasting plasma cholesterol of 160 ± 6 and 160 ± 8 mg/dL ($P = .98$), HDL cholesterol of 47 ± 3 and 46 ± 3 mg/dL ($P = .87$), low-density lipoprotein cholesterol of 82 ± 5 and 82 ± 6 mg/dL ($P = .98$), triglycerides of 157 ± 19 and 159 ± 19 mg/dL ($P = .88$), glucose of 128 ± 6 and 128 ± 7 mg/dL ($P = .84$), and serum insulin of 14 ± 2 and 17 ± 3 μU/mL ($P = .03$). Moderate consumption of alcohol in the form of wine did not raise plasma HDL cholesterol. However, alcohol did not have any harmful metabolic effect; and chronic consumption lowered fasting serum insulin. People with type 2 diabetes mellitus should not be discouraged from using alcohol in moderation.

1. Introduction

It is clear that some people should not consume alcohol. People who should abstain from alcohol include those with uncontrolled hypertension, hypertriglyceridemia, heart failure, liver disease, pancreatitis, porphyria, or a strong family history of alcoholism; those who are pregnant; and, of course, those who are not of legal age [1]. For other people, the use of alcohol in moderation may not be harmful and may even confer health benefits. In both men and women, moderate alcohol consumption was associated with reduced mortality rates [2-4]. Among male health care professionals, moderate use of alcohol was associated with reduced risk for angina pectoris [5], myocardial infarction [5,6], and stroke [7]. In both men and women, moderate use of alcohol was associated with protection against congestive heart failure [8]. The inverse association between alcohol consumption and cardiovascular disease was strongest in men with high plasma low-density lipoprotein (LDL) cholesterol levels [9]. Offsetting, to some extent, the potential beneficial effect of alcohol for women is an association between moderate alcohol consumption and increased risk of breast cancer [10]. However, despite the association with breast cancer, moderate alcohol consumption was associated with an overall reduction in mortality in women [4].

The association of alcohol with reduced health risks was not dependent on the type of alcohol-containing beverage consumed or whether the alcohol-containing beverages were consumed with meals [6]. A meta-analysis found evidence that all alcohol-containing drinks (wine, beer, and spirits) were associated with a lower risk of coronary heart disease

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and concluded that any benefit was associated with alcohol itself and not with the other components of alcohol-containing beverages [11]. If alcohol does reduce cardiovascular risk, the reduced risk may be mediated by raised high-density lipoprotein (HDL) cholesterol levels [1]. However, other potential beneficial mechanisms have been proposed including anti-inflammatory and antithrombotic effects [1].

Alcohol also appears to have effects on carbohydrate metabolism. In both men and women, moderate alcohol consumption was associated with protection against development of type 2 diabetes mellitus [12-14]. In a randomized crossover trial in postmenopausal women, moderate alcohol consumption was associated with reduced fasting insulin and triglyceride concentrations and increased insulin sensitivity [15]. The effects of alcohol in patients with diabetes have not been clearly defined. Moderate intake of alcohol by diabetic subjects does not acutely aggravate glycemia and may produce a modest decrease in plasma glucose [16]. In patients with type 1 diabetes mellitus, excess alcohol may induce severe hypoglycemia [17]. However, the effects on glycemia and lipemia of chronic consumption of alcohol by people with diabetes have not been reported. To address these issues, we studied both the acute and chronic effects of moderate alcohol intake by patients with type 2 diabetes mellitus. The hypotheses to be tested were (1) the use of alcohol in the form of wine with the evening meal would lower plasma glucose during the night and result in lower fasting plasma glucose the next morning and (2) the chronic use of alcohol in the form of wine would raise plasma HDL cholesterol.

2. Methods

2.1. Subjects

Eighteen subjects were recruited from the University of Minnesota outpatient clinics and from the community. Eligibility criteria were diagnosis of type 2 diabetes mellitus, age at least 40 years, hemoglobin A_{1c} (HbA_{1c}) <8.5%, constant dose(s) of oral diabetes medications (if any) and lipid-lowering medications (if any) for at least 1 month, and alanine aminotransferase and aspartate aminotransferase less than 2 times the upper limit of normal. Exclusionary criteria were history of alcoholism or alcohol abuse, use of insulin in the previous 6 months, blood pressure >150/90 mm Hg, fasting plasma triglycerides >400 mg/dL, heart failure, active liver disease, history of pancreatitis, history of porphyria, pregnancy or plans to become pregnant, and serum creatinine >1.8 mg/dL.

