# The Effect of Evening Alcohol Consumption on Next-Morning Glucose Control in Type 1 Diabetes

BENJAMIN C. TURNER, MRCP[1]
EMMA JENKINS, BSC[1]
DAVID KERR, MD, FRCP[1]
ROBERT S. SHERWIN, MD[2]
DAVID A. CAVAN, MD, FRCP[1]

**OBJECTIVE** — Alcohol is associated with acute hypoglycemia in patients with type 1 diabetes. After drinking alcohol in the evening, delayed hypoglycemia has also been described, although its cause is unknown. We performed a controlled study to investigate this phenomenon.

**RESEARCH DESIGN AND METHODS** — We admitted six men with type 1 diabetes (aged 19–51 years, $HbA_{1c}$ 7.0–10.3%) on two occasions, from 5:00 P.M. to 12:00 noon the following day. They received regular insulin injections before standardized meals, at 6:00 P.M. and 8:00 A.M., and a basal insulin infusion ($0.15\ mU \cdot kg^{-1} \cdot min^{-1}$) from 11:00 P.M. They drank either dry white wine (0.75 g/kg alcohol) or mineral water at 9:00 P.M. over 90 min. Blood glucose, alcohol, insulin, cortisol, growth hormone, and glucagon levels were measured.

**RESULTS** — Blood ethanol reached a mean (SEM) peak of 19.1 (1.2) mmol/l and was undetectable by 8:00 A.M. There were no significant differences in evening or overnight blood glucose levels between the studies. In the morning, fasting and postprandial blood glucose levels were significantly lower after consumption of wine (postprandial peak 8.9 [1.7] vs. 15 [1.5] mmol/l, $P < 0.01$), and from 10:00 A.M., five subjects required treatment for hypoglycemia (nadir 1.9–2.9 mmol/l). None of the subjects had hypoglycemia after consumption of water. After consumption of wine, growth hormone secretion was significantly reduced between midnight and 4:00 A.M. (area under the curve 2.1 [1.1] vs. 6.5 [2.1] $\mu g \cdot l^{-1} \cdot h^{-1}$, $P = 0.04$). There were no differences in insulin or other hormone levels.

**CONCLUSIONS** — In type 1 diabetes, moderate consumption of alcohol in the evening may predispose patients to hypoglycemia after breakfast the next morning. This is associated with reduced nocturnal growth hormone secretion. Patients should be informed of this risk and advised regarding appropriate preventative measures.

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Alcohol is a recognized risk factor for hypoglycemia in patients with type 1 diabetes. It is estimated that as many as one fifth of episodes of severe hypoglycemia are attributable to alcohol (1,2), and patients frequently ask for advice about the impact of drinking on diabetes. In terms of quantity, both British and American Diabetes Association guidelines give limits in line with those for the general population (3–5) and recommend no more than ~2 units absolute alcohol at a single sitting (1 unit = 8 g [10 ml or 0.35 fluid ounce], equivalent to 0.5 pint average-strength beer, one glass[4 fluid ounces] of wine, or a "single" of spirits). For insulin-treated patients, the guidelines emphasize that dietary carbohydrate should not be omitted, that alcohol should be consumed with food or shortly before eating, and that the risk of hypoglycemia may extend for several hours after drinking. Inhibition of gluconeogenesis is cited as the main metabolic effect, but it is also pointed out that the usual symptoms of hypoglycemia may be obscured or masked by the cerebral effects of alcohol. Indeed, even moderate consumption of ethanol (6–9 units) may reduce hypoglycemia awareness (6) and impair the counter-regulatory response to insulin-induced hypoglycemia (7,8).

Studies of diabetic patients have failed to show any short-term effect of moderate alcohol intake with a meal (9,10) or alcohol administered intravenously after an overnight fast (11). However, some authors report an increased risk of hypoglycemia in the morning, 12–16 h after consumption of an alcoholic beverage in the evening (12,13). The mechanism is unknown, although reduced cortisol levels were found in one study (13). Ethanol has been found to significantly lower overnight secretion of growth hormone in nondiabetic subjects (14,15), and reduced response of growth hormone to hypoglycemia in the presence of ethanol has also been reported (7). The effect of ethanol on nocturnal growth hormone levels in diabetes is unknown and may be relevant to delayed hypoglycemia. In the absence of specific advice to patients about the "hangover" period, we performed a controlled study to examine both glucose control and hormonal responses through to midday after consumption of an alcoholic beverage in the evening.

