Glycemic Effects of Moderate Alcohol Intake Among Patients With Type 2 Diabetes

A multicenter, randomized, clinical intervention trial

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OBJECTIVE — In a randomized controlled trial, we assessed the effect of daily moderate alcohol intake on glycemic control in the fasting and postprandial states in patients with type 2 diabetes who previously had abstained from alcohol.

RESEARCH DESIGN AND METHODS — We randomly assigned 109 patients (41–74 years old) with established type 2 diabetes who abstained from alcohol to receive 150 ml wine (13 g alcohol) or nonalcoholic diet beer (control) each day during a 3-month multicenter trial. The beverages were consumed during dinner. Diet and alcohol consumption were monitored.

RESULTS — During the intervention, 17% of participants (12% from the alcohol group) dropped out, leaving 91 who completed the trial. Within the alcohol group, fasting plasma glucose (FPG) decreased from 139.6 ± 41 to 118.0 ± 32.5 mg/dl after 3 months compared with 136.7 ± 15.4 to 138.6 ± 27.8 mg/dl in the control subjects ($P_v = 0.015$). However, alcohol consumption had no effect on 2-h postprandial glucose levels (difference of 18.5 mg/dl in the control group vs. 17.7 mg/dl in the alcohol group, $P_v = 0.97$). Patients in the alcohol group with higher baseline A1C levels had greater reductions in FPG (age-adjusted correlation −0.57, $P_v < 0.001$). No significant changes were observed in the levels of bilirubin, alkaline phosphatase, alanine aminotransferase, or aspartate aminotransferase, and no notable adverse effects were reported. Participants in the alcohol group reported an improvement in the ability to fall asleep ($P_v < 0.001$).

CONCLUSIONS — Among patients with type 2 diabetes who had previously abstained from alcohol, initiation of moderate daily alcohol consumption reduced FPG but not postprandial glucose. Patients with higher A1C may benefit more from the favorable glycemic effect of alcohol. Further intervention studies are needed to confirm the long-term effect of moderate alcohol intake.

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As summarized in a recent editorial (1), proving the beneficial effect of moderate alcohol intake awaits results of randomized controlled intervention trials. In observational studies, moderate alcohol intake is associated with lower incidence of type 2 diabetes, with an apparent J-shape association (2–4). Also, a recent meta-analysis of patients with type 2 diabetes (5) suggested that moderate alcohol consumption is associated with a lower risk of mortality and coronary heart disease.

Successful long-term control of hyperglycemia decreases diabetes complications (6) and is therefore a major goal in diabetes management. Ethanol metabolism increases the hepatic cytosolic NADH-to-NAD^+ ratio that inhibits gluconeogenesis, a process that is elevated in type 2 diabetes, particularly when impairment of glucose homeostasis is advanced. The decline in hepatic glucose production can provoke hypoglycemia when alcohol is ingested in the fasting state (7). Because ethanol does not appear to affect insulin secretion or glucose disposal directly, a hypoglycemic effect of ethanol is likely to be highly dependent on nutritional state (8). In several small, short-term studies of 5–20 patients with type 2 diabetes, a decrease in plasma glucose concentrations (9–11) with moderate alcohol consumption was reported. However, other studies showed no effect of alcohol on glycemic control (12–14). Inhibition of hepatic glucose production is the major therapeutic effect of established antidiabetic medications, such as metformin, so the potential impact of moderate alcohol consumption on glycemic control in diabetic subjects remains intriguing, but unproven. Therefore, we conducted a 3-month multicenter randomized controlled intervention study of alcohol (150

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Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; FPG, fasting plasma glucose.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

ml wine; 13 g alcohol/day) or a control nonalcoholic beer among 109 patients with type 2 diabetes who had abstained from alcohol and assessed the effect on fasting and postprandial glycemia.

