Acute Alcohol Consumption Improves Insulin Action Without Affecting Insulin Secretion in Type 2 Diabetic Subjects

ANGELO AVOGARO, MD, PHD[1]
RICHARD M. WATANABE, PHD[2]
ALESSANDRA DALL'ARCHE, MD[1]
SAULA VIGILI DE KREUTZENBERG, MD, PHD[1]
ANTONIO TIENGO, MD[1]
GIOVANNI PACINI, DSC[3]

OBJECTIVE — Long-term exposure to alcohol is associated with an improvement in insulin sensitivity. At this time, however, there is no definitive proof that alcohol per se has an effect on the insulin sensitivity index (S_i) in type 2 diabetes patients. The aim of the present study was to assess the role of acute moderate alcohol intake on insulin sensitivity and insulin secretion in comparable subjects with and without type 2 diabetes.

RESEARCH DESIGN AND METHODS — Frequently sampled intravenous glucose tolerance tests (FSIGTs) were performed twice on eight healthy and eight type 2 diabetic volunteers. Forty grams of alcohol (vodka 40% wt/vol) or tap water were sipped from time −60 min to the end of the FSIGT.

RESULTS — Lactate area under the curve (AUC) was higher in both groups during the alcohol study than in the control study. Free fatty acid (FFA) AUC was higher in type 2 diabetic subjects than in control subjects; alcohol slightly reduced FFA by 17% in control subjects (34 ± 4 mmol · min^{-1} · l^{-1}; $P = 0.1$) but significantly decreased FFA by 23% in type 2 diabetic subjects (54 ± 10; $P = 0.007$). β-Cell response was markedly reduced in type 2 diabetic subjects regardless of the type of study. Alcohol significantly increased S_i in both groups.

CONCLUSIONS — Acute alcohol consumption improves insulin action without affecting β-cell secretion. This effect may be partly due to the inhibitory effect of alcohol on lipolysis. Alcohol intake increases insulin sensitivity and may partly explain both the J-shaped relationship between the prevalence of diabetes and the amount of alcohol consumption and the decreased mortality for myocardial infarction.

Diabetes Care 27:1369–1374, 2004

Reports consistently suggest that the intake of a significant amount of alcohol induces a state of insulin resistance, assessed either with oral or intravenous glucose tolerance tests (1–3). However, a large body of epidemiological evidence from cross-sectional studies also suggests long-term exposure to alcohol is associated with an improvement in insulin sensitivity (4–8). Furthermore, a substantial number of prospective studies indicate that light to moderate chronic alcohol intake improves glucose metabolism and is protective against coronary artery disease in subjects with type 2 diabetes (9–13). Historically, alcohol use by the diabetic patient has been controversial; however, in light of these premises, moderate alcohol consumption should, at least in part, contribute to improved insulin sensitivity. Indeed, moderate alcohol intake taken with a meal has been shown to have little or no effect on postprandial glycemic excursions, whereas heavy intake yields opposite effects (14–20). At this time, however, there is no definitive proof that alcohol per se has an effect on insulin sensitivity in patients with type 2 diabetes. Therefore, the aim of the present study was to test the hypothesis that acute alcohol intake might improve insulin sensitivity and secretion in comparable subjects with and without type 2 diabetes. Moreover, we wished to understand the possible mechanism(s) through which alcohol may affect insulin action.

RESEARCH DESIGN AND METHODS

— Frequently sampled intravenous glucose tolerance tests (FSIGTs) were performed twice on eight (six men and two women) healthy subjects and on eight (seven men and one woman) subjects with type 2 diabetes. All study subjects gave written informed consent before participation. Clinical characteristics are shown in Table 1. All subjects were customary wine drinkers (<500 ml of wine [10–12% wt/vol] per day) and continued their customary daily alcohol intake (130 ± 32 ml of wine per day) during the 30 days before the study started. All participants underwent a full medical history and physical examination and followed an isocaloric diet recorded by a dietitian with three meals daily (50% carbohydrate, 35% fat, and 15% protein) for at least 30 days before the study. The subjects were in good health and maintained a regular lifestyle with no excessive exercise or smoking. Subjects with type 2 diabetes were free from clinical and instrumental evidence of atherosclerotic cardiovascular disease. Glycemic control was achieved with diet alone or with diet plus sulfonylurea or biguanide preparations. Pharmacological treatment for hyperglycemia was stopped at least 3 days before the study; antihypertensive drugs

From the [1]Department of Experimental Medicine, University of Padova Medical School, Padova, Italy; the [2]Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, California; and the [3]Metabolic Unit, Institute of Biomedical Engineering, National Research Council, Padova, Italy.

