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Effect of moderate alcoholic beverage consumption on insulin sensitivity in insulin-resistant, nondiabetic individuals

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Abstract

Although moderate alcohol consumption has been associated with a decrease in plasma insulin concentrations, relatively few studies have been conducted to evaluate the effect of alcohol on insulin sensitivity, particularly in nondiabetic, insulin-resistant individuals. Because enhanced insulin sensitivity could contribute to the reported association between moderate alcohol consumption and reduced risk of heart disease and diabetes, we believed it is important to address this issue. Consequently, we evaluated the ability of moderate alcohol consumption to improve insulin sensitivity, as measured by determining the steady-state plasma glucose (SSPG) concentration during the insulin suppression test, in 20 nondiabetic, insulin-resistant individuals. Measurements were made of SSPG, glucose, insulin, and lipoprotein concentrations before and after consuming 30 g of alcohol for 8 weeks, either as vodka (n = 9) or red wine (n = 11). The SSPG concentrations (insulin resistance) decreased by approximately 8% in the total group (P = .08), and high-density lipoprotein cholesterol concentration increased by a mean of 0.09 mmol/L (P = .02). Trends were similar in individuals who consumed vodka or red wine. Men tended to have greater decline in SSPG and increase in high-density lipoprotein cholesterol compared with women. There were no other metabolic changes in fasting plasma glucose, insulin, and triglyceride concentrations. These data demonstrate that 8 weeks of moderate alcohol consumption had minimal impact on enhancing insulin sensitivity in nondiabetic, insulin-resistant individuals, raising questions as to the role, if any, of improved insulin sensitivity in the purported clinical benefits associated with moderate alcohol consumption.

1. Introduction

Although moderate alcohol consumption has been reported [1-6] to be associated with lower risk for both cardiovascular disease (CVD) and type 2 diabetes mellitus (DM2), an explanation for these epidemiologic observations is not clear. It is known that alcohol consumption increases high-density lipoprotein cholesterol (HDL-C) concentrations [1,7] and, in moderate amounts, has been associated with lower triglyceride and insulin concentrations [8,9]. Because these metabolic changes are associated with enhanced insulin sensitivity and insulin resistance increases risk of both CVD and DM2 [10,11], it could be postulated that moderate alcohol consumption decreases the risk of these syndromes by improving insulin sensitivity.

Appealing as this formulation seems to be, the 3 studies [12-14] in which the effects of moderate alcohol consumption on insulin sensitivity have been assessed with methods that specifically quantify insulin-mediated glucose uptake have led to conflicting results. Specifically, 2 of the studies were performed in apparently healthy subjects, with no significant improvement in insulin sensitivity seen after 4 weeks of red wine in 34 individuals [12] or 17 days of whisky in 23 subjects [13]. In the latter study, however, there was a trend for improvement in a subgroup of 10 subjects classified as being "insulin resistant" (P = .11). In contrast, the third study [14] discerned an improvement in insulin sensitivity after 2 weeks of red wine in 9 individuals with DM2.

One possible explanation for these divergent findings might be that the ability of moderate alcohol consumption to improve insulin sensitivity is confined to individuals who are insulin resistant before the intervention, there being no reason to see any change in insulin-sensitive individuals. This formulation is consistent with the beneficial results

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seen in patients with DM2 [14] and the tendency for insulin sensitivity to improve in the subgroup of healthy individuals said to be insulin resistant [13]. Therefore, using this framework for the current study, we quantified the ability of moderate alcohol consumption to improve insulin-mediated glucose uptake in a group of nondiabetic individuals, classified as being insulin resistant before the experimental intervention. In addition, because the relative short duration of previous studies may have contributed to the contradictory findings, we have conducted the current study in which we have evaluated the effect of 8 weeks of moderate alcoholic beverage consumption (either as vodka or red wine) on insulin sensitivity in insulin-resistant individuals.

2. Methods

2.1. Subjects

Participants consisted of 20 individuals from the San Francisco Bay area who volunteered for this study in response to a newspaper advertisement. Individuals were separately recruited to drink vodka (n = 9) or red wine (n = 11). Individuals who reported consuming greater than 2 drinks per week were asked to abstain from alcohol for 4 weeks before assessment of insulin sensitivity. All individuals who enrolled were insulin resistant as defined by the insulin suppression test described below. They were also nondiabetic [15] and not taking any medications known to affect carbohydrate metabolism. Individuals were excluded from the study if they had personal or family history of alcoholism and were screened for alcohol-associated problems using the Alcohol Use Disorders Identification Test [16]. Other criteria included the following: age between 35 and 65 years, hematocrit greater than 32%, alanine transaminase less than 2 times the upper limit of normal, and triglyceride concentration less than 4.5 mmol/L.