RESEARCH DESIGN AND METHODS

— We enrolled patients from three diabetes units in academic medical centers in Israel (Hadassah Hebrew University Medical Center, Jerusalem; Wolfson Medical Center, Holon; and Soroka University Medical Center, Beer-Sheva). Inclusion criteria were *1*) established diagnosis of type 2 diabetes, *2*) abstinence from alcohol (not >1 drink/week), *3*) age between 40 and 75 years, and *4*) clinically stable condition, with no history of stroke or myocardial infarction or major surgery within the previous 3 months. Exclusion criteria were *1*) >2 insulin injections/day or insulin pump therapy, *2*) triglycerides >500 mg/dl, *3*) A1C >10%, *4*) serum creatinine >2 mg/dl, *5*) liver dysfunction (>2-fold elevation of alanine aminotransferase [ALT] or aspartate aminotransferase [AST]), *6*) evidence of severe diabetes complications (such as proliferative retinopathy or overt nephropathy), *7*) autonomic neuropathy manifested as postural hypotension or hypoglycemia unawareness, *8*) use of drugs that might significantly interact with alcohol such as sedatives, antihistamines, or anticoagulants, *9*) the presence of active cancer or chemotherapy within the past 3 years, *10*) major illness that may require hospitalization, *11*) a high potential for addictive behavior based on physician's assessment or personal or family history of addiction, alcoholism, or alcohol abuse, *12*) pregnancy or lactation (women), or *13*) participation in another trial with active intervention.

The study was coordinated by the International Center for Health and Nutrition, Ben-Gurion University, Beer-Sheva, Israel, and was independently approved by the institutional review boards of each of the three medical centers. All volunteers gave written informed consent and did not receive compensation for their participation.

We screened 201 patients with type 2 diabetes, of whom 126 were eligible. Of these, we randomly assigned 109 and 91 completed the study (see Fig. 1 of the online appendix available at http://dx.doi.org/10.2337/dc07-1103). The randomization design used a 2:1 ratio (intervention-to-control), to obtain better estimates of any adverse effects of the al-

Table 1—*Levels of measurements before and after the 12-week alcohol intervention*

	Alcohol group			Control group		
Variable	Time 0	Time 12	Difference	Time 0	Time 12	Difference
FPG (mg/dl)	139.57 ± 41.04	118.01 ± 32.46*	−21.55 ± 41.18†	136.71 ± 15.4	138.64 ± 27.8	1.92 ± 25.69
2 h postmeal glucose (mg/dl)	128.76 ± 28.01	146.45 ± 33.04	17.68 ± 34.40	135.55 ± 39.48	150.02 ± 52.50	18.46 ± 66.68
Weight (kg)	83.64 ± 15.57	83.66 ± 15.54	0.02 ± 1.93	81.88 ± 17.03	81.40 ± 17.16	−0.48 ± 2.07
Waist (cm)	98.84 ± 12.41	96.40 ± 12.52*	−2.44 ± 5.01	101.53 ± 14.92	100.03 ± 15.23	−1.50 ± 4.67
Systolic blood pressure (mm/Hg)	133.82 ± 15.48	131.32 ± 16.89	−2.50 ± 14.47	127.73 ± 14.23	127.94 ± 15.69	0.21 ± 16.14
Diastolic blood pressure (mm/Hg)	77.66 ± 10.89	76.84 ± 8.76	−0.82 ± 11.42	70.21 ± 9.25	72.31 ± 9.26	2.10 ± 9.79
A1C (%)	7.37 ± 1.21	7.07 ± 00.91‡	−0.29 ± 00.99	7.08 ± 00.96	6.84 ± 0.75	−0.24 ± 00.86
Triglycerides (mg/dl)	135.53 ± 54.48	158.58 ± 85.78	23.05 ± 81.10	146.86 ± 63.1	157.26 ± 120.95	10.40 ± 87.86
HDL cholesterol (mg/dl)	48.95 ± 12.81	46.61 ± 12.30	−2.34 ± 9.85	49.60 ± 12.68	46.60 ± 11.25‡	−3.00 ± 4.55
LDL cholesterol (mg/dl)	96.65 ± 29.23	85.11 ± 28.31*	−11.53 ± 29.22	92.49 ± 30.62	92.61 ± 29.78	0.12 ± 24.03
Bilirubin (mg/dl)	0.54 ± 0.20	0.59 ± 0.26	0.04 ± 0.18	0.61 ± 0.33	0.61 ± 0.24	0.002 ± 0.25
Alkaline phosphatase (units/l)	60.34 ± 19.94	56.84 ± 18.70	−3.50 ± 15.54	62.00 ± 9.45	59.90 ± 10.18	−2.09 ± 6.62
ALT (units/l)	23.44 ± 10.30	33.71 ± 55.93	10.26 ± 54.07	29.23 ± 15.57	26.38 ± 11.42	−2.85 ± 6.37
AST (units/l)	21.23 ± 1.10	30.92 ± 7.69	9.68 ± 47.40	23.92 ± 8.42	23.00 ± 8.14	−0.92 ± 3.79

Data are means ± SD. $n = 91$. *$P_v < 0.01$, within-group difference, paired t test, compared with time 0. †$P_v < 0.05$, between-group differences, group t test of **Δ**s; ‡$P_v < 0.05$, within-group difference.