## RESEARCH DESIGN AND METHODS

### Patients

We recruited six men with type 1 diabetes (age <30 years at diagnosis, insulin treatment from outset) from the hospital diabetes clinic. The mean (range) age was 33

From the [1]Bournemouth Diabetes and Endocrine Centre, Royal Bournemouth Hospital, Bournemouth, U.K.; and the [2]Yale University School of Medicine, New Haven, Connecticut.

Address correspondence and reprint requests to Dr. Benjamin C. Turner, Diabetes and Endocrine Day Centre, 6/F North Wing, St. Thomas' Hospital, Lambeth Palace Rd., London, SE1 7EH U.K. E-mail: ben.turner@gstt.sthames.nhs.uk

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**Abbreviations:** AUC, area under the curve; FFA, free fatty acid.

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

(19–51) years and the mean (range) duration of diabetes was 13 (2–37) years. All gave written informed consent to take part in the study, which had been approved by the East Dorset Local Ethics Committee. Subjects were excluded if they had unstable diabetes, diabetic complications other than background retinopathy, or drank alcohol in excess of 21 units/week. None of the subjects had symptoms of gastrointestinal disease or were taking any medications orally. They underwent baseline blood testing to ensure normal hepatic and thyroid function and normal hematological indices. All subjects were being treated with a basal-bolus regimen of premeal regular (short-acting) insulin and bedtime NPH insulin. Each subject underwent detailed evaluation of their day-to-day glucose control for optimization before the formal studies. This included a 4-day record of preprandial and bedtime glucose levels, insulin doses, and dietary intake, which was evaluated with the aid of the DIAS (Diabetes Advisory System) decision-support system (16). From this, we were able to identify risk periods for hypoglycemia and adjust therapy accordingly. $HbA_{1c}$ was measured at or just before admission. Subjects were asked to refrain from consuming alcohol and caffeine for 24 h before each study period.

### Study design

Each subject was admitted for a 20-h period beginning at 5:00 P.M., on two occasions 1–2 weeks apart. The study did not proceed if the subjects reported symptomatic hypoglycemia on the day of admission. At 5:00 P.M., an intravenous cannula was placed in a forearm vein of each arm. At 5:45 P.M., subjects injected regular insulin into the abdominal wall, at a dose of 70% of their usual evening meal dose to reduce the likelihood of hypoglycemia between 6:00 and 9:00 P.M. All insulin injections were observed by a physician, and the site was recorded in relation to the umbilicus at the first admission then replicated in the second. At 6:00 P.M., the subjects ate a meal over 15–20 min, in which overall nutritional composition (by calorie distribution) was constant for all the subjects, i.e., 50% carbohydrate, 30% fat, and 20% protein. The carbohydrate content was matched to the average evening meal carbohydrate level given in the prestudy food diary. No more food was eaten until breakfast.

At 9:00 P.M., the subjects were given either dry white wine (Chilean Chenin Blanc, alcohol 13% vol.) or an equal volume of mineral water (as a control) to drink steadily over 90 min. Three subjects received wine on their first visit, and three subjects were given water. The wine contained 70 g ethanol and 2–3 g carbohydrate per 750-ml bottle. A volume was measured to provide 0.75 g ethanol per kg body wt (equivalent to 6.6 units [19.9 fluid ounces] for a 70-kg subject). Blood pressure and pulse were measured during drinking.

At 11:00 P.M., an intravenous insulin infusion was started at 0.15 $mU \cdot kg^{-1} \cdot min^{-1}$. The rate was chosen to provide a basal insulin level sufficient to maintain near-normoglycemia under the control conditions. No subcutaneous insulin was given at bedtime. The infusion continued until the end of the study period at 12:00 noon. Subjects slept from 11:00 P.M. until 7:00 A.M., when they were awakened if necessary. At 7:20 A.M., an in-house questionnaire on hangover symptoms (nausea, headache, thirst, etc.) was completed. Ten symptoms were scored using a 10-cm visual analog scale, including an overall score for how "hung over" the subject felt. At 7:30 A.M., the usual prebreakfast insulin dose was given. At 8:00 A.M., the subjects ate breakfast, comprising cereal with milk and/or toast with fruit juice. The carbohydrate content was calculated to match their usual intake and, as with the evening meal, was identical in both admissions. Nothing more was eaten until the end of the study at 12:00 noon. The subjects remained at rest throughout the study period. Room temperature was noted on each admission.