2.2. Study design

This was a nonrandomized, open-label study of moderate alcohol consumption for 8 weeks. The study was approved by the Institutional Review Board at Stanford, and all individuals gave written consent before participation.

Individuals consumed 30 g of alcohol per day in the form of vodka or red wine (Cabernet Sauvignon, Alexander Valley, Castle Rock, Napa Valley, CA). Individuals weighing less than 70 kg (n = 3) or individuals who could not tolerate 30 g (n = 1) were given 20 g of alcohol per day. Vodka had an alcohol content of 40% by volume, and individuals were given their daily quantity in individual containers. Red wine was provided in bottles and had an alcohol content of 13.9% by volume. Individuals were given a measuring cup marked for the appropriate daily volume. Both alcohol beverages were consumed with dinner or before bedtime; no additional alcoholic beverages were allowed throughout the study duration. Individuals were seen on a weekly basis to pick up study beverages and return containers/bottles to monitor compliance with the alcoholic beverages. Their weights and blood pressures were also monitored weekly; and at each visit, they were encouraged to maintain their baseline weight and activity level.

All metabolic testing occurred in the General Clinical Research Center at Stanford Medical Center after fasting for 12 hours. Experimental measurements were conducted 4 weeks after alcohol abstinence (baseline) and after 8 weeks of alcohol intervention and included assessment of insulin sensitivity and lipid panel (core laboratory, Stanford University). Insulin resistance was estimated by a modification [17] of the original insulin suppression test [18] that has a high correlation ($r > 0.9$) with the euglycemic clamp technique [19]. After an overnight fast, an intravenous catheter was placed in each of the subject's arms. One arm was used for the administration of a 180-minute infusion of octreotide (0.27 μg/[m^2 min]), insulin (32 mU/[m^2 min]), and glucose (267 mg/[m^2 min]); the other arm was used for collecting blood samples. Blood was drawn at baseline and at 10-minute intervals from 150 to 180 minutes of the infusion to determine the steady-state plasma glucose (SSPG) and insulin concentrations. Because steady-state insulin concentrations are similar in all subjects, the SSPG concentration provides a direct measure of the ability of insulin to mediate disposal of an infused glucose load; therefore, the higher the SSPG concentration is, the more insulin resistant is the individual. *Insulin resistance* was defined as an SSPG concentration greater than 7.8 mmol/L, which represents the cut point for the upper tertile of SSPG in individuals with normal glucose tolerance who have been shown to have high risk to develop diabetes mellitus and CVD [20,21]. Glucose concentrations were measured by the oxidase method (Beckman Analyzer 2, Brea, CA) and insulin concentrations by radioimmunoassay (Linco, St Charles, MO).

2.3. Power calculation

In a case-control study of healthy volunteers, we previously found a 4-mmol/L or 37% difference in SSPG concentration between individuals who reported no or minimal alcohol consumption and moderate consumption (10-30 g of alcohol per day) [22]. With 10 subjects, we had 80% power to detect a 2.9-mmol/L difference with a standard deviation for SSPG of 2.2 mmol/L. With a total of 20 individuals, we could detect a 2-mmol/L or approximately 15% difference in SSPG concentration in an insulin-resistant population. For comparison, modest weight loss of 7% to 9% of initial body weight leads to 20% to 30% improvement in SSPG concentrations [23,24].

2.4. Statistical analysis

All statistical analyses were performed using SPSS (version 16 for Windows; SPSS, Chicago, IL). To compare baseline characteristics between the 2 alcohol groups, the Wilcoxon rank sum test was used for continuous variables and Fisher exact test for categorical variables. Paired *t* tests were used to compare differences before and after alcohol

Table 1
Baseline characteristics of the 2 alcohol groups

	Red wine	Vodka	*P*
n	11	9	–
Age (y)	56 ± 5	51 ± 9	.15
BMI (kg/m^2)	30.2 ± 2	34.8 ± 6	.01
Sex (M/F)	(6/5)	(5/4)	.99
Non-Hispanic white (n)	7	6	.99
SSPG (mmol/L)	13.0 ± 1.2	12.9 ± 2.9	.70

Mean ± standard deviations presented unless otherwise noted. BMI indicates body mass index.

intervention in the 2 alcohol groups separately and combined. Insulin concentrations were log transformed before analysis and are presented as median (interquartile range). As epidemiologic studies have shown greater benefits of alcohol in men [2,25], we did a post hoc, exploratory subgroup analysis based on sex for our primary outcome of insulin sensitivity and also HDL-C concentration. We also stratified by amount of alcohol consumed, as 4 individuals required 20 g of alcohol. Analyses were not adjusted for multiple comparisons.