Address correspondence and reprint requests to Angelo Avogaro, MD, Dipartimento Medicina Sperimentale Policlinico–Via Giustiniani 2, 35128 Padova, Italy. E-mail: angelo.avogaro@unipd.it.

Received for publication 14 August 2003 and accepted in revised form 22 February 2004.

Abbreviations: AIR_g, acute insulin response to glucose; AUC, area under the curve; FFA, free fatty acid; FSIGT, frequently sampled intravenous glucose tolerance test.

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

Table 1—*Subjects' clinical characteristics*

	Control subjects	Type 2 diabetic subjects	*P*
Age (years)	58 ± 3	65 ± 2	NS
Sex (women/men)	2/6	1/7	NS
Duration of diabetes (years)	—	9 ± 2	
BMI (kg/m^2)	28.9 ± 2.4	29.3 ± 0.9	NS
Waist circumference (cm)	93 ± 2	98 ± 4	NS
Systolic blood pressure (mmHg)	137 ± 3	139 ± 5	NS
Diastolic blood pressure (mmHg)	81 ± 2	83 ± 3	NS
HbA_{1c} (%)	—	8.2 ± 0.6	
Plasma cholesterol (mmol/l)	5.12 ± 0.28	5.64 ± 0.31	NS
Plasma HDL cholesterol (mmol/l)	1.24 ± 0.052	1.40 ± 0.13	NS
Plasma triglycerides (mmol/l)	1.13 ± 0.18	1.62 ± 0.18	NS

Data are means ± SEM.

were continued. All participants were asked to fast for at least 12 h before the examination. All subjects were studied at isoglycemia. The Ethical Committee of the School of Medicine of the University of Padova approved the experimental protocol.

Each subject participated in two tests (the study with alcohol and the control study) in random order on separate days. At least 1 week elapsed between two consecutive tests. Subjects were admitted to the University Hospital of Padova after an overnight fast. A 20-gauge butterfly needle was inserted into a dorsal hand vein at 0730, and a blood sample was taken. The hand was then placed in a box heated at 60°C to arterialize venous blood. The patency of the needle was maintained with a controlled saline infusion throughout the study. An 18-gauge cannula was then placed into the controlateral antecubital vein for the injection of glucose and insulin.

For the alcohol study, 40 g of alcohol (administered as vodka 40% wt/vol) were sipped from time −60 min until the end of the FSIGT (180 min) to allow steady-state blood alcohol concentrations. Blood samples for hormones and substrate measurements were obtained 30 min, 15 min, and immediately before the glucose injection, which occurred at 0830 (time 0). The glucose load (0.3 g/kg body wt) was administered over 1 min. Frequent samples for plasma glucose, lactate, insulin, C-peptide, and free fatty acid (FFA) concentrations were obtained at: 2, 3, 4, 5, 6, 8, 10, 12, 15, 20, 25, 30, 35, 40, 60, 80, 100, 120, 140, and 180 min. At 20 min, plasma insulin concentration was enhanced by an exogenous square-wave intravenous infusion of regular insulin (0.03 U/kg) lasting 5 min. During the control study, a volume of tap water similar to that for the alcohol study was sipped throughout the test.

Analytical methods

Plasma glucose was measured with the glucose oxidase method on a Beckman glucose analyzer. Blood lactate was measured with a fluorimetric technique that had an overall coefficient of variation (CV) of 5.2 ± 3.8% (21). The total FFA concentration was determined with a microenzymatic technique (CV 6.9 ± 2.3%) (22). Plasma insulin and C-peptide were measured by conventional radioimmunoassay (6 ± 4% and 5.3 ± 3.2%, respectively) (23). Blood ethanol was determined with an enzymatic technique (12 ± 8%). Glycated hemoglobin was assayed with a chromatographic method (24).