2.2. Methods

To study the acute effects of alcohol, subjects were admitted to the General Clinical Research Center (GCRC) at the University of Minnesota for a 2-day inpatient stay. At 5:00 PM on study day 1, blood samples were obtained for measurement of plasma glucose and serum insulin. Dinner providing 825 kcal (34% carbohydrate, 21% protein, and 45% fat) was served at 5:30 PM with, added to the meal, 240 mL of white wine or 240 mL of white grape juice. No bedtime snack was provided. Additional blood samples were obtained for plasma glucose and serum insulin every 2 hours until 7:00 the next morning (8 samples total). Research procedures resumed at 5:00 PM on study day 2 and were identical to procedures on day 1 except for the beverage served with dinner (white wine or white grape juice). The dinner on day 2 was otherwise identical to the dinner served on day 1. Treatment order was randomly assigned in a balanced way.

To study the chronic effects of alcohol, subjects consumed at least 120 but not more than 240 mL of wine daily for 1 month and abstained from all alcohol for 1 month. Wine was consumed with dinner or between dinner and bedtime. After 1 month (28-32 days), subjects reported to the GCRC in the morning after a fast of 10 to 12 hours. Subjects were weighed, and blood pressure was obtained twice in a seated position. Fasting blood samples were obtained for plasma lipids, plasma glucose, serum insulin, HbA_{1c}, serum C-reactive protein, and plasminogen. Subsequently, subjects originally assigned to wine were switched to abstinence; and those originally assigned to abstinence were switched to wine. After another month (28-32 days), subjects again reported to the GCRC in the morning after a fast of 10 to 12 hours; and outcome measures were obtained in the same way as before. Treatment order was randomly assigned in a balanced way. A selection of white and red wines was provided to subjects free of charge. Subjects kept diaries during both treatment periods to record daily wine consumption, consumption of other alcohol-containing beverages, and episodes of symptomatic hypoglycemia. The diaries were used to assess compliance, quantitate alcohol consumption, and determine the frequency of hypoglycemia. Subjects who completed the study received a stipend of $500. The research protocol was approved by the University of Minnesota Institutional Review Board. Informed written consent was obtained from all subjects.

All laboratory tests were performed in the University of Minnesota Hospital clinical laboratory. Plasma glucose was measured by glucose oxidase colorimetric reflectance spectrophotometry with an Ortho Clinical Diagnostics Vitros 950 Analyzer. Serum insulin was measured by chemiluminescent immunoassay with a DPC Immulite 2000 Analyzer. Blood HbA_{1c} was measured by automated high-performance liquid chromatography with a Tosoh A1c 2.2 Plus Glycohemoglobin Analyzer. Plasma cholesterol was measured by colorimetric reflectance spectrophotometry, plasma HDL cholesterol by colorimetric reflectance spectrophotometry after precipitation of non-HDL cholesterol with phosphotungstic acid and magnesium chloride, and plasma triglycerides by colorimetric reflectance spectrophotometry, all with an Ortho Clinical Diagnostics Vitros 950 Analyzer. Serum C-reactive protein was measured by immunorate reflectance spectrophotometry with a high-sensitivity Beckman Immage

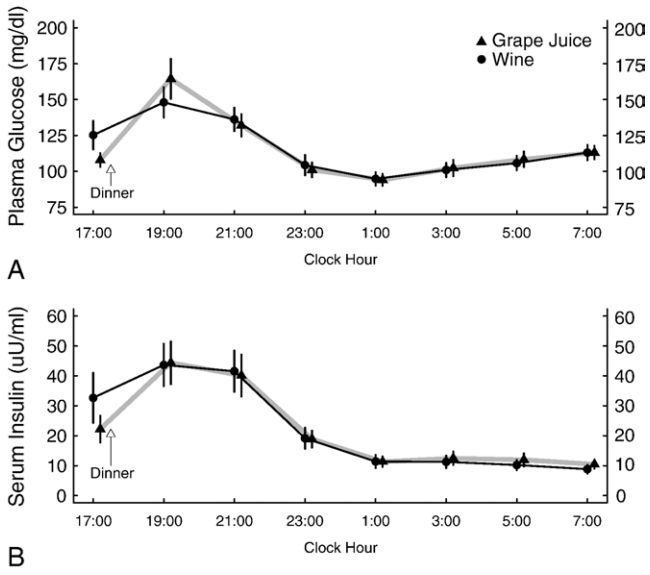

Fig. 1. Mean ± SEM plasma glucose (A) and serum insulin (B) values before and after consumption of grape juice or wine with dinner. To convert glucose to millimoles per liter, multiply by 0.05551; to convert insulin to picomoles per liter, multiply by 6.0.