Table 2
Metabolic changes associated with 8 weeks of alcohol consumption

	Baseline	8 wk	*P*
Weight (kg)			
Red wine	85 ± 3	86 ± 3	.70
Vodka	92 ± 6	93 ± 6	.20
Both	89 ± 3	89 ± 3	.28
SBP (mm Hg)			
Red wine	130 ± 3	130 ± 4	.94
Vodka	123 ± 4	127 ± 5	.35
Both	127 ± 3	129 ± 3	.44
DBP (mm Hg)			
Red wine	76 ± 2	76 ± 3	.54
Vodka	76 ± 3	78 ± 3	.54
Both	76 ± 2	77 ± 2	.82
Pulse (beats/min)			
Red wine	65 ± 3	65 ± 3	.90
Vodka	69 ± 3	70 ± 4	.53
Both	67 ± 2	67 ± 2	.66
LDL-C (mmol/L)			
Red wine	3.0 ± 0.2	2.7 ± 0.2	.09
Vodka	2.9 ± 0.3	3.0 ± 0.3	.21
Both	2.9 ± 0.2	2.9 ± 0.2	.55
HDL-C (mmol/L)			
Red wine	1.09 ± 0.10	1.16 ± 0.13	.29
Vodka	1.16 ± 0.07	1.28 ± 0.08	.02
Both	1.12 ± 0.06	1.21 ± 0.08	.02
Triglycerides (mmol/L)			
Red wine	1.4 ± 0.1	1.4 ± 0.2	.79
Vodka	1.6 ± 0.1	1.5 ± 0.2	.59
Both	1.5 ± 0.1	1.5 ± 0.1	.80
Fasting glucose (mmol/L)			
Red wine	5.7 ± 0.2	5.7 ± 0.2	.37
Vodka	5.4 ± 0.1	5.4 ± 0.2	.63
Both	5.6 ± 0.1	5.6 ± 0.2	.77
Fasting insulin (pmol/L)			
Red wine	125 (118,160)	118 (97,167)	.07
Vodka	125 (97,208)	139 (104,188)	.94
Both	125 (104,181)	125 (104,174)	.24
SSPG (mmol/L)			
Red wine	13.0 ± 0.4	11.7 ± 0.7	.12
Vodka	12.9 ± 1	12.4 ± 1.1	.46
Both	13.0 ± 0.4	12.0 ± 0.6	.08

Mean ± standard error of mean or median (interquartile range) presented. SBP indicates systolic blood pressure; DBP, diastolic blood pressure; LDL-C, low-density lipoprotein cholesterol.

3. Results

In total, we screened 100 individuals with the insulin suppression test. Thirty-six met the criteria for insulin resistance (SSPG >7.8 mmol/L). Seven decided not to participate further, and 3 were disqualified based on the exclusion criteria. Initially, 12 enrolled in the vodka group and 14 in the red wine group. However, 3 individuals dropped out (2 men and 1 woman) in the vodka group and 3 women dropped out in the red wine group secondary to inability to tolerate daily consumption of alcohol (n = 4), family emergency (n = 1), and concern about alcohol toxicity (n = 1). There was no difference in mean (±SD) baseline age, body mass index, or SSPG concentration between individuals who dropped out (54 ± 7 years, 32 ± 3 kg/m^2, and 12.5 ± 3.2 mmol/L, respectively) and those who continued the study (54 ± 7 years, 32 ± 5 kg/m^2, and 13.0 ± 2.1 mmol/L, respectively). Individuals who continued the study had 90% to 100% compliance with the alcoholic beverages by container (vodka) and bottle (red wine) count.

Table 1 shows the baseline characteristics of the 2 alcohol groups. They were similar in age, sex, and racial distribution. Although the vodka group was heavier, the degree of insulin resistance (SSPG) was similar.