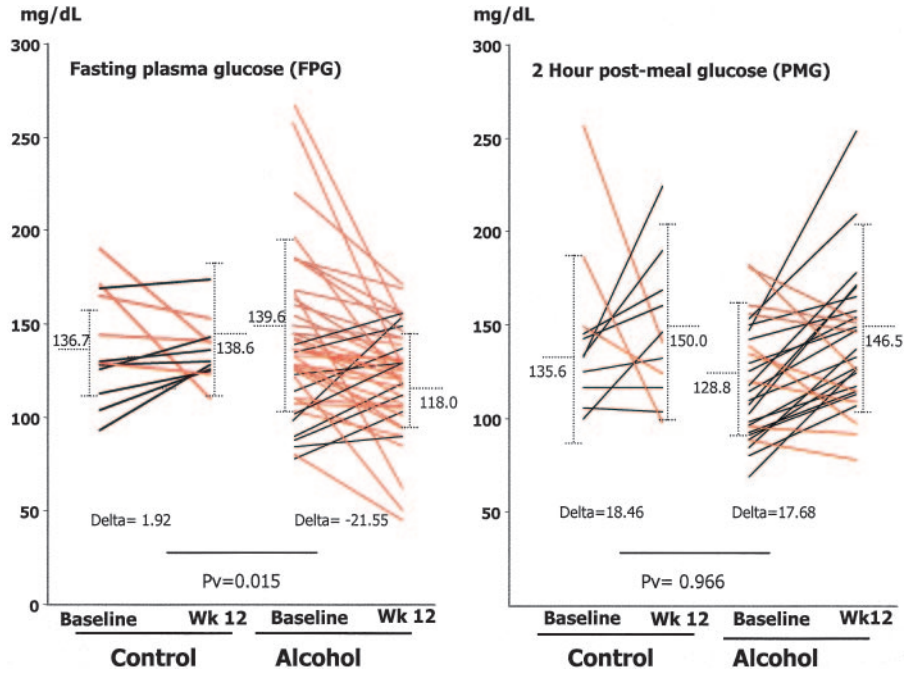

Figure 1—*Individual changes in FPG and 2-h postmeal glucose after 12 weeks of moderate alcohol intervention among patients with type 2 diabetes. Vertical lines indicate means ± SD.*

cohol intervention. Participants met with the nurse study coordinator in the diabetes center on eight occasions during the trial and with the physicians and the dietitians at weeks 1, 7, and 12 (Table 1 of the online appendix). Three months after the end of the study, we interviewed participants who completed the alcohol arm by telephone to assess voluntary continuation of alcohol consumption as well as adverse effects.

Intervention

All participants received individual dietary counseling by registered dietitians trained to work with type 2 diabetic patients. Each dietitian reinforced identical nutritional strategies to achieve glycemic control in both study groups but did not specifically try to promote weight loss. Reinforcement of dietary counseling for both groups was based on the American Diabetes Association recommendations for patients with type 2 diabetes, which include 45–60% calories from carbohydrates, up to 30% from fat (with restriction of saturated fat to <7% of total calories and minimization of trans fat), and 15–20% from protein. Caloric intake was calculated according to age, sex, and level of physical activity. Based on these calculations, patients were instructed to consume an isocaloric diet. To compensate for the calories in the assigned beverages, the alcohol group was instructed to reduce carbohydrates by 100 kcal, but not at dinner, to decrease the likelihood of alcohol-induced hypoglycemia (6). The control group was instructed to deduct 30 kcal from carbohydrates. Participants completed 3-day food diaries and drink pattern questionnaires before each visit to enable the dietitians to monitor adherence to the diet and alcohol intake. Patients assigned to consume alcohol were instructed to start drinking gradually (over a 2-week period) 150 ml of wine (13% alcohol, 13 g) that we provided, using a standard measured glass, during dinner. The patients could choose either dry red (Merlot) or white (Sauvignon Blanc) wine; 75% chose red wine. Participants randomly assigned to the control group were instructed to drink 150 ml of the nonalcoholic diet malt beer we provided, using the same standard measured glass, during dinner. Every other week, the study coordinator provided either three bottles of wine (750 ml each) or two bottles of nonalcoholic diet malt beer (1.5 liters each), after the return of empty bottles from the previous fortnight.