Blood samples were collected for immediate glucose analysis every 30 min during the periods of 6:00–8:00 P.M., 9:00–11:00 P.M., and 8:00 A.M. onward, with hourly sampling at other times. Measurements were made using a glucose analyzer (Yellow Springs Instruments; Yellow Springs, OH), but the subjects remained blind to the results. If hypoglycemia occurred (glucose <4 mmol/l), it was treated either at the patient's request in response to symptoms or if glucose decreased to <2.5 mmol/l. We used 10–20 g Hypostop glucose gel (Biodiagnostics, Worcestershire, U.K.), followed by longer-acting carbohydrate as required. Blood samples were collected hourly, beginning at 8:00 P.M. for measurement of insulin, cortisol, and glucagon and every 30 min for growth hormone. Samples were stored on ice for up to 3 h, centrifuged at −4°C, and then stored at −20°C for future analysis. Blood alcohol was measured every 30 min for 2 h from the start of drinking and then hourly for an additional 8 h. Intravenous cannulas were kept patent by regular flushing with 2 ml heparinized saline.

$HbA_{1c}$ was measured by high-performance liquid chromatography (normal range 4.1–6.5%). Alcohol was measured by a standard gas chromatography method, using a stationary phase of 10% 400 polyethylene glycol on 100–120 mesh celite at a constant column temperature of 90°C, with flame ionization detection. Samples were injected directly, and isopropanol was used as an internal standard. The detection limit of the assay was 1.09 mmol/l, and within-batch precision was <2%.

### Hormone assays

Blood samples for insulin, cortisol, and growth hormone assays were collected as 3-ml samples in EDTA tubes. Plasma free insulin and cortisol were measured by double-antibody radioimmunoassay, with polyethylene glycol precipitation. Plasma growth hormone was measured by highly sensitive immunoradiometric assay. For glucagon assay, 2 ml blood was collected in a lithium-heparin tube containing 0.2 ml (2,000 KIU) aprotinin (Trasylol). Glucagon was measured by double-antibody radioimmunoassay.

### Statistical analysis

Comparisons were made using Student's paired *t* test (two-tailed). Tests of significance were applied both to values at given time points and integrated (area under the curve [AUC]) responses as indicated. Blood glucose values after treatment of hypoglycemia were not included in the calculation of mean values at subsequent time points or used in significance testing. Statistics were obtained using Microsoft Excel data analysis software package (version 7.0; Microsoft, Redmond, WA). Values are expressed as mean (SEM) unless otherwise stated.

**RESULTS** — The subjects had a mean (range) $HbA_{1c}$ of 8.5% (7.0−10.3%). The quantities of wine (or water), carbohydrate, and insulin used are summarized in Table 1. Average wine consumption

**Table 1—*Drink, carbohydrate, and insulin of the six subjects***

| | Mean | Range |
|---|---|---|
| Wine or water (ml) | 587 | 540–635 |
| Carbohydrate intake (g) | | |
| Evening meal | 87 | 70–105 |
| Breakfast | 55 | 45–60 |
| Insulin dose (units) | | |
| Evening meal | 10.3 | 6–17 |
| Breakfast | 10 | 6–14 |