During the study, weight remained stable (Table 2). As seen in Table 2, there was no significant change in blood pressure, triglyceride concentration, or fasting glucose or insulin concentrations. The HDL-C concentrations increased in both groups, but the change was only statistically significant in those drinking vodka. There was a trend for decrease in SSPG concentration (P = .08) in the overall group, with no significant change in median steady-state

Table 3
Changes in insulin resistance (SSPG) and HDL-C concentration by sex and amount of alcohol consumed

	SSPG (mmol/L)			HDL-C (mmol/L)		
	Baseline	8 wk	*P*	Baseline	8 wk	*P*
Sex						
Male (n = 11)	13.4 ± 0.6	11.9 ± 0.9	.04	1.02 ± 0.05	1.15 ± 0.06	.003
Female (n = 9)	12.4 ± 0.7	12.2 ± 0.8	.81	1.25 ± 0.12	1.29 ± 0.16	.54
Amount						
30 g (n = 16)	13.7 ± 0.3	12.4 ± 0.6	.02	1.07 ± 0.05	1.16 ± 0.07	.048
20 g (n = 4)	9.9 ± 0.9	10.5 ± 1.7	.65	1.35 ± 0.24	1.42 ± 0.29	.31

Mean ± standard error of mean presented.

plasma insulin concentration (interquartile range) (baseline, 521 [431,604]; after 8 weeks, 479 [417,563]; $P = .25$).

We did a subgroup analysis by sex and amount of alcohol consumed (Table 3). Men had a significant decrease in SSPG and increase in HDL-C concentrations, but not women. Of the 11 men, 7 had at least a 5% decline in SSPG concentration, 3 had no change, and 1 had an increase. In comparison, of the 9 women, 4 had an increase in SSPG concentration and 5 had a decline. Individuals who consumed 30 g of alcohol also had a significant decline in SSPG and increase in HDL-C concentrations, but not those who consumed 20 g. Women comprised 3 of the 4 who drank 20 g of alcohol, and all of these women had an increase in SSPG concentrations.

4. Discussion

The goal of this study was to seek an explanation that would reconcile prior conflicting findings [12-14] concerning the ability of moderate alcohol ingestion to improve insulin sensitivity. Specifically, it was to test the hypothesis that the beneficial effects of moderate alcohol consumption on insulin sensitivity would be most clearly demonstrated in individuals selected to be insulin resistant. Unfortunately, the results provide little support for this notion. At best, we could only discern a trend toward enhanced insulin sensitivity in the total group of approximately 8%, with significant improvement of a modest degree in men (~11%) and in those who consumed 30 g of alcohol per day (~10%). In light of these data, it appears that 8 weeks of moderate alcohol consumption, either as vodka or red wine, did not significantly improve insulin sensitivity in the nondiabetic, insulin-resistant individuals enrolled in this study.

To the best of our knowledge, this is the first experimental study of moderate alcohol consumption where individuals were enrolled based on a specific measure of insulin resistance. Although there are no definitive criteria to delineate an individual as insulin resistant or sensitive, we defined *insulin resistance* as an SSPG concentration greater than 7.8 mmol/L because this cut point has been shown in 2 prospective studies to predict the development of such diseases as CVD and DM2 [20,21]. The current results, in which 8 weeks of moderate alcohol consumption decreased SSPG by only approximately 8% in this high-risk population of insulin-resistant individuals, should be viewed in the context of previous studies showing that modest weight loss (7%-9% of initial weight) decreases SSPG concentration by 20% to 30% [23,24], a change in weight associated with lower risk for developing diabetes mellitus in large prospective studies [26,27].

The only study [14] in which a direct measure of insulin-mediated glucose uptake (the euglycemic, hyperinsulinemic clamp) indicated that moderate alcohol consumption significantly improved insulin sensitivity (43%) was performed in patients with DM2. Although the method we used to quantify insulin-mediated glucose disposal is somewhat different, measurements of insulin sensitivity with the clamp and insulin suppression test are highly correlated [19]; therefore, technical differences are unlikely to explain the difference in results. On the other hand, the study populations were quite different: we enrolled nondiabetic, insulin-resistant individuals, in contrast to patients with long-standing DM2, some of whom were on oral hypoglycemic medications. It is also interesting to note that, despite the reported 43% improvement in insulin sensitivity in the diabetic subjects, there were no significant changes in fasting glucose or insulin concentrations that have been shown to decrease after lesser degrees of improvement in insulin sensitivity (15%-25%) associated with weight loss in individuals with DM2 [28]. Lastly, although the amount of alcohol consumed per day in the patients with diabetes was not specified, the 9 patients likely consumed approximately 43 g of alcohol per day based on ingestion of 360 mL of Chianti with average alcohol volume of 13.5%. Thus, it could be postulated that the higher alcohol ingestion may have had a greater effect on insulin sensitivity than seen in the current study where individuals consumed 30 g of alcohol per day. Dose effect of alcohol has been observed for elevating HDL-C [2]; and in 1 study of postmenopausal women, there appeared to be a dose effect for lowering insulin concentrations with greater decrease after 30 g vs 15 g of alcohol per day [8]. However, this is unlikely to be the only factor, given that individuals in the other 2 experimental studies [12,13] in which direct measures of insulin sensitivity did not improve after alcohol intake also consumed 40 g of alcohol per day.