FSIGT data analysis

Total β-cell secretion per unit volume is indirectly described by the total area under the concentration curve (AUC) of C-peptide concentration, by the acute insulin response to glucose (AIR_g) from 3 to 10 min, and by the AUC of insulin during the early response (0–15 min). Parameter insulin sensitivity index (S_i) is obtained from FSIGT data using minimal model analysis, which is a well-accepted measure of whole-body insulin sensitivity (25). The product $S_i \times AIR_g$ provides the disposition index, an index of β-cell function, or compensation (26). This index is of relevance for understanding the physiological adaptation of insulinemia to the ambient insulin sensitivity.

Calculations and statistical analysis

AUC were calculated by integrating with the trapezoidal rule in the early "endogenous" phase (0–15 min) or during the entire 180 min of the test. All data are presented as mean ± SEM. Statistical comparisons between the different groups and within the groups were performed using the unpaired and paired Student's *t* test, respectively.

RESULTS — Blood alcohol levels (Fig. 1) were constant during the FSIGT of the alcohol study in both control and type 2 diabetic subjects. No difference was detected among groups: in control subjects blood alcohol levels were 4.5 ± 0.3 mg/dl (95% CI 3.8–5.1), 4.9 ± 0.3 (4.2–5.6), and 4.5 ± 0.2 (4.1–4.9) at 60, 120, and 180 min, respectively; in type 2 diabetic subjects, blood alcohol levels were 3.6 ± 0.2 mg/dl (95% CI 3.0–4.1), 5.4 ± 0.4 (4.6–6.3), and 3.5 ± 0.2 (2.9–4.1) at 60, 120, and 180 min, respectively. Basal val-

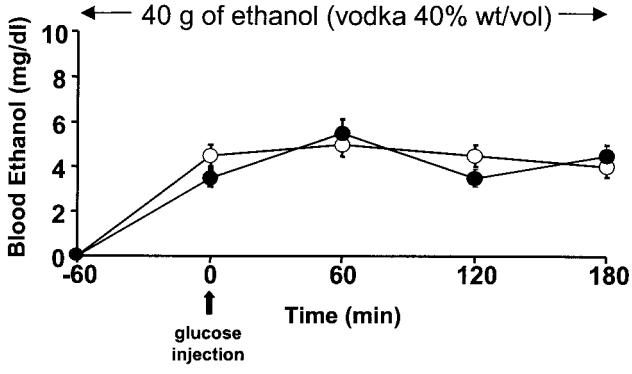

Figure 1—*Blood ethanol levels during the FSIGT with alcohol in control subjects (○) and type 2 diabetic subjects (●). No significant difference was detected at any data point.*

Table 2—*Basal levels before the FSIGT*

	Control subjects		Type 2 diabetic subjects	
	Basal	Alcohol	Basal	Alcohol
Glucose (mmol/l)	5.5 ± 0.2	5.6 ± 0.2	8.8 ± 0.8*	9.1 ± 0.8*
Insulin (pmol/l)	40 ± 7	142 ± 17	59 ± 7	67 ± 16
C-peptide (nmol/l)	0.549 ± 0.062	0.602 ± 0.119	0.615 ± 0.092	0.569 ± 0.079
Lactate (mmol/l)	0.637 ± 0.042	0.616 ± 0.050	0.782 ± 0.133	0.999 ± 0.145†
FFAs (mmol/l)	0.318 ± 0.044	0.359 ± 0.020	0.637 ± 0.094*	0.547 ± 0.112

Data are means ± SEM. No value was statistically different from the corresponding one of the test without alcohol (control study). *$P < 0.01$; †$P < 0.05$; type 2 diabetic vs. control subjects.

ues (Table 2) showed no difference in fasting conditions between the two groups except for glucose and FFA, which were higher in type 2 diabetes. No difference was observed for any basal variable between the two studies within groups. Time courses of FSIGT glucose concentrations and the relative insulin AUC are shown in Fig. 2.

Lactate time courses are reported in Fig. 3. Total lactate AUC in control subjects was 126 ± 10 mmol · min^{-1} · l^{-1} without alcohol compared with 156 ± 9 mmol · min^{-1} · l^{-1} with alcohol (P = 0.075). In type 2 diabetic subjects, lactate AUC significantly increased with alcohol from 150 ± 24 to 228 ± 30 mmol · min^{-1} · l^{-1} (P = 0.0075). With alcohol, lactate AUC was higher in type 2 diabetic subjects compared with control subjects (P = 0.038).

