Light-to-Moderate Alcohol Intake Is Associated With Enhanced Insulin Sensitivity

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OBJECTIVE — To test the hypothesis that insulin-mediated glucose uptake is enhanced in light-to-moderate alcohol consumption.

RESEARCH DESIGN AND METHODS — This is a case-control study of healthy volunteers, divided into nondrinkers and light-to-moderate drinkers based on their history of alcohol consumption. The study was performed at the General Clinical Research Center at Stanford University Medical Center and involved 40 volunteers, 20 men and 20 women. Measurements were made of the plasma glucose and insulin responses to an oral glucose challenge, fasting plasma lipid and lipoprotein concentrations, and steady-state plasma insulin (SSPI) and steady-state plasma glucose (SSPG) concentrations in response to a continuous infusion of somatostatin, insulin, and glucose.

RESULTS — Light-to-moderate drinkers (10–30 g/day) had lower integrated plasma glucose (17.8 ± 0.8 vs. 19.8 ± 0.9 mM/h, $P < 0.02$) and insulin (600 ± 65 vs. 1,075 ± 160 pM/h, $P < 0.01$) responses to the glucose challenge and higher fasting plasma high-density lipoprotein (HDL) cholesterol concentrations (1.46 ± 0.08 vs. 1.25 ± 0.08, $P < 0.02$). Despite similar SSPI concentrations of ~300 pM, SSPG concentrations were lower ($P < 0.01$) in light-to-moderate drinkers (6.7 ± 0.8 vs. 10.7 ± 1.2 mM). Results were independent of age, body mass index, ratio of waist-to-hip girth, and estimates of level of habitual physical activity.

CONCLUSIONS — Light-to-moderate alcohol consumption in healthy men and women is associated with enhanced insulin-mediated glucose uptake, lower plasma glucose and insulin concentrations in response to oral glucose, and a higher HDL-cholesterol concentration. The changes in glucose and insulin metabolism may contribute to the lower risk of coronary heart disease described in light-to-moderate drinkers.

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SSPI, steady-state plasma insulin; SSPG, steady-state plasma glucose; HDL, high-density lipoprotein; CHD, coronary heart disease; TG, triglyceride; BMI, body mass index; MET, metabolic equivalent; ANOVA, analysis of variance; VLDL, very-low-density lipoprotein; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein.

Recent publications (1,2) have demonstrated that the chronic intake of ethanol in light-to-moderate amounts was associated with a decrease in coronary heart disease (CHD), presumably caused by the concomitant increase in high-density lipoprotein (HDL) cholesterol concentration (1–3). Women drinking a moderate amount of alcohol also have been shown to have lower fasting plasma insulin and triglyceride (TG) concentrations, in addition to higher HDL-cholesterol levels, than female nondrinkers (4). Because lower plasma insulin and TG and higher HDL-cholesterol concentrations have been associated with enhanced insulin sensitivity (5), it seemed possible that insulin-mediated glucose disposal might be enhanced in individuals chronically ingesting light-to-moderate amounts of alcohol. This study was initiated to test this hypothesis.

RESEARCH DESIGN AND METHODS

— All participants enrolled in this study were individuals who responded to a newspaper advertisement indicating our interest in studying factors modulating insulin action and glucose tolerance in healthy human beings. When potential participants were initially interviewed, their habitual intake of alcohol was estimated by a modified version (6) of the original Straus and Bacon (7) usual quantities questionnaire. Use of this questionnaire is based on estimating frequency of drinking occasions and amounts consumed per occasion of wine, beer, spirits, and mixed drinks. Based on an average estimated alcohol content of 10, 4, 40, and 20% (weight), respectively, for wine, beer, spirits, and mixed drinks (i.e., cocktails), light-to-moderate drinking individuals were defined as consuming 10–30 g of alcohol/day, an amount roughly equivalent to 1–3 drinks/day. Potential subjects fulfilling this criterion, with body mass index (BMI) <30 $kg \cdot m^{-2} \cdot ^{-1}$ day, were screened further by medical history, physical examination, and chemical

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Table 1—*Baseline characteristics of experimental groups*

	Women		Men	
	Nondrinkers	Drinkers	Nondrinkers	Drinkers
n	11	11	9	9
Age (years)	41 ± 4	45 ± 4	47 ± 5	46 ± 6
Height (cm)	166 ± 2	166 ± 3	174 ± 2	182 ± 2
Weight (kg)	69 ± 4	69 ± 4	78 ± 7	86 ± 5
BMI (kg/m^2)	25.1 ± 1.5	24.9 ± 1.5	25.7 ± 1.8	25.8 ± 1.3
Waist-to-hip ratio	0.89 ± 0.03	0.88 ± 0.04	0.91 ± 0.03	0.91 ± 0.03
Energy expenditure ($kcal \cdot ml^{-2} \cdot day^{-1}$)	1,569 ± 96	1,541 ± 46	1,797 ± 90	1,840 ± 120
Family history (*n*)				
Hypertension	7	7	3	4
Diabetes	6	6	1	2

Data are means ± SE.

screening battery. The 20 subjects finally selected for this study were entirely normal by these criteria and were not taking any drugs known to affect carbohydrate or lipid metabolism.