Although there are debates regarding the relative benefits of red wine vs other alcoholic beverages, all alcoholic beverages have been associated with lower risk for CVD [2,3] and diabetes mellitus [5]. Given the distinctive taste of certain alcoholic beverages, it would be difficult to conduct a blinded, randomized trial to assess differences between alcohol types. In the current study, there appeared to be similar metabolic effects from moderate consumption of red wine and vodka. In particular, the general trends in insulin sensitivity and HDL-C appeared the same in the 2 groups.

In contrast to type of alcohol consumed, men appeared to have greater decrease in insulin resistance, albeit still low (~11%), and increase in HDL-C concentrations than women. This difference may be partially explained by more women consuming less alcohol (20 g) per day. In epidemiologic studies, however, women appear to incur greater risks for overall mortality at greater than 1 drink (~15 g) per day [25], whereas men appear to have the greatest benefit at 2 drinks (~30 g) per day [6]. Therefore, the benefits of alcohol are not straightforward for women.

This study has several limitations that should be addressed. First, we had a small sample size, which could detect a decrease in SSPG concentration of approximately 15%. Because our goal was to identify clinically relevant changes in insulin resistance equivalent to the magnitude (~20%) seen with modest weight loss [23,24], it appears that this degree of change was not seen after moderate ingestion

of alcoholic beverages. Secondly, consumption of alcohol was not blinded; however, given the known physiologic effects of alcohol and distinct tastes of certain types, this would have been difficult to achieve. Lastly, although our study duration of 8 weeks is relatively long compared with other published intervention studies, it still may not represent the potential beneficial effects of long-term effects of moderate alcohol consumption.

To summarize, 8 weeks of moderate alcohol consumption does not appear to have a clinically significant beneficial effect on insulin sensitivity in nondiabetic, insulin-resistant individuals. There was a trend for enhanced insulin sensitivity in the overall group and for a significant improvement in men and in those who consumed 30 g of alcohol. However, the magnitude of improvement in each of these cases was small and unlikely to be clinically relevant. This is the third study in nondiabetic individuals, in which specific methods to quantify insulin action have been used, unable to discern significant beneficial effects of moderate alcohol consumption on insulin sensitivity. These findings stand in contrast to the results of the study showing an improvement in insulin sensitivity in patients with DM2 [14]. The disparity cannot be attributed to the length of the period of alcohol consumption or to the fact that the inclusion of normally insulin-sensitive individuals blunted the beneficial effects of alcohol to improve insulin sensitivity. Furthermore, the amount of alcohol consumed does not seem to account for the differences in that the nondiabetic subjects in 2 prior studies [12,13] consumed 40 g of alcohol, as compared with the 43 g ingested by the patients with DM2 [14]. The only explanation that appears to account for the difference in results is the nature of the patient population—nondiabetic vs DM2. Obviously, additional data are needed to resolve these differences; but in the absence of this information, it seems reasonable to suggest that any beneficial effect of moderate alcohol consumption to decrease risk of CVD or DM2 in nondiabetic subjects is unlikely to be related to an improvement in insulin sensitivity.

Finally, although our study evaluated the ability of moderate consumption of alcoholic beverages to improve insulin sensitivity in insulin-resistant individuals, our inability to detect this effect does not negate its clinical benefits. Thus, many other mechanisms have been suggested to account for the benefits of moderate alcohol consumption, including alcohol's effect on lipids [29], thrombogenesis [2], endothelial function [30], and inflammation [31]. The only consistent finding centers on alcohol's effect on HDL-C that has been seen in both observational and experimental studies [1,2,7,22]. In this study, HDL-C concentration significantly increased by a mean of 0.09 mmol/L in the overall group, which is consistent with expected changes from drinking 30 g of alcohol per day [2]. The elevation in HDL-C is believed to account for 50% of the benefits of alcohol consumption in lowering the risk for CVD [29] and remains as the most salient benefit of moderate alcohol consumption.

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