Time courses of FFA are shown in Fig. 4. AUC was higher in type 2 diabetic subjects than in control subjects in the control study (70 ± 13 vs. 41 ± 3 mmol · min^{-1} · l^{-1}; P = 0.04). Alcohol slightly reduced FFA by 17% in control subjects (34 ± 4 mmol · min^{-1} · l^{-1}; P = 0.1), whereas alcohol significantly lowered FFA by 23% in type 2 diabetes (54 ± 10 mmol · min^{-1} · l^{-1}; P = 0.007), reaching levels not different (P = 0.09) from those of control subjects.

Glucose-stimulated insulin and C-peptide responses were markedly reduced in type 2 diabetic subjects, regardless of the type of study (Table 3). Similarly, AIR_g was much lower in type 2 diabetic subjects, but no difference was observed when considering the total AUC of insulin and C-peptide in both groups and between both studies within groups. This means that type 2 diabetic subjects had lost the early phase but were still able to release an amount of hormone similar to that of control subjects during the second longer phase (see C-peptide AUC from 20 to 180 min in Table 3). In summary, none of these indicators of β-cell function were affected by alcohol in any group.

S_i was significantly lower in type 2 diabetic subjects (Table 3). Alcohol increased S_i in both groups, such that the S_i of type 2 diabetic subjects became not significantly different from that of control subjects after alcohol (P = 0.083) and virtually similar to that of control subjects in the control study (P = 0.662). No correlation was found between S_i and lactate ($r = -0.11$; P = 0.55), whereas a negative regression was found between S_i and FFA ($r = -0.36$; P = 0.04). The disposition index, which was significantly lower in type 2 diabetic than in control subjects, was increased with alcohol in both groups, although it remained lower in type 2 diabetes. No significant differences were observed in glucose effectiveness.

CONCLUSIONS — The present study shows that alcohol intake improves insulin sensitivity and glucose tolerance in type 2 diabetic subjects, and this amelioration is proportionally greater compared with matched healthy volunteers. Moreover, alcohol in type 2 diabetic patients acts by increasing lactate and decreasing FFA without any direct action on insulin secretion.

Previous population studies consistently showed that light-to-moderate alcohol consumption is associated with an amelioration of glucose metabolism. Recently, we have shown that alcohol intake was positively correlated with insulin-

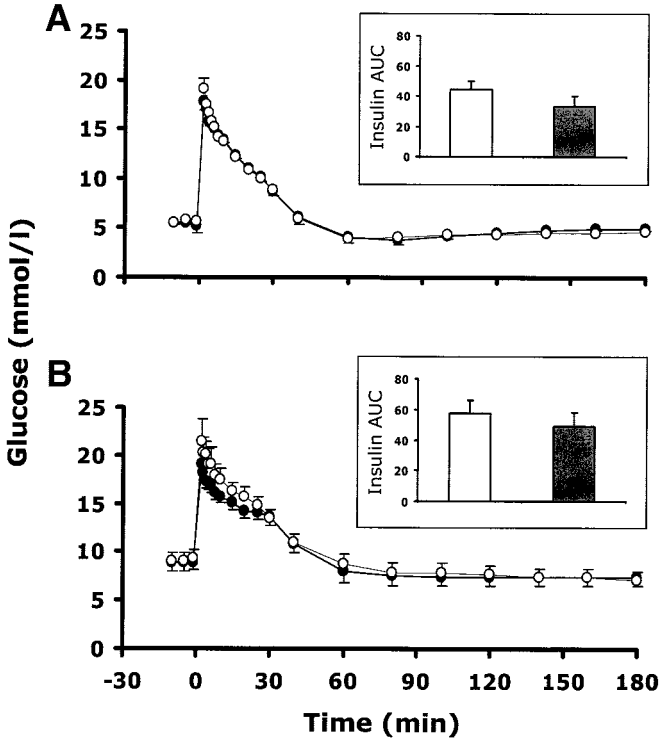

Figure 2—*Time course of plasma glucose concentration during intravenous glucose tolerance test without (○) and with (●) alcohol consumption in control* (A) *and type 2 diabetic* (B) *subjects. Glucose bolus (0.3 g/kg) is given at time 0, and insulin (0.03 U/kg) is infused from 20 to 25 min.* Insets *show the comparison between the values of the total insulin area (10^3 pmol/l in 180 min) under the concentration curves* (empty bars*: without alcohol;* solid bars*: with alcohol); no significant difference was detected within groups.*