equated to 6.8 units of alcohol, yielding a mean peak blood ethanol concentration of 19.1 (1.2) mmol/l between 11:00 P.M. and midnight. By 8:00 A.M., ethanol was undetectable in all subjects. After drinking mineral water, one subject had transient biochemical hypoglycemia (3.8 mmol/l) at 11:00 P.M., but no further hypoglycemia was recorded. After consuming wine, one subject had continuous mild hypoglycemia (>3.0 mmol/l) between 11:00 P.M. and 4:00 A.M., again from 9:30 to 10:30 P.M., and then at 7:30 to 8:00 A.M. Neither of these subjects had symptoms at these times. However, five subjects later experienced symptomatic hypoglycemia after breakfast and required treatment (Fig. 1). Nadir blood glucose in these five ranged from 1.9 to 2.9 mmol/l, occurring between 10:00 A.M. and midday. In the control study, the lowest postbreakfast glucose level ranged from 5.2 to 11.8 mmol/l. There was blunting of the postbreakfast glucose increase after alcohol consumption, with a 2-h AUC response of 1.9 (1.8) vs. 5.7 (1.9) mmol · $l^{-1}$ · h ($P = 0.02$). Although there was a small difference in blood glucose between alcohol and control studies at the start of drinking, correcting for this still yielded significantly lower glucose values after consumption of wine over the same period. The most marked hypoglycemia (nadir 1.9 mmol/l) occurred in the patient with the lowest $HbA_{1c}$ (7.0%), and the patient who did not develop hypoglycemia after alcohol had the most stable control before the study ($HbA_{1c}$ 8.0%).

During the entire period of sleep (11:00 P.M. to 7:00 A.M.), there was a lower AUC growth hormone response after wine, though this was not statistically significant (4.8 [1.4] vs. 8.5 [2.2] μg · $l^{-1}$ · $h^{-1}$, $P = 0.15$) (Fig. 2). However, the peak growth hormone level between midnight and 4:00 A.M. was significantly lower after consumption of wine (2.0 [1.0] vs. 5.3 [1.5] μg/l, $P = 0.036$) (Fig. 3), as was AUC growth hormone response during this period (2.1 [1.1] vs. 6.5 [2.1] μg · $l^{-1}$ · $h^{-1}$, $P = 0.038$). Insulin decreased to similar overnight basal levels after consumption of water or wine, with no significant difference in the rise after breakfast. Cortisol and glucagon levels were unaffected by alcohol. There was a sharp increase in mean growth hormone from approximately 10:30 A.M. in the wine study, although no parallel cortisol or glucagon response.

Sleep quality during the studies was not formally assessed, although subjective assessments were made during sampling. The average number of episodes (between midnight and 7:00 A.M.) in which a subject was recorded as "awake" or with "eyes open" was 4.5 in the control study and 5.5 after consumption of wine. The hangover questionnaire yielded higher scores after consumption of wine for most symptoms, but statistical significance was only approached for thirst (4.3 vs. 0.6, $P = 0.05$). Room temperature differed by no more than 1.5°C between control and alcohol nights.

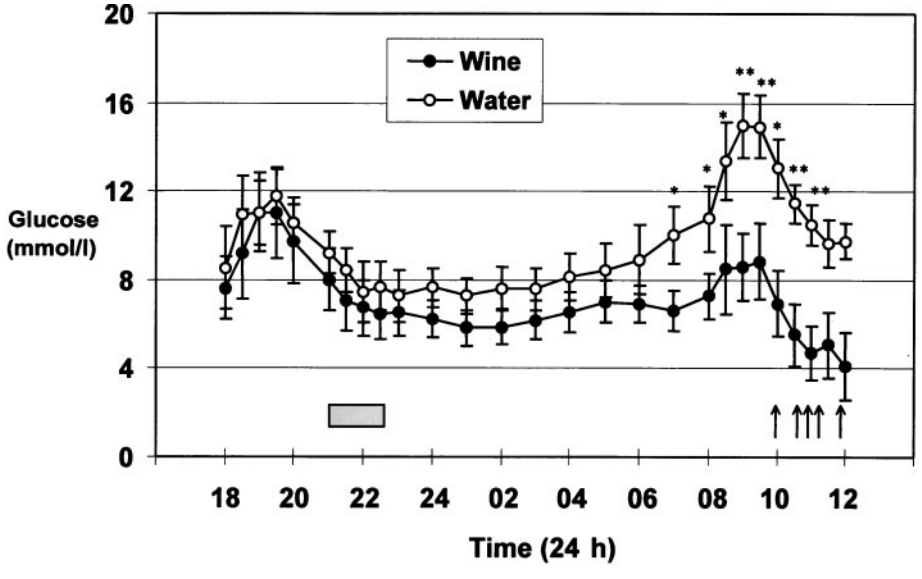


**Figure 1—*Mean (SEM) blood glucose values of the six subjects. The period of drinking is indicated by the shaded bar. The approximate times of symptomatic hypoglycemia after consumption of wine are indicated by vertical arrows. Meals were at 1800 and 0800. *P < 0.05, **P < 0.01.***