We then selected another 20 individuals from the volunteer pool who most closely resembled the group of drinkers in terms of age, sex, and BMI and who also fulfilled the other criteria for inclusion, but who stated that they never consumed alcohol ($n = 14$) or used it only on rare occasions ($n = 6$). The level of habitual physical activity was estimated by a modified version of a self-reporting questionnaire (8) in which subjects describe the time spent during the previous week performing various activities. Empirical constants are used to calculate the amount of energy used per day, i.e., sleep is assumed to require 1 metabolic equivalent (MET) per hour, with 1 MET = 1 $kcal \cdot kg^{-1} \cdot h^{-1}$; sweeping, walking, etc., requiring 4 METS; or swimming requiring 7 METS. We have expressed these data as $kcal \cdot m^{-2} \cdot day^{-1}$ to take into account differences in surface area. Baseline characteristics of the two experimental groups are presented in Table 1, and they seem to be quite comparable in all variables with the exception of alcohol consumption. Parenthetically, only 2 of 40 participants smoked, and this variable was not considered any further.

Volunteers were admitted to the Stanford General Clinical Research Center, and the following measurements were made. Venous blood was obtained on two occasions after an overnight fast for determination of fasting plasma TG (9) and cholesterol concentrations (10). Plasma also was separated by ultracentrifugation (11) for measurement of lipoprotein cholesterol and TG concentration. The lipid and lipoprotein data that were reported represent the average of these two fasting samples. On one morning, after an overnight fast, plasma glucose (12) and insulin (13) concentrations were determined before and 30, 60, 120, and 180 min after the administration of a 75-g oral glucose challenge. Finally, insulin-mediated glucose uptake was estimated by a modification of the insulin suppression test originally described by our research group (14,15). This study also was performed after an overnight fast and involved the continuous intravenous infusion for 180 min of somatostatin (5 μg/min), insulin ($25\ mU \cdot m^{-2} \cdot min^{-1}$), and glucose ($240\ mg \cdot m^{-2} \cdot min^{-1}$) into an indwelling Teflon catheter in a superficial antecubital vein. Venous blood samples were obtained from a similar catheter inserted in a contralateral antecubital vein and kept patent by a slow infusion of 0.9% sodium chloride. Blood was obtained every 10 min during the last 30 min for measurement of plasma glucose and insulin concentrations, and the mean value of these four measurements was used to calculate the steady-state plasma insulin (SSPI) and steady-state plasma glucose (SSPG) concentrations. Because the SSPI is similar in all individuals, the SSPG concentration provides a measure of insulin-mediated glucose disposal; the higher the SSPG, the more insulin-resistant the individual.

Statistical analysis

Results are expressed as means ± SE. Plasma glucose and insulin responses were defined as the total integrated area from 0 to 180 min. Statistical significance of differences between the two groups was determined by one-way analysis of variance (ANOVA). When multiple time points were involved, two-way ANOVA was used to assess the differences between the two groups.

RESULTS — Plasma glucose and insulin concentrations before and after the oral glucose challenge are shown in Fig. 1. Plasma glucose concentrations were somewhat lower in low-to-moderate drinkers in response to the glucose challenge, and the total integrated glucose response was significantly lower in this group (17.8 ± 0.8 vs. 19.8 ± 0.9 mM/h, $P < 0.02$). The difference in the total integrated plasma insulin response between the two groups was even greater in magnitude and was significantly lower ($P < 0.01$) in light-to-moderate (600 ± 65 pM/h) than in nondrinkers (1,075 ± 160 pM/h). When analyzed by two-way ANOVA, using group and time as the two factors, the statistical significance of the difference of both the plasma glucose and insulin responses between the two groups also was highly significant ($P < 0.001$).