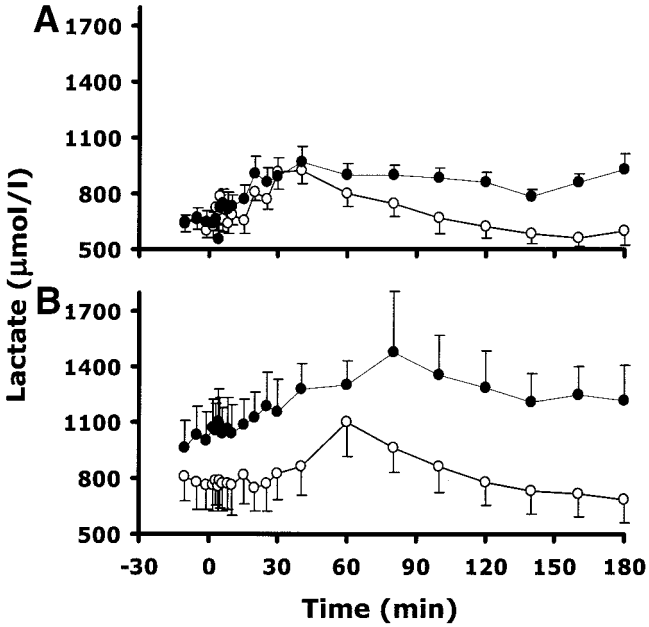

Figure 3—*Time course of plasma lactate concentration during intravenous glucose tolerance test without (○) and with (●) alcohol consumption in control* (A) *and type 2 diabetic* (B) *subjects.*

mediated glucose uptake (27); the present study demonstrates a similar positive effect in type 2 diabetes. Alcohol has many different effects on carbohydrate metabolism, and results from different studies often have appeared contradictory (28). However, in nondiabetic volunteers, alcohol has been reported to increase skeletal muscle insulin sensitivity. Unfortunately, persuasive data on type 2 diabetes has been lacking.

This study convincingly shows that alcohol intake improves insulin action and the disposition index not only in healthy volunteers but also in type 2 diabetic subjects. Therefore, it is noteworthy that alcohol can overcome the state of insulin resistance, the typical metabolic feature of these patients, without affecting β-cell secretion. Indeed, studies have shown that moderate alcohol intake with a meal has little or no effect on postprandial glycemic excursions (14–19). This study for the first time specifically quantifies this improvement and offers some hypothesis for the alcohol-induced amelioration of insulin sensitivity. In the normal subjects, a plausible explanation comes from our FFA findings. We not only confirm that alcohol intake has an antilipolytic effect, but we extend this observation to diabetic patients despite their higher FFA levels. Therefore, we speculate that alcohol is able to improve substrate competition in both nondiabetic and diabetic subjects as supported by the inverse, albeit weak, correlation between S_i and plasma FFA levels. It is unclear whether diabetic patients are more responsive to both the antihyperglycemic and antilipolytic effect of alcohol intake, justifying future studies. Lactate has been shown to be powerfully antilipolytic (29). Therefore, the differential response to alcohol may partly be explained by the higher alcohol-induced lactate concentrations observed during the alcohol studies in type 2 diabetic subjects compared with control subjects. Another hypothesis may involve the role of the inhibitory effect of moderate alcohol intake on growth hormone secretion, but this effect has not been explored in the present study (30,31).

Changes of insulin resistance occur without a significant effect of alcohol on β-cell secretion. No change in insulin secretory pattern was observed when estimated either as the AIR_g or as the area under the C-peptide concentration curve in both groups. Therefore, alcohol does not cause significant acute modifications of β-cell function. We have previously shown that alcohol specifically enhances the sensitivity of the second-phase insulin secretion irrespective of the timing of alcohol administration (32). The lack of an effect on β-cell secretory capacity may be determined by the modality of alcohol administration, i.e., slowly sipping versus acute load.