**CONCLUSIONS** — We found that the consumption of a moderate amount of alcohol 2–3 h after an evening meal greatly increased the likelihood of hypoglycemia after breakfast the following morning. This was associated with reduced secretion of growth hormone in the 4 h after midnight.

Both lower fasting blood glucose level and a reduced increase in postprandial glucose preceded late-morning hypoglycemia. Lange et al. (12) reported a similar pattern, but their study was less detailed in its control of diet, exercise, and insulin injections. They also reported several episodes of symptomatic nocturnal hypoglycemia in the control studies but did not specify how these were treated. Furthermore, to eliminate potentially confounding variability in insulin absorption between alcohol and control nights, we used an insulin infusion in place of the bedtime injection of NPH insulin. In light of similar morning insulin levels, the average reduction in glucose of 5–6 mmol/l is striking, and the depth of hypoglycemia was sufficient to prompt treatment in all cases.

Ethanol is known to affect various aspects of glucose metabolism, raising several possible explanations for our findings. Without glucose turnover data, however, we can only make inferences about glucose production and utilization. Inhibition of gluconeogenesis by ethanol is well recognized, and in nondiabetic subjects, one would expect ~45% inhibition at the peak ethanol concentration in our study (17). In type 1 diabetes, gluconeogenesis is responsible for a signifi-