SSPG and SSPI concentrations for the two groups are shown in Fig. 2. Because the SSPI concentrations were sim-

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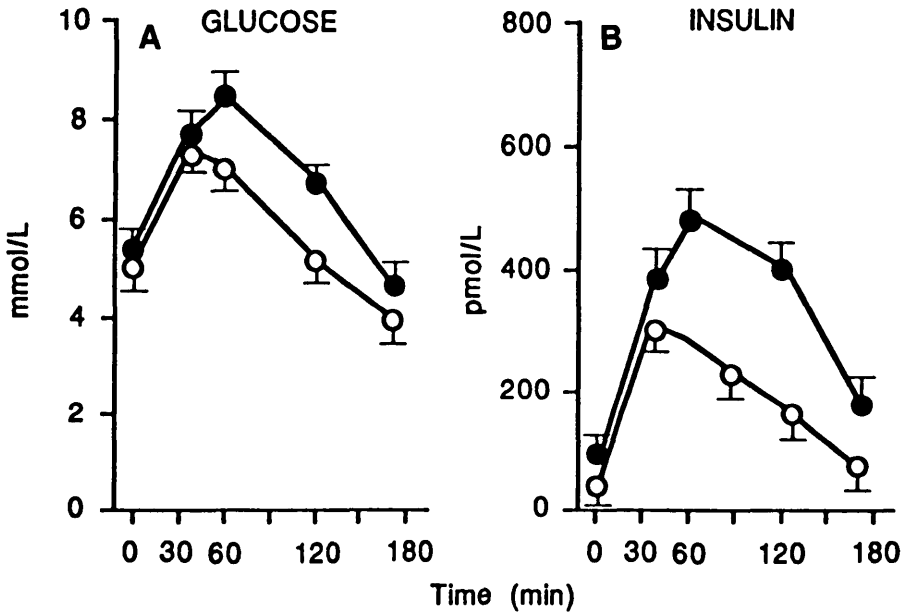

Figure 1—*Plasma glucose (A) and insulin (B) concentrations before and 30, 60, 120, and 180 min after 75 g of oral glucose in nondrinkers (●——●) and light-to-moderate drinkers (○——○).*

ilar, lower SSPG concentrations in light-to-moderate drinkers (6.7 ± 0.8 vs. 10.7 ± 1.2 mM, $P < 0.01$) means that this group was relatively less insulin-resistant compared with nondrinkers.

Plasma lipid and lipoprotein cholesterol concentrations are listed in Table 2. These results indicate that the only difference between the two groups was a significantly higher ($P < 0.02$) value for HDL-cholesterol concentration in low-to-moderate drinkers.

CONCLUSIONS— The data presented demonstrate that individuals classified as being light-to-moderate drinkers are relatively more insulin sensitive and have lower plasma insulin levels than do nondrinkers. Because the two experimental groups were well matched in age, sex distribution, BMI, and degree of habitual physical activity, i.e., variables known to affect insulin action and insulin concentration, it seems reasonable to conclude that the difference in alcohol intake was responsible for the observed changes in insulin metabolism.

This observation that insulin levels are lower in mild-to-moderate drinkers is consistent with results of the recent epidemiological study by Razay et al. (4). Because plasma insulin levels and insulin-mediated glucose uptake are inversely correlated in nondiabetic subjects (16), the results presented by Razay et al. (4) also suggest that insulin sensitivity is enhanced in individuals consuming light-to-moderate amounts of alcohol. Although our results and those of Razay et al. (4) seem to be at odds with at least three previous publications that concluded ethanol consumption decreased insulin-mediated glucose uptake (17–19), the difference may be more apparent than real. For example, previous studies quantified the acute, not the chronic, effects of alcohol on insulin-mediated glucose uptake and were performed in a relatively small number of individuals (7, 10, and 6 in references 17–19, respectively). Furthermore, in these studies, relatively large amounts of alcohol were administered intravenously over quite short time periods, i.e., total doses ranging from a low of 22 g in 7 h to a high of ~60 g in 30 min. Obviously, the amounts are greatly in excess of the daily 10–30 g of alcohol consumed by the light-to-moderate drinkers in this study. No a priori reason existed to assume that the acute effects of large amounts of alcohol on insulin-mediated glucose up-