Blood and clinical measurements

Baseline and 12-week blood samples were drawn in the morning, after an 8-h fast. All biochemical determinations were performed in the central laboratories of the medical centers using Olympus analytical equipment and reagents. LDL cholesterol was calculated by the Friedewald formula (15). A1C was determined using COBAS INTEGRA reagents and analytical equipment. A value <5.8% is considered normal. Blood pressure was measured with the subject sitting, after 5 min of rest, using an Omron M41 digital apparatus. Waist circumference was measured halfway between the last rib and the iliac crest. The patients were instructed to measure glucose, preprandially and 2 h postprandially at dinnertime, three times weekly using their own self-glucose monitoring device. The glucometers used were Accutrend Sensor (Roche Diagnostics), Elite (Bayer Diagnostics), or Freestyle (Thera Sense, Alameda, CA).

Statistical analysis

We used χ^2 analyses to determine differences between categorical variables and paired *t* tests to compare changes in measurements within the two groups. In the main analyses, we compared the mean of the individual changes, from baseline to 12 weeks, in the two arms of the trial. We also calculated age-adjusted correlations and performed interaction tests between the intervention groups and strata of sex, median BMI, and median age. The levels of individual postmeal glucose represent an average of three reports, taken 2 h after dinner in the same week. We compared the proportion of positive responders in both groups to the following question: "Do you think that, since the beginning of this study, the addition of the drink to your dinner was associated with an increase in the following symptoms/adverse effects?" Statistical analyses were performed using SPSS software (version 14.0).

RESULTS — The randomly assigned patients, 61 men and 48 women, ranged in age from 41 to 74 years, had an average fasting plasma glucose (FPG) level of 144.5 mg/dl, A1C of 7.39%, blood pressure of 133.7/76.5 mm/Hg, and BMI of 30.1 kg/m^2. These characteristics were similarly distributed between the randomized groups, as were other parameters such as duration of the disease, smoking status, physical activity, regular consumption of nutritional supplements, waist circumference, and years of education (Table 2 of the online appendix). After random assignment but before the intervention began, 12 participants withdrew from the trial, 5 (7%) from the alcohol group and 7 (21%) from the control group. During the intervention, 4 addi-

tional participants withdrew from the alcohol group and 2 from the control group. The 18 patients who withdrew from the study (12% of the intervention and 26% of the control groups) were generally similar to the 91 patients who completed the study, but they had significantly higher baseline levels of FPG (167 vs. 140 mg/dl) and were younger (Table 3 of the online appendix).

The individual changes in FPG and 2-h postmeal glucose between baseline and at the end of the trial are shown in Fig. 1. The alcohol group experienced a significant 9.2% decrease in FPG levels, dropping from 139.6 ± 41 at baseline to 118.0 ± 32.5 mg/dl after 3 months ($P_v <$ 0.001), whereas there was no material change in FPG levels in the control group (136.7 ± 15.4 at baseline and 138.6 ± 27.8 mg/dl at week 12, $P_v = 0.783$). The difference between the groups was significant ($P_v = 0.015$). The postprandial values represent an average of three self-measurements that were taken after dinner, at baseline, and during weeks 11–12. We observed nonsignificant increases in the 2-h postmeal glucose levels of similar magnitude in both groups (18.5 in the control group vs. 17.7 in the alcohol groups, *P* for difference = 0.97). Within the alcohol group, but not among control subjects (Fig. 2), we found a significant inverse correlation between baseline levels of A1C and changes of FPG levels (age-adjusted correlation −0.567, $P_v <$ 0.001), suggesting that patients with type 2 diabetes with higher baseline A1C levels had greater reductions in FPG after moderate alcohol consumption. We found no modification of the alcohol effect by sex, age, BMI, or specific medical center (data not shown), although the statistical power to observe such interactions was limited.

We observed significant decreases (Table 2 of the online appendix) in levels of A1C, LDL cholesterol, and waist circumference in the alcohol group and an unexpected significant reduction in HDL cholesterol in the control group after 12 weeks compared with baseline levels. However, none of these changes differed significantly between the two groups. We found no significant changes in weight, blood pressure, or triglycerides among patients in either group and no material changes in levels of bilirubin, alkaline phosphatase, ALT, or AST.

We elicited reports of symptoms (Fig. 2 of the online appendix) that participants attributed to the intervention. In the alcohol group, one woman dropped out because of gastric pain and 5% reported episodes of hypoglycemia, headaches, or muscle weakness, symptoms that were not reported in the control group. No other adverse effects were reported. Participants in the alcohol group (8%) but none in the control group reported increased sexual desire. The only item that differed significantly was improved ability to fall asleep in the alcohol group compared with control subjects ($P_v < 0.001$).