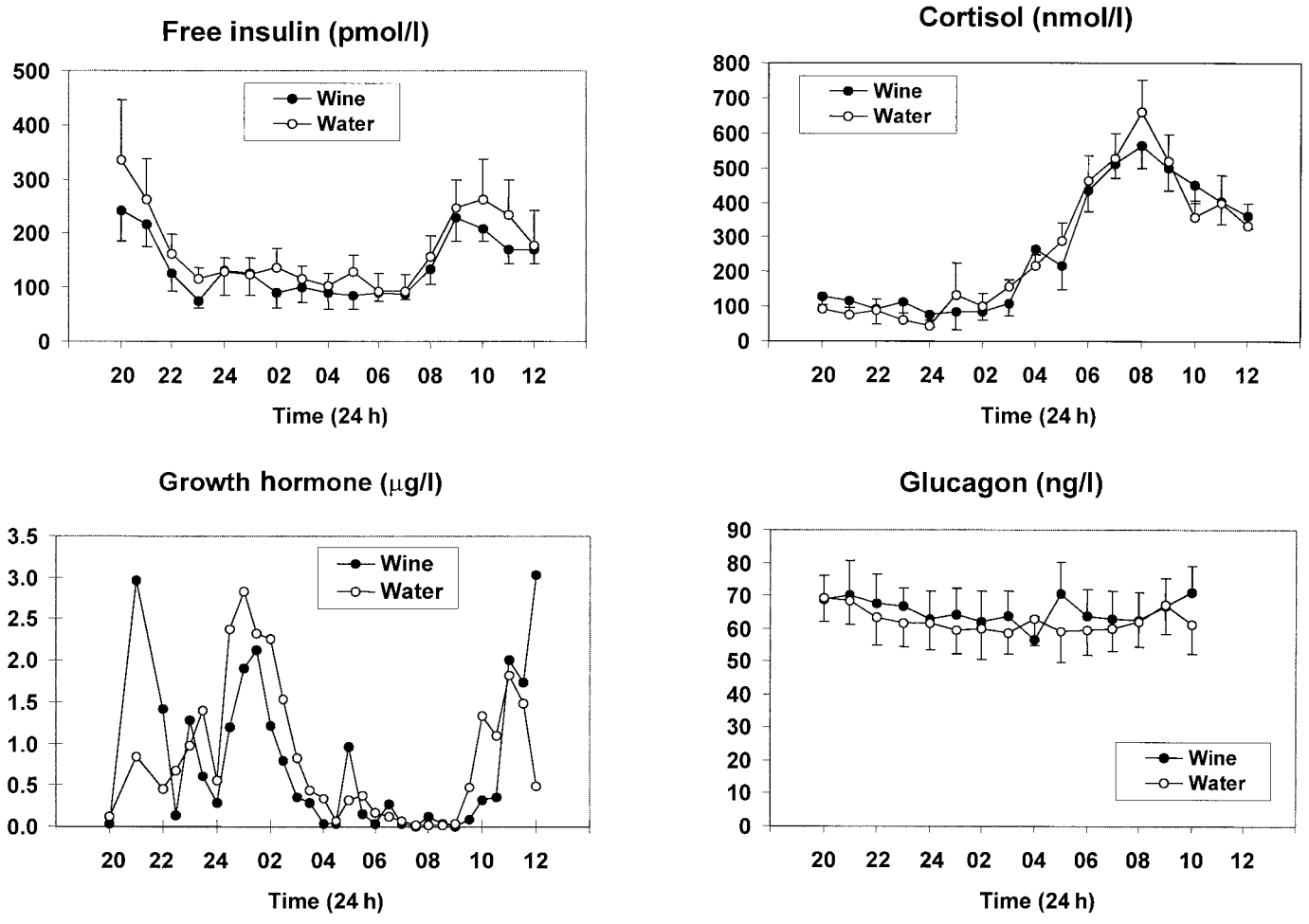


**Figure 2—** *Mean (SEM) hormone levels of the six subjects.*

cant proportion of increased basal hepatic glucose output, and patients may therefore be more sensitive to ethanol. However, in a study of fasted type 1 diabetes controlled by hypoinsulinemic clamp, there was no difference in glucose response to a 1-h infusion of ethanol (peak level 26.2 mmol/l) or saline (11). In nondiabetic subjects, reduced glucose production seems to be matched by inhibition of glucose utilization (probably by acetate) at low and moderate ethanol concentrations (4–14 mmol/l) (18). Alcohol hypoglycemia has been reproduced by sustained (8-h) administration of ethanol, with blood levels up to 97 mmol/l (19). The effect is more potent after 2–3 days of fasting and potentially lethal in patients with chronic alcoholism who are treated with insulin (20). However, in circumstances in which gluconeogenesis is not critical to maintaining blood glucose, its suppression by ethanol seems less likely to cause hypoglycemia. In the patients in our study, there was certainly no immediate decrease in glucose after consumption of wine, and we would have to postulate reduced basal glucose output persisting 2–4 h beyond elimination of ethanol if this were the sole mechanism.

In rats and humans, there is evidence that both basal and stimulated release of growth hormone is impaired by ethanol. In rats, there are also data to support a dose-response effect both in vivo (21) and in vitro (22). Rat pituitary exposed to ethanol showed a 60% reduction in 4-h secretion of growth hormone at the lowest concentration (10.9 mmol/l) and maximal suppression (~92%) at a concentration of 43.6 mmol/l (22). In humans, no dose-ranging studies have been reported, but in nondiabetic subjects after evening ethanol intake of 0.8−1.5 g/kg, a more than two-thirds reduction in integrated response of growth hormone (15) or fewer peaks of growth hormone between 2:00 and 6:00 A.M. (14) have been observed. In nondiabetic subjects, the physiological nocturnal increase in growth hormone does not seem to influence carbohydrate metabolism the next morning (23). By contrast, administration of

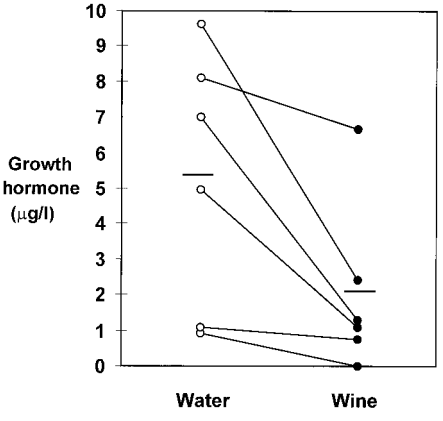


**Figure 3—** *Peak growth hormone levels of each subject between midnight and 4:00 A.M. Horizontal bars indicate the mean.* P = *0.036.*