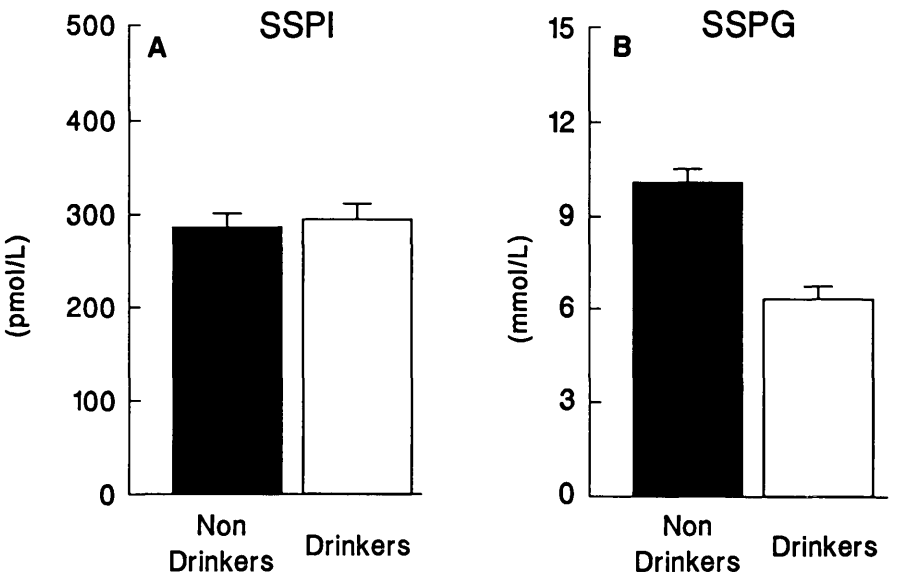

Figure 2—*SSPI (A) and SSPG (B) concentrations after a 180-min infusion of somatostatin, insulin, and glucose in nondrinkers (■) and light-to-moderate drinkers (□).*

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Table 2—*Lipid and lipoprotein concentrations*

	Nondrinkers	Drinkers	*P* value
Cholesterol (mM)			
Total	4.56 ± 0.15	4.68 ± 0.20	NS
VLDL	0.48 ± 0.15	0.41 ± 0.08	NS
IDL	0.33 ± 0.10	0.25 ± 0.05	NS
LDL	2.49 ± 0.15	2.56 ± 0.18	NS
HDL	1.25 ± 0.08	1.46 ± 0.08	<0.02
TG (mM)			
Total	1.21 ± 0.11	1.18 ± 0.12	NS
VLDL	0.76 ± 0.10	0.72 ± 0.11	NS
IDL	0.16 ± 0.03	0.14 ± 0.01	NS
LDL	0.19 ± 0.01	0.20 ± 0.01	NS
HDL	0.11 ± 0.01	0.11 ± 0.01	NS

Data are means ± SE.

take should be the same as the chronic effects of much smaller amounts. Thus, our results and those of Razay et al. (4) are not necessarily in conflict with previous publications.

Comment also should be made regarding the effects of mild-to-moderate drinking on lipid and lipoprotein concentrations. Not surprisingly, HDL-cholesterol concentrations were higher in these individuals, both in our study and in that of Razay et al. (4). Somewhat unexpected was our finding that plasma TG concentrations were not higher in the light-to-moderate drinkers and were actually lower in the report by Razay et al. (4). These results appear to be in conflict with evidence that plasma TG concentrations are positively correlated with alcohol intake (20). However, as pointed out by Razay et al. (4), the relationship between alcohol and TG concentrations may be U-shaped, with mild-to-moderate drinkers having lower levels than in either nondrinkers or heavy drinkers.

Note that this study was not initiated to test the hypothesis that light-to-moderate alcohol consumption will enhance insulin-mediated glucose uptake. Nor should the results be interpreted to mean that alcohol consumption should be encouraged to improve insulin-mediated glucose disposal; the dangers of excessive alcohol intake are well appreciated and need not be repeated in the context. Rather, the study was initiated in response to recent reports stating that light-to-moderate alcohol consumption was associated with a decrease in CHD (1,2) considered to be secondary to the increase in HDL cholesterol observed in individuals consuming alcohol (1–3). Several reports have shown that HDL-cholesterol concentrations are inversely related to degree of resistance to insulin-mediated glucose disposal and/or endogenous hyperinsulinemia (5,21–23), raising the possibility that the associations between alcohol consumption, decreased risk of CHD, and increased HDL-cholesterol concentration were all related to differences in resistance in insulin-mediated glucose uptake and/or hyperinsulinemia. Although these results are consistent with this possibility, it is obvious that mechanistic relationships cannot be defined by cross-sectional studies.

Parenthetically, these results also are germane to the idea that the association between alcohol consumption and decreased CHD risk is attributable to higher HDL-cholesterol concentrations (1–3). The fact that general agreement exists that CHD risk is inversely related to HDL-cholesterol concentrations (24,25) should not obscure the fact that substantial evidence has been found that higher postglucose load plasma glucose and insulin concentrations also have been identified as increasing the risk of CHD in nondiabetic individuals (26–31). Finally, it must be made unequivocally clear that the changes in insulin-mediated glucose disposal, relative glucose intolerance, and hyperinsulinemia noted in light-to-moderate drinkers are not necessarily caused by alcohol consumption per se. Although we tried to take into account all relevant variables known to affect insulin action and glucose tolerance (Table 1), some other variable, present in the drinkers and not the nondrinkers, was possibly responsible for the changes noted. On the other hand, even if this were the case, it would not mitigate against the results we presented. The goal of this study was to determine whether nondrinkers were relatively insulin resistant, glucose intolerant, and hyperinsulinemic compared with light-to-moderate drinkers. We believe that the results support the view that this is the case.

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