In the absence of a history of alcohol-related problems or other contraindications, we would encourage the use of small amounts of alcohol to improve insulin sensitivity and, perhaps, stave off

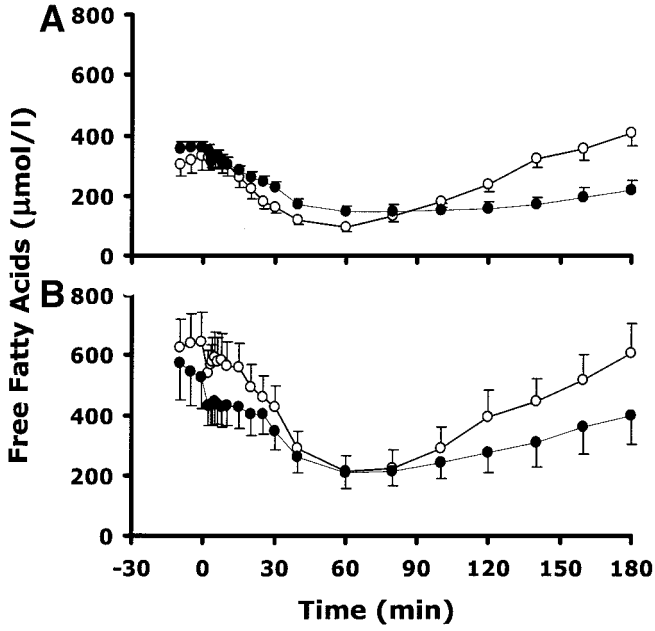

Figure 4—*Time course of plasma FFA concentration during intravenous glucose tolerance test without (○) and with (●) alcohol consumption in control* (A) *and type 2 diabetic* (B) *subjects.*

Table 3—*Insulin and C-peptide AUC for different time intervals and metabolic parameters during FSIGT without (control) and with alcohol*

Parameter	Unit	Control subjects			Type 2 diabetic subjects			*P* value between control studies	*P* value between alcohol studies
		Control study	Alcohol study	*P*	Control study	Alcohol study	*P*		
Total insulin AUC	pmol/l in 180 min	44.1 ± 5.9	33.4 ± 6.5	NS	57.1 ± 8.8	48.6 ± 9.1	NS	NS	NS
Total C-peptide AUC	nmol/l in 180 min	149 ± 19	175 ± 29	NS	130 ± 23	144 ± 24	NS	NS	NS
Suprabasal insulin AUC (early phase [0–15])	pmol/l in 15 min	0.6 ± 0.12	0.72 ± 0.24	NS	0.24 ± 0.06	0.30 ± 0.12	NS	0.003	0.009
Suprabasal C-peptide AUC (early phase [0–15])	nmol/l in 15 min	13.9 ± 2.6	16.6 ± 4.3	NS	9.3 ± 1.3	8.9 ± 1.3	NS	0.0006	0.004
Total C-peptide AUC (second phase [20–180])	nmol/l in 180 min	120 ± 16	141 ± 23	NS	115 ± 21	129 ± 23	NS	NS	NS
Glucose effectiveness	min^{-1}	0.027 ± 0.002	0.025 ± 0.003	NS	0.019 ± 0.003	0.023 ± 0.003	NS	NS	NS
S_i	10^{-4} min^{-1} · μU^{-1} · ml	2.88 ± 0.76	4.52 ± 0.95	0.028	0.93 ± 0.26	2.47 ± 0.57	0.009	0.029	NS
AIR_g	pmol/l	232 ± 62	278 ± 24	NS	16 ± 7	23 ± 8	NS	0.003	0.009
Disposition index	10^{-4} min^{-1}	83 ± 19	157 ± 38	0.025	3 ± 2	10 ± 4	0.022	0.008	0.007

Data are means ± SEM unless otherwise indicated. Time intervals (minutes) during which the variables are calculated are reported in brackets.

potential cardiac complications of diabetes. Our recommendations are supported by several large studies showing a reduced risk of coronary heart disease among diabetic patients who consume alcohol compared with those who do not.

Study limitations

This study assessed the effect of acute alcohol administration in daily consumers of moderate amounts of alcohol in type 2 diabetic and healthy subjects. Therefore, we did not provide information on how lactate and FFA concentrations are influenced by diabetes itself during alcohol intake in nondrinking diabetic patients. However, we elected to exclude from this study subjects who were not habitual drinkers to avoid the confounding effects of alcohol intoxication.

This is an acute study, therefore, we can only provide information on the metabolic effect of this amount of alcohol only over a limited amount of time without knowing whether the same amount, administered chronically, could potentially affect blood pressure (33,34) or other risk factors for coronary artery disease, such as triglycerides, which are known to be affected by alcohol (35,36). We also cannot determine whether the same amount of alcohol consumed in a more limited amount of time would have given differing results.