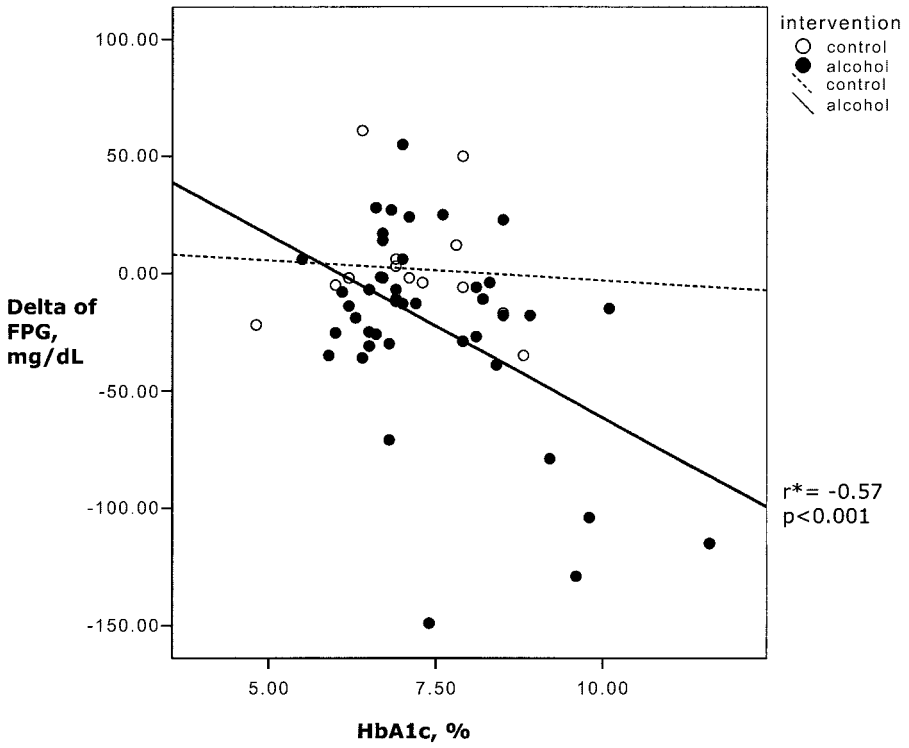

Figure 2—*Correlations between baseline levels of A1C and change of FPG levels after 12 weeks of moderate alcohol intervention among patients with type 2 diabetes. *Age-adjusted correlation among the alcohol group.*

Three months after the study ended, 61% of the participants in the alcohol group reported that they thought that the alcohol was beneficial to them, and 49% reported continuing to drink alcohol in moderation (frequency ranging from one drink a week to one drink a day). None reported an increase of the quantity of alcohol consumed.

CONCLUSIONS — In the present randomized trial among patients with type 2 diabetes who had previously abstained from alcohol, we showed that moderate alcohol consumption significantly decreased fasting but not postprandial glucose levels. Those with higher baseline A1C levels appeared to benefit more. Initiating moderate daily alcohol consumption in type 2 diabetic patients aged >40 years who had previously been abstainers caused no notable adverse effects or changes in liver function biomarkers during the 3-month intervention.

Several limitations of the study warrant consideration. Neither the participants nor the diabetes clinic staff could be blinded to the intervention (alcohol versus control nonalcoholic beverage), and although adherence was good, the dropout rates were not negligible. However, participants who dropped out generally had clinical profiles similar to those of participants completing the study, and, in fact, two-thirds of the dropouts occurred immediately after the randomization and before the intervention began, and rates were higher among control subjects, suggesting that adverse effects of alcohol caused few if any dropouts. The 3-month intervention period, although longer than most alcohol trials, could not capture all of the possible long-term adverse or beneficial effects of alcohol, limiting our ability to draw conclusions about the long-term risks and benefits. We believe our inclusion criteria (particularly age >40 years and screening for past addictive behavior) largely limited the danger of promoting alcohol addictive behavior. In a telephone interview 3 months after the

end of the trial, all participants reported alcohol consumption of one drink a day or less. The alcohol dose of 13 g/day may be a less than optimal dose to achieve maximal effects in patients with type 2 diabetes. Red and white wine presumably contain different amounts of polyphenols, possibly confounding the effects of the alcohol per se. Finally, we assayed fasting and postmeal glucose levels and A1C but have no data on levels of insulin and glucagon, degree of insulin resistance, or hepatic glucose output. This lack of data limits our ability to dissect out the relevant importance of mechanisms mediating the alcohol-induced decrease in FPG and the differential effects on FPG and postprandial glucose.