pulsed growth hormone to type 1 diabetic subjects has a marked effect on hepatic glucose output, and even moderate elevations in growth hormone can lead to poor metabolic control within 8–10 h (24). Moreover, complete abolition of nocturnal secretion of growth hormone has been shown to ameliorate the dawn phenomenon in type 1 diabetic subjects, associated with a sustained reduction in glucose production (25). Using an identical basal insulin infusion rate, we found a similar blunting of the dawn glucose increase after consumption of wine, with a two-thirds reduction in integrated response of growth hormone (and reduced peak amplitude) between midnight and 4:00 A.M. We do not believe the latter has been demonstrated previously in diabetes. The growth hormone levels in the control study were lower than expected, which may have been due to poor sleep quality or because most of our subjects had reasonable glucose control. If the subsequent postprandial hypoglycemia were attributable to lower nocturnal secretion of growth hormone, it might be mediated by a relative increase in peripheral insulin sensitivity.

Ethanol seemed to have no effect on subsequent cortisol or glucagon secretion, although there was no increase in either hormone after hypoglycemia. An absent glucagon response is common in type 1 diabetes, and although impaired cortisol secretion might delay recovery from hypoglycemia, more prolonged sampling would be necessary to confirm this finding. We did not measure catecholamine or free fatty acid (FFA) levels. Ethanol causes a dose-dependent increase in norepinephrine (with reduced clearance) and of epinephrine during acute intoxication (26). These effects might lead to reduced peripheral uptake of glucose, perhaps ameliorating any acute glucose-lowering effect of suppressed gluconeogenesis. Acutely, moderate alcohol doses inhibit release of FFA from adipose tissue, probably through the action of acetate (27). Prolonged infusion leads to a progressive increase in FFA levels (19), potentially via increases in catecholamine levels. The suppression of FFA by ethanol may be responsible for the impaired recovery from hypoglycemia seen in type 1 diabetes, via increased glucose utilization (7). In our study, the acute increase in blood ethanol occurred as insulin was decreasing. This would have yielded competing influences on FFA levels, and we can only speculate about the net short-term effect. FFA levels might have increased as ethanol waned overnight, but it seems unlikely that any acute effect on FFA turnover could explain the much later occurrence of hypoglycemia.

One further mechanism to be considered is the ability of ethanol to induce acute inflammatory changes in the upper gastrointestinal tract, which are associated with carbohydrate malabsorption (28,29). The duration of this malabsorption is unknown, as studies have focused on acute effects. If persistent for 10–12 h, it could certainly limit the postbreakfast glucose increase and predispose subjects to hypoglycemia. Further research is required in this area.

We chose the quantity of alcohol in our study to represent an average evening's drinking in young adults and an amount that would generate a peak blood level just above the legal limit for driving in the U.K. (17.4 mmol/l). We used wine to keep the total volume of beverage to a reasonable level and separated drinking from eating to ensure consistent gastric absorption of ethanol. Although the subjects did not experience a "hangover" as such, they had increased scores on several associated symptoms. Several possible mechanisms, perhaps acting in concert, might account for our findings. Smaller ethanol doses, as recommended by the British and American Diabetes Associations, would be expected to have less effect on secretion of growth hormone and gluconeogenesis and be less toxic to the gastrointestinal tract. However, it is unknown whether there is a risk of delayed hypoglycemia at these doses. Although recognizing the small sample size in our study, we would warn anyone with type 1 diabetes to be alert to the possibility of late-morning hypoglycemia after an evening consumption of alcohol and to be sure that some rapid-acting carbohydrate is available. Reduction in the breakfast insulin dose might also be advisable. Additional glucose testing should be recommended in circumstances in which hypoglycemia could be dangerous, such as driving or operating machinery.

In summary, we have shown that in patients with type 1 diabetes, evening consumption of alcohol causes lowering of blood glucose the next morning and increases the risk of hypoglycemia after breakfast. This is associated with but not necessarily due to a reduction in nocturnal secretion of growth hormone. Patients should be alerted to this possibility and advised regarding appropriate preventative measures.

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