In conclusion, we have found that acute moderate alcohol consumption improves insulin action without affecting β-cell secretion in type 2 diabetic patients. This effect may be partly due to the inhibitory effect of alcohol on lipolysis. These evidences may explain previous findings that indicate that alcohol intake is associated with an amelioration in glucose metabolism.

References

1. Yki-Jarvinen H, Nikkila EA: Ethanol decreases glucose utilization in healthy man. *J Clin Endocrinol Metab* 61:941–945, 1985
2. Wannamethee SG, Shaper AG, Perry IJ, Alberti KG: Alcohol consumption and the incidence of type II diabetes. *J Epidemiol Community Health* 56:542–548, 2002
3. Avogaro A, Valerio A, Miola M, Crepaldi C, Pavan P, Tiengo A, Del Prato S: Ethanol impairs insulin-mediated glucose uptake by an indirect mechanism. *J Clin Endocrinol Metab* 81:2285–2290, 1996
4. Cooper DE, Goff DC Jr, Bell RA, Zaccaro D, Mayer-Davis EJ, Karter AJ: Is insulin sensitivity a causal intermediate in the relationship between alcohol consumption and carotid atherosclerosis: the insulin resistance and atherosclerosis study. *Diabetes Care* 25:1425–1431, 2002
5. Dixon JB, Dixon ME, O'Brien PE: Alcohol consumption in the severely obese: relationship with the metabolic syndrome. *Obes Res* 10:245–252, 2002
6. Goude D, Fagerberg B, Hulthe J, AIR Study Group: Alcohol consumption, the metabolic syndrome and insulin resistance in 58-year-old clinically healthy men (AIR study). *Clin Sci* 102:345–352, 2002
7. Bell RA, Mayer-Davis EJ, Martin MA, D'Agostino RB Jr, Haffner SM: Associations between alcohol consumption and insulin sensitivity and cardiovascular disease risk factors: the Insulin Resistance and Atherosclerosis Study. *Diabetes Care* 23:1630–1636, 2000
8. Zilkens RR, Burke V, Watts G, Beilin LJ, Puddey IB: The effect of alcohol intake on insulin sensitivity in men: a randomized controlled trial. *Diabetes Care* 26:608–612, 2003
9. Nakanishi N, Suzuki K, Tatara K: Alcohol consumption and risk for development of impaired fasting glucose or type 2 diabetes in middle-aged Japanese men. *Diabetes Care* 26:48–54, 2003
10. Wannamethee SG, Camargo CA Jr, Manson JE, Willett WC, Rimm EB: Alcohol drinking patterns and risk of type 2 diabetes mellitus among younger women. *Arch Intern Med* 163:1329–1336, 2003
11. Mukamal KJ, Rimm EB: Alcohol's effects on the risk for coronary heart disease. *Alcohol Res Health* 25:255–261, 2001
12. Tanasescu M, Hu FB, Willett WC, Stampfer MJ, Rimm EB: Alcohol consumption and risk of coronary heart disease among men with type 2 diabetes mellitus. *J Am Coll Cardiol* 38:1836–1842, 2001
13. Rimm E: Alcohol and coronary heart disease: can we learn more? *Epidemiology* 12: 380–382, 2001
14. Bell DS: Alcohol and the NIDDM patient. *Diabetes Care* 19:509–513, 1996