800 Immunochemistry System. Blood plasminogen was measured by chromogenic (synthetic substrate) activity assay using a Stago STA Analyzer and Stachrome Plasminogen Kit 658. The reference range was 80% to 120%. Plasma LDL cholesterol was calculated according to the formula LDL cholesterol = total cholesterol − (HDL cholesterol + triglycerides/5) [18].

2.3. Biostatistical methods

The acute (inpatient) phase was analyzed by comparing the 2 treatments at each time point separately using a repeated-measures model with terms for sequence (wine–grape juice or grape juice–wine), subject, and day. A Bonferroni correction for multiple comparisons was applied to the 8 comparisons of plasma glucose and serum insulin, so that $P < .05/8 = 0.006$ was required for a significant difference at the 5% level. The chronic (outpatient) phase was analyzed with a parallel model and also with a model including sex effects. Occurrence of hypoglycemia during the 2 outpatient months was compared within subjects with the McNemar test. Statistical analyses were performed with SAS Version 9.1 (SAS Institute, Cary, NC), and graphics were drawn using R (R Foundation for Statistical Computing, Vienna, Austria; http://www.R-project.org). All results for continuous end points were reported as mean with standard error.

3. Results

Participants were 11 women and 7 men with mean (range) age of 64 years (45-82 years), duration of diabetes of 8 years (2-29 years), BMI of 31.7 kg/m^2 (21.3-41.2 kg/m^2), HbA_{1c} of 6.9% (5.5%-8.4%), cholesterol of 160 mg/dL (110-212 mg/dL), HDL cholesterol of 43 mg/dL (23-71 mg/dL), LDL cholesterol of 88 mg/dL (58-140 mg/dL), and triglycerides of 143 mg/dL (44-369 mg/dL). Eleven subjects were taking metformin and a sulfonylurea, one was taking metformin and repaglinide, 5 were taking metformin alone, and one was taking no diabetes medication. Thirteen subjects were taking statin medications. Baseline consumption of alcohol-containing beverages was <1 per week in 9 subjects, 1 to 7 per week in 8 subjects, and 8 to 14 per week in 1 subject. After completing the acute study, one subject developed a cardiac problem requiring urgent cardiac catheterization and did not complete the chronic study.

As shown in Fig. 1, alcohol had no acute effect on plasma glucose or serum insulin. After ingestion of 240 mL wine containing 24 g alcohol with dinner, plasma glucose and serum insulin were not different at any time point from 7:00 PM to 7:00 AM than after ingestion of grape juice with dinner. The greatest difference in plasma glucose values occurred at 7:00 PM, but the value of 148 mg/dL after wine was not significantly different from the value of 165 mg/dL after grape juice ($P = .21$). In the acute study, there was no sequence (carryover) effect.

During the 30 days of chronic wine consumption, mean daily consumption was 171 mL of wine containing 18 g alcohol (men, 21 g alcohol; women, 16 g alcohol), whereas during the 30 days of abstinence, mean daily alcohol consumption was <0.1 g. At the end of the 30-day treatment periods, there was no significant difference between wine consumption and abstinence in values for fasting plasma cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, plasma glucose, HbA1c, serum C-reactive protein, blood plasminogen, blood pressure, weight, or episodes of mild hypoglycemia (Table 1). There was no episode of serious

Table 1
Mean ± SEM values after 30 days of daily wine consumption and 30 days of abstinence from alcohol

	Wine	Abstinence	*P*
Fasting cholesterol (mg/dL)	160 ± 6	160 ± 8	.98
Fasting HDL cholesterol (mg/dL)	47 ± 3	46 ± 3	.87
Fasting LDL cholesterol (mg/dL)	82 ± 5	82 ± 6	.98
Fasting triglycerides (mg/dL)	157 ± 19	159 ± 19	.88
Fasting glucose (mg/dL)	128 ± 6	128 ± 7	.84
Fasting insulin (μU/mL)	14 ± 2	17 ± 3	.03
HbA_{1c} (%)	6.7 ± 0.2	6.7 ± 0.2	.63
C-reactive protein (mg/L)	0.32 ± 0.1	0.31 ± 0.1	.87
Plasminogen (%)	114 ± 4	114 ± 3	.98
Systolic BP (mm Hg)	131 ± 3	130 ± 4	.72
Diastolic BP (mm Hg)	71 ± 2	72 ± 1	.54
Weight (kg)	87.4 ± 3.9	87.4 ± 3.9	.91
Episodes of hypoglycemia (all subjects combined)	4	8	.50

n = 17; to convert to millimoles per liter, multiply cholesterol by 0.02586, triglycerides by 0.0112, and glucose by 0.05551; to convert insulin to picomoles per liter, multiply by 6.0. BP indicates blood pressure.

hypoglycemia during either treatment. Fasting serum insulin was 3 μU/mL lower after wine than after abstinence. In the chronic study, there was no sequence (carryover) effect.