There are several strengths to this study: The number of participants is larger than that of most other alcohol intervention trials and adherence to the intervention protocols was high. Most importantly, the randomized trial design permitted assessment of the independent effect of initiating moderate alcohol consumption in abstainers. Nutritional counseling to both groups of participants was adjusted for the added calories, but new dietary instructions aimed to promote weight loss were not introduced.

Moderate alcohol consumption has been associated with a lower risk of cardiovascular disease (16) and type 2 diabetes (2,17). The apparent beneficial effects for cardiovascular disease are probably mediated via effects on lipid metabolism (18), coagulation, fibrinolysis (19), and insulin sensitivity (20,21). We have previously shown (22) that among >700 men with type 2 diabetes, moderate alcohol intake was associated with decreasing levels of inflammatory biomarkers (soluble tumor necrosis factor receptor-2, soluble intercellular adhesion molecule-1, and fibrinogen) as well as elevated circulating levels of adiponectin. Prospective studies showed an inverse relationship between alcohol consumption and diabetes incidence, with moderate drinkers having a 43–46% reduction in risk for diabetes compared with nondrinkers (23–25). In addition, alcohol is linked to lower cardiovascular risk among patients with type 2 diabetes (26). In a recent meta-analysis of cohort studies among patients with diabetes (4), alcohol consumers had a 21–36% lower total mortality rate and a 25–66% lower rate of total and fatal coronary heart disease than abstainers. The magnitude of these associations is stronger than that seen in the general population (27).

Although beneficial effects of moderate alcohol consumption have been strongly suggested by observational studies, data from randomized trials of alcohol, especially among patients with type 2 diabetes, are sparse. In a randomized controlled crossover trial (28) of 63 healthy postmenopausal women over 8 weeks, consumption of 30 g/day of alcohol (two drinks per day) reduced insulin and triglyceride concentrations and improved insulin sensitivity in these nondiabetic women, but fasting glucose concentrations were not materially affected. In a trial among patients with diabetes after a first myocardial infarction (29), red wine taken with meals significantly reduced oxidative stress and proinflammatory cytokines.

The major glycemic effect in our trial was a decrease in fasting, but not postmeal, plasma glucose levels. The mechanisms for this effect probably involve enhanced insulin secretion (3) and the well-documented effect of alcohol metabolism, which, by increasing the hepatic cytosolic NADH-to-NAD^+ ratio, inhibits gluconeogenesis, a process largely controlling fasting, rather than postmeal, glycemia. The nonsignificant increase of postprandial glucose levels could be a consequence of increased consumption of simple carbohydrates in the evening meal. The contribution of increased flux through the gluconeogenesis pathway to hyperglycemia is a characteristic of dysregulated glucose homeostasis in diabetes. Thus, it is plausible that patients with higher A1C have elevated gluconeogenic flux and, hence, exhibit more pronounced fasting hypoglycemic effects when moderate alcohol consumption is started.

In our study, patients in the alcohol group significantly reduced their waist circumference and LDL cholesterol and A1C levels, but these changes were not statistically significant compared with the change in these parameters in the placebo group. Intriguingly, we observed that diabetic subjects consuming 13 g alcohol daily for 3 months showed no increase in HDL. The likely explanations for this observation are related to the alcohol dose or duration or to unique characteristics of the study population. Significant increases in HDL could be observed in healthy men as early as 17 days after initiation of 40 g/day of alcohol (30). Alternatively, it is possible that the HDL-elevating effect of alcohol is less readily detectable among diabetic subjects, particularly when they are also treated with glucose- and lipid-lowering medications. This notion is supported by observations made during a previously mentioned trial among diabetic subjects after a myocardial infarction, in which a significant increase in HDL was observed only after 9 months of alcohol intake (R. Marfella, personal communication). Thus, in the diabetic population, alcohol apparently exerts a more rapid glucose-lowering effect, whereas the elevation in HDL requires more prolonged intervention. In doses shown in epidemiological studies to confer cardiovascular disease and glycemic benefits, not all metabolic changes attributed to alcohol can be captured within 3 months in patients with type 2 diabetes. Longer intervention studies are needed to determine the long-term efficacy and safety of initiating moderate alcohol intake among abstainers with type 2 diabetes, with assessment of clinical or intermediate outcomes.

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