15. Koivisto VA, Tulokas S, Toivonen M, Haapa E, Pelkonen R: Alcohol with a meal has no adverse effects on postprandial glucose homeostasis in diabetic patients. *Diabetes Care* 16:1612–1614, 1993
16. Gin H, Morlat P, Ragnaud JM, Aubertin J: Short-term effect of red wine (consumed during meals) on insulin requirement and glucose tolerance in diabetic patients. *Diabetes Care* 15:546–548, 1992
17. Christiansen C, Thomsen C, Rasmussen O, Balle M, Hauerslev C, Hansen C, Hermansen K: Wine for type 2 diabetic patients? *Diabet Med* 10:958–961, 1993
18. Christiansen C, Thomsen C, Rasmussen O, Hauerslev C, Balle M, Hansen C, Hermansen K: Effect of alcohol on glucose, insulin, free fatty acid and triacylglycerol responses to a light meal in non-insulin-dependent diabetic subjects. *Br J Nutr* 71: 449–454, 1994
19. Gin H, Rigalleau V, Caubet O, Masquelier J, Aubertin J: Effects of red wine, tannic acid, or ethanol on glucose tolerance in non-insulin-dependent diabetic patients and on starch digestibility in vitro. *Metabolism* 48:1179–1183, 1999
20. Ben GP, Gnudi L, Maran A, Gigante A, Duner E, Iori E, Tiengo A, Avogaro A: Effects of chronic alcohol intake on carbohydrate and lipid metabolism in type II noninsulin dependent diabetic subjects. *Am J Med* 90:70–76, 1991
21. Lloyd B, Burrin J, Smythe P, Alberti KGMM: Enzymic fluorometric continuous flow assays for blood glucose, lactate, pyruvate, alanine, glycerol, and 3-hydroxybutyrate. *Clin Chem* 34:1727–1729, 1978
22. Shimuzu S, Inque K, Tani Y, Yamada H: Enzymatic microdetermination of serum free fatty acids. *Anal Biochem* 98:341–345, 1978
23. Kuzuya H, Blix PM, Horwitz DL, Steiner DF, Rubenstein AH: Determination of free and total insulin and C-peptide in insulin-treated diabetics. *Diabetes* 26:22–29, 1977
24. Cole RA, Soeldner JS, Dunn PJ, Bunn HF: A rapid determination of glycosylated hemoglobins using high-performance liquid chromatography. *Metab Clin Exp* 35:289–291, 1978
25. Bergman RN: Toward physiological understanding of glucose tolerance: minimal model approach. *Diabetes* 38:1512–1527, 1989
26. Kahn SE, Prigeon RL, McCulloch DK, Boyko EJ, Bergman RN, Schwartz MW, Neifing JL, Ward WK, Beard JC, Palmer JP: Quantification of the relationship between insulin sensitivity and β-cell function in human subjects: evidence for a hyperbolic function. *Diabetes* 42:1663–1672, 1993
27. Avogaro A, Watanabe RM, Gottardo L, de Kreutzenberg S, Tiengo A, Pacini G: Glucose tolerance during moderate alcohol intake: insights on insulin action from glucose/lactate dynamics. *J Clin Endocrinol Metab* 87:1233–1238, 2002
28. Marks V: Alcohol and carbohydrate metabolism. *Clin Endocrinol Metab* 7:333–349, 1978
29. Ferrannini E, Natali A, Brandi LS, Bonadonna R, De Kreutzemberg SV, DelPrato S, Santoro D: Metabolic and thermogenic effects of lactate infusion in humans. *Am J Physiol* 265:E504–E512, 1993
30. Emanuele MA, Kirsteins L, Reda D, Emanuele NV, Lawrence AM: The effect of in vitro ethanol exposure on basal growth hormone secretion. *Endocr Res* 14: 283–291, 1988
31. Valimaki M, Tuominen JA, Huhtaniemi I, Ylikahri R: The pulsatile secretion of gonadotropins and growth hormone, and the biological activity of luteinizing hormone in men acutely intoxicated with ethanol. *Alcohol Clin Exp Res* 14:928–931, 1990
32. Trojan N, Pavan P, Iori E, Vettore M, Marescotti MC, Macdonald IA, Tiengo A, Pacini G, Avogaro A: Effect of different times of administration of a single ethanol dose on insulin action, insulin secretion and redox state. *Diabet Med* 16:400–407, 1999
33. Klatsky AL: Alcohol and cardiovascular disease–more than one paradox to consider: alcohol and hypertension: does it matter: yes. *J Cardiovasc Risk* 10:21–24, 2003
34. Cushman WC: Alcohol consumption and hypertension. *J Clin Hypertens (Greenwich)* 3:166–170, 2001
35. Sijbrands EJ, Smelt AH: Alcohol consumption had no beneficial effect on serum lipids in a substantial proportion of patients with primary hyperlipidemia. *J Clin Epidemiol* 53:1020–1024, 2000
36. Ayaori M, Ishikawa T, Yoshida H, Suzukawa M, Nishiwaki M, Shige H, Ito T, Nakajima K, Higashi K, Yonemura A, Nakamura H: Beneficial effects of alcohol withdrawal on LDL particle size distribution and oxidative susceptibility in subjects with alcohol-induced hypertriglyceridemia. *Arterioscler Thromb Vasc Biol* 17:2540–2547, 1997