With 17 subjects, we had an 80% chance (power 0.80) to detect a true mean difference greater than 2.2 mg/dL in the primary end point, HDL cholesterol. Mean HDL cholesterol values for women were 52 mg/dL after wine and 50 mg/dL after abstinence, whereas mean HDL cholesterol values for men were 40 mg/dL after both wine and abstinence. Thus, HDL cholesterol was higher in women than in men but did not change significantly with the treatments in either sex. When the subgroup of 5 subjects not taking statin medications was analyzed separately, there was no trend toward higher HDL cholesterol after wine consumption.

4. Conclusions

Our study did not demonstrate any acute effect of consumption of a moderate amount of alcohol in the form of wine with dinner on plasma glucose or serum insulin during the following evening and night. Although alcohol has been shown to inhibit hepatic gluconeogenesis in subjects with type 2 diabetes mellitus, it does so without decreasing hepatic glucose output [19]. Presumably, any decrease in gluconeogenesis is compensated for by increased glycogenolysis.

Our data also did not demonstrate any effect of chronic wine consumption on plasma HDL cholesterol or other plasma lipid fractions in subjects with type 2 diabetes mellitus. Our study had an 80% chance of finding a true mean difference greater than 2.2 mg/dL in HDL cholesterol. It is possible that we did not have sufficient power to demonstrate an effect and that a larger study with more subjects might show an effect on HDL cholesterol. Most of our subjects were overweight or obese, and it is possible that leaner diabetic individuals would have responded differently. Because most of our subjects were taking statin medications, it is also possible that statins blocked an effect of alcohol on HDL cholesterol. However, analysis of data from the 5 subjects not taking statins did not show a trend toward higher HDL cholesterol values with alcohol consumption.

It is possible that the amount of alcohol we used (mean, 18 g daily) was too little to produce an effect on HDL cholesterol. In physically inactive men, consumption of 39 g alcohol daily from beer for 3 weeks raised HDL cholesterol [20], whereas in women, consumption of 35 g alcohol daily from wine for 3 weeks had no effect on HDL cholesterol [21]. However, alcohol intake of more than 30 g (two drinks) daily has been associated with increased mortality [3,4] and probably should be considered excessive. The amount of alcohol we used slightly exceeded the maximum intake recommended for women with diabetes, which is 1 drink per day (15 g alcohol), but was less than the maximum intake recommended for men with diabetes, which is 2 drinks per day (30 g alcohol) [22].

Our data suggest that any cardioprotective effect of moderate alcohol intake in people with diabetes is not mediated by increased plasma HDL cholesterol. This raises the possibility that diabetes negates the potential HDL cholesterol–raising effect of alcohol found in the general population. We also could not demonstrate any effect of alcohol on inflammation as measured by high-sensitivity C-reactive protein or the fibrinolytic system as measured with a functional plasminogen assay.

We did find that fasting serum insulin was lower after chronic wine consumption than after abstinence. This is consistent with data in nondiabetic populations where alcohol intake was associated with reduced serum insulin and improved insulin sensitivity [15,23,24]. Although our study was not designed to assess insulin sensitivity, the reduction in fasting serum insulin after 30 days of wine consumption suggests that alcohol may reduce insulin resistance in people with type 2 diabetes mellitus. The significance of this is uncertain, but this might be a mechanism whereby alcohol exerts a cardioprotective effect in people with diabetes.

In conclusion, our data demonstrate that moderate consumption of alcohol in the form of wine did not raise plasma HDL cholesterol in subjects with type 2 diabetes mellitus. However, alcohol did not have an adverse effect on body weight, blood pressure, lipemia, or rates of hypoglycemia. Alcohol did lower fasting serum insulin when used chronically and thus might improve insulin sensitivity. People with type 2 diabetes mellitus should not be discouraged from using alcohol in moderation.

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